NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Upadacitinib for previously treated moderate to severe active rheumatoid arthritis [ID1400]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Upadacitinib for previously treated moderate to severe active rheumatoid arthritis [ID1400]

Contents:

The following documents are made available to consultees and commentators:

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

Pre-technical engagement documents

1. **Company submission** from **AbbVie**
   a. Submission
   b. Addendum

2. **Clarification questions and company responses**
   a. Company response to clarification
   b. Company additional clarification response (B4, B18, B23)
   c. Company additional clarification response

3. **Patient group, professional group and NHS organisation submission** from:
   a. British Society for Rheumatology
   b. National Rheumatoid Arthritis Society

4. **Expert personal perspectives** from:
   - Professor Christopher Edwards – clinical expert, nominated by AbbVie

5. **Evidence Review Group report** prepared by **Peninsula Technology Assessment Group**

6. **Evidence Review Group report – addenda**
   a. Biosimilars
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Post-technical engagement documents

8. **Technical engagement response from AbbVie**
   a. Technical engagement response
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Technical engagement responses from experts:

There were no technical engagement responses from experts

9. Technical engagement responses from consultees and commentators:

a. Biogen
b. Pfizer
c. UCB

10. Evidence Review Group critique of company response to technical engagement prepared by **Peninsula Technology Assessment Group**

11. Final Technical Report

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 moderate to severe rheumatoid arthritis
ID1400

Document B

Company evidence submission

July 2019

File name	Version	Contains confidential information	Date
ID1400_Upadacitinib_RA_NICE Document B_[ACIC]_FINAL	1.0	Yes	05/07/2019

Contents

Tables and figures

List of abbreviations

Acronym	Definition
ABA	Abatacept
ABT	Adalimumab
ACPA	Anti-citrullinated protein antibody
ACR	American College of Rheumatology
ADA	Adalimumab
AE	Adverse Event
AG	Academic group
ANCOVA	Analysis of covariance
BAR	Baricitinib
bDMARDs	biologic disease-modifying anti-rheumatic drugs
BID	Twice daily
BIW	Twice weekly
BMI	Body mass index
BRC	Baricitinib
BSC	Best supportive care
BSRBR	British Society of Rheumatology Biologics Register
BSRBR-RA	British Society of Rheumatology Biologics Register for Rheumatoid Arthritis
CCP	Cyclic citrullinated peptide
CDAI	Clinical Disease Activity Index
csDMARDs	conventional synthetic disease-modifying anti-rheumatic drug(s)
CEA	Cost-effectiveness analysis
CFB	Change from Baseline
CHMP	Committee for Medicinal Products for Human Use
CPK	Creatine phosphokinase
CRP	C-reactive protein
CTZ	Certolizumab pegol
DAS	Disease activity score
DES	Discrete-event simulation
DIC	Deviance Information Criterion
DMARD	Disease-modifying anti-rheumatic drugs
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
DVT	Deep vein thrombosis
EMA	European Medicines Agency
EOW	Every other week
ESR	Erythrocyte sedimentation rate
ETN	Etanercept
EULAR	European League Against Rheumatism
FACIT - F	Functional Assessment of Chronic Illness Therapy — Fatigue
GBP	Great Britain Pound
GOL	Golimumab
HAQ	Health Assessment Questionnaire
HAQ - DI	Health Assessment Questionnaire — Disability Index

HCHS	hospital & community health services
HRQOL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IFX	Infliximab
INF	Infliximab
JAK	Janus kinase
JSN	Joint Space Narrowing
LCGM	Latent class growth model
LDA	Low disease activity
LOCF	Last Observation Carried Forward
LSM	Least squared mean
LYG	Life years gained
MACE	Major adverse cardiovascular events
MCID	Minimal clinically important differences
MCS	Mental component summary
MIMS	Monthly Index of Medical Specialties
MJS	Morning joint stiffness
MMRM	Mixed Effect Model Repeat Measurement
MOA	Mechanism of Action
MONO	Monotherapy
mTSS	modified total Sharp score
MTX	Methotrexate
NDB	National Data Bank for Rheumatic Diseases
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analyses
NOAR	Norfolk Arthritis Register
NRI	Non-responder imputation
NSAIDs	non-steroidal anti-inflammatory drugs
PAS	Patient access scheme
PBO	Placebo
PCS	Physical component summary
PRO	Patient reported outcomes
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life years
QD	once daily
RA	Rheumatoid arthritis
RF	Rheumatoid factor
RTX	Rituximab
SAE	Serious Adverse Events
SAF	Safety set
SAR	Sarilumab
SC	Subcutaneous
SDAI	Simplified Disease Activity Index

SF-36	Short Form-36
SLR	Systemic literature review
SMC	Scottish Medicines Consortium
SRL	Sarilumab
STA	Single Technology Appraisal
STAT	Signal transducers and activators of transcription
TCZ	Tocilizumab
TFC	Tofacitinib
TNF	Tumor necrosis factor
TOF	Tofacitinib
ULN	Upper limit of normal
UPA	Upadacitinib
VARA	Veterans Affairs Rheumatoid Arthritis
VAS	Visual Analog Scale
VBA	Visual Basic for Applications
VTE	Venous thromboembolic events
WIS	Work Instability Scale
WTP	Willingness-to-pay

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

B.1.1 Decision problem

The full marketing authorisation for upadacitinib is expected to be for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs). Upadacitinib may be used as monotherapy or in combination with methotrexate or other conventional synthetic DMARDs (csDMARDs).

Upadacitinib does not currently have marketing authorisation in the UK for any indication. An application for a marketing authorisation in the above indication was submitted to the European Medicines Agency (EMA) in December 2018. Upadacitinib is anticipated to be launched in the UK in [redacted] and a submission will also be prepared to the Scottish Medicines Consortium (SMC).

The submission covers the technology's expected full marketing authorisation for this indication. The submission specifically addresses the clinical efficacy and safety, the comparative effectiveness and cost-effectiveness of upadacitinib 15mg once daily (QD), as monotherapy or in combination with methotrexate (MTX), in adult patients with moderate to severe RA for whom methotrexate, csDMARDs or biologic (bDMARDs) have been inadequately effective or not tolerated. For the purposes of this submission, bDMARDs and targeted synthetic DMARDs (tsDMARDs) will be referred to collectively as 'advanced therapies'.

The decision problem addressed is consistent with the final National Institute for Health and Care Excellence (NICE) scope for this appraisal, as outlined in Table 1.

Table 1: The decision problem

	Final scope issued by NICE/reference case	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with moderate to severe, active RA whose disease has responded inadequately to, or who are intolerant of one or more disease modifying anti-rheumatic drugs (DMARDs), including conventional or biologic DMARDs	Adults with moderate to severe, active RA whose disease has responded inadequately to, or who are intolerant of one or more DMARD, including conventional synthetic DMARDs (csDMARDs) or advanced therapies. Specifically, the following populations: 1. Moderate active RA that has not responded adequately to therapy with one csDMARD a. For patients with MTX intolerance/contraindication b. For patients who tolerate MTX and it is ***not*** contraindicated 2. Moderate active RA that has not responded adequately to therapy with two or more csDMARDs a. For patients with MTX intolerance/contraindication b. For patients who tolerate MTX and it is ***not*** contraindicated 3. Severe active RA that has not responded adequately to therapy with two or more csDMARDs: a. For patients with MTX intolerance/contraindication b. For patients who tolerate MTX and it is ***not*** contraindicated 4. Severe active RA that has not responded adequately to therapy with advanced therapies: a. For patients with MTX intolerance/contraindication b. For patients who are rituximab (RTX) intolerant or contraindicated to RTX and who tolerate MTX and it is ***not*** contraindicated 5. Severe active RA that has not responded adequately to therapy with advanced and who are tolerant to MTX and RTX	The current NICE treatment pathway and related technology appraisal guidance specify that all NICE recommended advanced therapies (such as adalimumab, etanercept, baricitinib etc.) can only be used as monotherapy in patients who cannot take MTX because it is contraindicated or because of intolerance. However the manufacturer perspective is that upadacitinib represents a cost-effective option as a monotherapy regardless of MTX tolerance. The populations and associated comparators have therefore been categorised by tolerance or intolerance to MTX.

	Final scope issued by NICE/reference case	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
		6. Severe active RA that has not responded adequately to therapy with MTX+RTX.	
Intervention	Upadacitinib (as monotherapy and in combination with other conventional DMARDs, including methotrexate)	Upadacitinib, 15mg QD as monotherapy or in combination with other csDMARDs, including methotrexate	N/A
Comparator(s)	For moderate active RA that has not responded adequately to therapy with conventional DMARDs: o Combination therapy with conventional DMARDs (including methotrexate and at least one other DMARD, such as sulfasalazine and leflunomide) o Conventional DMARD monotherapy with dose escalation o Best supportive care (only where conventional DMARDs are not appropriate due to intolerance) For severe active RA that has not responded adequately to therapy with conventional DMARDs only: o Biological DMARDs in combination with methotrexate (adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab, abatacept or sarilumab) o Adalimumab, etanercept, certolizumab pegol,	**1 and 2:** For moderate active RA that has not responded adequately to therapy with csDMARDs (comparators will vary dependent upon MTX tolerance/contraindication and one or two csDMARD failure): o Combination therapy with csDMARDs (including methotrexate and at least one other DMARD, such as sulfasalazine and leflunomide). o csDMARD monotherapy with dose escalation. o Best supportive care (only where csDMARDs are not appropriate due to intolerance). **3a & 3b:** For severe active RA that has not responded adequately to therapy with csDMARDs only and who tolerate methotrexate and it is not contraindicated: o Advanced therapies in combination with MTX (adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab, abatacept, baricitinib, tofacitinib or sarilumab). **3a:** For severe active RA that has not responded adequately to therapy with csDMARDs only and who do not tolerate methotrexate, or it is contraindicated: o Adalimumab, etanercept, certolizumab pegol, tocilizumab, baricitinib, tofacitinib or sarilumab (each as monotherapy) **4a:** For severe active RA that has not responded adequately to therapy with advanced therapies and when RTX is contraindicated or withdrawn due to adverse events and who do not tolerate MTX, or it is contraindicated: o Adalimumab, etanercept, certolizumab pegol, tocilizumab, tofacitinib, baricitinib or sarilumab (each as monotherapy)	The populations and associated comparators have been categorised by tolerance or intolerance to MTX. Specifically: • Severe active RA that has not responded adequately to therapy with csDMARDs • Severe active RA that has not responded adequately to therapy with advanced therapies and when rituximab is contraindicated or withdrawn due to adverse events. Severe active RA that has not responded adequately to therapy with RTX and MTX was added as a specific population in line with recommendations from clinical experts through an advisory Board (1).

	Final scope issued by NICE/reference case	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	tocilizumab or sarilumab (each as monotherapy) o Tofacitinib or baricitinib (monotherapy or in combination with methotrexate) For severe active RA that has not responded adequately to therapy with DMARDs including at least one TNF inhibitor: o Rituximab in combination with methotrexate When rituximab is contraindicated or withdrawn due to adverse events: o Adalimumab, etanercept, infliximab, abatacept tocilizumab, certolizumab pegol, golimumab or sarilumab, each in combination with methotrexate o Adalimumab, etanercept, certolizumab pegol or sarilumab (each as monotherapy) o Tofacitinib or baricitinib (monotherapy or in combination with methotrexate)	**4b:** For severe active RA that has not responded adequately to therapy with advanced therapies and when RTX is contraindicated or withdrawn due to adverse events and who tolerate MTX and it is not contraindicated: o Adalimumab, etanercept, infliximab, abatacept tocilizumab, certolizumab pegol, golimumab, baricitinib, tofacitinib, or sarilumab, each in combination with MTX **5:** For severe active RA that has not responded adequately to therapy with advanced therapies either in combination with methotrexate or as monotherapy and who tolerate MTX and RTX and it is not contraindicated: o RTX in combination with methotrexate **6:** For severe active RA that has not responded adequately to therapy with rituximab and methotrexate: o Tocilizumab, sarilumab in combination with MTX	
Outcomes	The outcome measures to be considered include: • disease activity • physical function • joint damage, pain • mortality • fatigue • radiological progression	• disease activity (ACR20; ACR50; ACR70; EULAR response; DAS28-hsCRP; DAS28-ESR; SDAI; CDAI) • physical function (MJS, HAQ-DI) • joint damage, pain (mTSS, pain captured as part of the ACR core set) • mortality • fatigue (FACIT–F) • radiological progression (mTSS)	Extra-articular manifestations of disease were not captured as a specific outcome in the SELECT clinical trial programme. However, the relevant related outcomes are reported in the

	Final scope issued by NICE/reference case	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• extra-articular manifestations of disease • adverse effects of treatment • health-related quality of life	• extra-articular manifestations of disease (rates of oral candidiasis, GI complications/symptoms, cardiac disorders, renal function) • adverse effects of treatment (disutility of SAE) • health-related quality of life (HAQ mapped to EQ-5D)	safety analysis in Section B.2 Clinical effectiveness
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies will be taken into account. The availability and cost of biosimilar products should be taken into account.	A cost-utility analysis of upadacitinib versus comparators has been carried out. Lifetime time horizon: a lifetime time horizon, consistent with the academic group (AG) model in TA375. Costs were considered from a UK NHS and PSS perspective. A patient access scheme for upadacitinib has been included as part of the analysis.	NA
Subgroups to be considered	If the evidence allows the following subgroups will be considered. These	The following subgroups will be considered in this submission:	NA

	Final scope issued by NICE/reference case	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	include people with moderate disease activity (DAS28 between 3.2 and 5.1) and severe active disease (DAS28 greater than 5.1). Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	• people with moderate disease activity (DAS28 between 3.2 and 5.1) after two csDMARD failure • people with severe active disease (DAS28 greater than 5.1) after two csDMARD failure • After one csDMARD failure (moderate or severe RA)	

Abbreviations: ACR: American College of Rheumatology; ACR20/50/70: American College of Rheumatology 20%, 50%, 70% response; AG: academic group; bDMARD: biologic disease-modifying anti-rheumatic drug; BMI: body mass index; CCP: cyclic citrullinated peptide; CDAI: Clinical Disease Activity Index; CRP: C-reactive protein; csDMARDs: conventional synthetic disease-modifying anti-rheumatic drug(s); DAS28: Disease Activity Score 28; eow: every other week; FACIT-F: Functional Assessment of Chronic Illness Therapy — Fatigue; HAQ-DI: Health Assessment Questionnaire — Disability Index; hsCRP: high-sensitivity C-reactive protein; JAK: Janus kinase; LDA: low disease activity; MJS: morning joint stiffness; mTSS: modified total Sharp score; MTX: methotrexate; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; NSAIDs: non-steroidal anti-inflammatory drugs; PCS: physical component summary; PSS: Personal Social Services; QD: once daily; RA: rheumatoid arthritis; RF: rheumatoid factor; RTX: Rituximab; SAE: Serious Adverse Events; SF-36: Short Form-36; TNF: Tumor necrosis factor; ULN: upper limit of normal; WIS: Work Instability Scale

B.1.2 Description of the technology being appraised

Upadacitinib is a small molecule selective Janus kinase 1 (JAK1) inhibitor developed for the treatment of moderately to severely active RA. Table 2 summarises the details of the technology being appraised in this submission. The draft summary of product characteristics (SmPC) is provided in Appendix C.

Mechanism of Action

Upadacitinib was engineered with the aim of delivering optimal benefit risk profiles in inflammatory diseases, allowing it to achieve the highest possible clinical outcomes while minimising effects on JAK2-mediated haematopoiesis and JAK3-mediated immune defence pathways. Upadacitinib targets the Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway to reduce inflammation and modify the clinical course of RA. The JAK-STAT pathway is a downstream signalling pathway, and is abnormally regulated in patients with RA and is a therapeutic target (2). Unlike individual cytokine inhibitors, such as anti-tumor necrosis factor (anti-TNF) or IL-6 antibodies, JAK inhibitors can partially inhibit downstream signalling produced by more than one cytokine. In a complex disease state such as established RA, there may be multiple cytokines that are dysregulated, and therefore a blockade of one cytokine alone may not inhibit all pathogenic pathways.

Upadacitinib has increased selectivity for JAK1 over JAK2, JAK3 and TYK2, with the ability to inhibit signalling of key cytokines involved in the pathogenesis of RA. Upadacitinib is administered as a once-daily, oral, 15 mg dose, and can be given as monotherapy or in combination with MTX or csDMARDs. Regulatory approval for upadacitinib in Europe is expected [redacted]

Table 2: Technology being appraised

UK approved name and brand name	Upadacitinib (brand name unknown)
Mechanism of action	Upadacitinib targets the JAK-STAT pathway to reduce inflammation and modify the clinical course of RA. Upadacitinib has increased selectivity for JAK1 over JAK2, JAK3 and TYK2, with the ability to inhibit signaling of key cytokines involved in the pathogenesis of RA. Upadacitinib is an oral, reversible JAK1-selective inhibitor, which was engineered with the aim of delivering optimal benefit risk profiles in inflammatory diseases, allowing it to achieve the highest possible clinical outcomes while minimizing effects on JAK2-mediated hematopoiesis and JAK3-mediated immune defence pathways.
Marketing authorisation/CE mark status	An application for marketing authorisation for upadacitinib was submitted to the EMA at the end of 2018. The regulatory process being followed is the EMA centralised procedure for a full submission. CHMP opinion is expected in [redacted], and the anticipated date of regulatory approval is [redacted].
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The following indication is expected for upadacitinib in RA: Upadacitinib is indicated for the treatment of moderate to severe active RA in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs). Upadacitinib may be used as monotherapy or in combination with methotrexate or other conventional synthetic DMARDs. Please refer to appendix C for a draft SmPC.
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 csDMARDs including MTX.
Additional tests or investigations	None
List price and average cost of a course of treatment	List price: [redacted]
Patient access scheme (if applicable)	The manufacturer has submitted an application for a simple patient access scheme (PAS) to PASLU: PAS price: [redacted]

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

Disease overview

RA is an inflammatory autoimmune disease that typically affects the synovial tissue of the small joints of the hands and feet but can affect any synovial joint, causing swelling, stiffness, pain and progressive joint destruction. It is a systemic disease

and can affect the whole body, including the lungs, heart and eyes. RA is usually a chronic relapsing condition which has a pattern of flare-ups followed by periods of lower disease activity; however, for some people, the disease is constantly progressive.

Severity of disease can be classified into 3 categories, based on the disease activity score (DAS28) scoring system. DAS 28 is a composite measure based upon the number of joints impacted by disease and biomarkers of inflammation. It also usually includes a patient reported outcome for global health assessment based on a 100mm visual analogue scale scored from 0-100. A DAS28 score greater than 5.1 indicates high disease activity or severe disease, between 3.2 and 5.1 indicates moderate disease activity, and less than 3.2 indicates low disease activity. A score less than 2.6 indicates remission (3). The signs and symptoms associated with early stages of the disease are usually reversible as there is no evidence of joint destruction at this stage. However, as patients progress to moderate and severe RA, the associated joint damage and disability become increasingly irreversible. (4)

The cause of RA is unknown; however, it is thought to be the result of complex interactions between genetic and environmental factors (4). There is currently no laboratory test, histologic finding, or radiographic feature that confirms a definitive RA diagnosis. Instead, various factors, such as joint activity, patient history, presence of serological markers, and acute phase reactants are considered (5).

Epidemiology

The incidence of RA in England is 40 per 100,000 person years (6). There are approximately 22,000 people diagnosed with RA every year in England(6, 7). The majority of epidemiological studies have been carried out in Northern Europe and North America, and these studies have estimated the global prevalence of RA at between 0.5% and 1% of the population, with a higher susceptibility in females and elderly patients (8). An ageing Western population is likely to see total RA prevalence increase by 2030, despite the recent decline in incidence rates.

Approximately 50% of the risk of developing RA can be attributed to non-modifiable genetic factors; however, environmental risk factors also play a considerable role (9).

Approximately 43% of patients have moderate RA, 27% have severe RA and 31% mild RA (10).

Approximately 26% of moderate RA patients fail on one csDMARD and are receiving their 2nd csDMARD. Of these, 43% of those have poor prognostic factors. 13% of moderate RA patients are on their 3rd or subsequent csDMARD (10).

Disease burden

RA is a debilitating chronic, progressive autoimmune disease that is associated with increased morbidity and mortality, significantly affecting productivity and shortening lifespan by an average of over 10 years in uncontrolled patients (11). Patients with RA experience a significantly greater incidence of disability than patients in the general population, with globally an estimated 6.1 million disability-adjusted life years (DALYs) associated with the disease each year (8). Joint damage and disease activity are the primary causes of disability in patients with RA (12).

Patients with both severe RA and moderate RA experience substantial disease burden as demonstrated by the impact on joints. Hands and feet joints are often affected first in RA, though it can start in any joint (13). Joints impacted by RA include shoulders, elbows, wrists, fingers and knees (14). A UK database study of patients with moderate RA (mean DAS of 4.4), receiving csDMARDs (n=1543) followed up for a period of 24 months demonstrated a mean reduction in tender and swollen joint counts of 0.56 and 0.77 respectively suggesting the limited impact of current available treatments on joint damage (15). Corticosteroids are also widely used in RA, being prescribed in approximately 70% of RA patients in the UK (16). Rates of corticosteroid use are higher among patients with poorer prognostic factors and with higher disease activity, compared to patients in remission (17).

Patients with RA report worse health-related quality of life (HRQoL) than patients with other chronic conditions such as type 2 diabetes mellitus and myocardial infarction (18). Reduced HRQoL in patients with RA can largely be attributed to the considerable symptoms associated with the disease; some of the more burdensome symptoms include pain, fatigue, sleep problems, and morning stiffness. Irreversible joint damage can also decrease QoL (12).

RA affects patients in the most productive years of their life. A retrospective study of patients diagnosed with RA in the UK found that the majority of patients were diagnosed between the ages of 45–65 (6). Patients with a chronic disease such as RA are at an increased risk for adverse work outcomes, including presenteeism, absenteeism, and eventual disability or unemployment (19). RA patients miss between 13-82 days of work per year. Patients with RA can expect to be employed for fewer years than the general population, as work disability increases steadily through the course of the disease (20). Consequently, early retirement has been reported in up to 85% of patients with severe disability (21).

Aim of treatment and clinical guidelines

There is no cure for RA and treatment aims to improve quality of life and to prevent or reduce joint damage. NICE clinical guideline [NG100] ('Rheumatoid arthritis in adults: management') stipulates RA should be treated with the aim of achieving a target of remission or low disease activity if remission cannot be achieved. Disease activity is lowered by preventing loss of function, controlling joint damage, reducing stiffness and fatigue, maintaining pain control and enhancing self-management (22).

For those with poor prognostic factors with an increased risk of radiological progression (e.g. the presence of anti-cyclic citrullinated peptide (anti-CCP) antibodies or erosions on X-ray at baseline assessment), NICE guidelines suggest making the target remission rather than low disease activity. With this in mind, the guidelines recommend that as soon as possible after establishing a diagnosis of RA that unless already carried out an X-ray of the hands and feet is performed to establish whether erosions are present and anti-CCP antibodies are measured.

Since DAS28 is used as the basis of measuring both low disease activity (LDA) and clinical remission, NICE clinical guidelines recommend in adults with active RA, measuring C-reactive protein (CRP) and disease activity (using a composite score such as DAS28) monthly in specialist care until the target of remission or low disease activity is achieved.

Clinical pathway of care

Newly diagnosed

For people with newly diagnosed RA, NICE clinical guideline [NG100] (22) recommends first-line treatment with csDMARD monotherapy using oral MTX, leflunomide or sulfasalazine as soon as possible and ideally within 3 months of onset of persistent symptoms.

Inadequate responders

If patients are intolerant to or do not respond to the first csDMARD, additional csDMARDs (oral MTX, leflunomide, sulfasalazine or hydroxychloroquine) should be offered in combination in a step-up strategy when the treatment target (remission or low disease activity) has not been achieved despite dose escalation (22).

In contrast to UK treatment guidelines, EULAR (European) guidance recommends the introduction of advanced therapies at an earlier stage in the clinical care pathway. Specifically, if the treatment target is not achieved with the **first** csDMARD strategy, and when poor prognostic factors are present, advanced therapies such as the addition of a bDMARD or a tsDMARD should be considered; current practice would be to start a bDMARD (23). Poor prognostic factors include:

- Moderate to high disease activity according to composite measures; high acute phase reactant levels; high swollen joint counts; presence of RF and/or anti-citrullinated protein antibody (ACPA), especially at high levels; presence of early erosions or failure of two or more csDMARDs (23).

Moderate RA

All advanced therapies licensed to date (bDMARDs, JAK inhibitors, IL-6) have been licensed for use in moderate and severe RA. However, NICE guidance to date has recommended such treatments for use in severe RA only. Use in severe RA patients is recommended following the failure of intensive combination therapy with csDMARDs.

NG100 specifies that patients with moderate disease should only be offered additional csDMARDs (oral MTX, leflunomide, sulfasalazine or hydroxychloroquine) in combination in a step-up strategy when the treatment target (remission or low disease activity) has not been achieved despite dose escalation. Where combination therapies are not appropriate (for example where there are comorbidities or pregnancy) csDMARD monotherapy is recommended.

Severe patients

For patients with severe RA and where the disease has not responded to intensive combination therapy with csDMARDs, NICE Technology appraisal guidances 375, 466, 480 and 485 recommend bDMARDs (adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab, abatacept and sarilumab) or other tsDMARDs (baricitinib and tofacitinib) each in combination with MTX (if not intolerant/contraindicated) for **severe** RA only (24-28). Most bDMARDs are required to be taken in combination with MTX for optimal efficacy (23, 29). Approved JAK inhibitors are similarly recommended for use after failure of intensive combination therapy with csDMARDs, according to the latest American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) guidance (23, 29).

It should be noted that the limitation of the use of advanced therapies to after intensive combination therapy with csDMARDs is a restriction relative to their licences which only stipulate after one or more DMARD failure. In addition, limiting use in severe RA is a further restriction compared to their licences which cover use in both moderate and severe RA (24, 25, 27, 30). For those people with severe RA who cannot take MTX because it is contraindicated or because of intolerance, the guidance recommends that adalimumab, etanercept, certolizumab pegol, tocilizumab, baricitinib, sarilumab or tofacitinib can be used as monotherapy.

Where the disease has not responded adequately or in the case of intolerance to advanced therapies, RTX in combination with MTX is recommended for **severe** active disease only (NICE Technology appraisal guidance 195)(31). Where RTX is contraindicated or withdrawn because of an adverse event, advanced therapies (adalimumab, etanercept, infliximab, abatacept, golimumab, tocilizumab, certolizumab pegol, sarilumab, tofacitinib and baricitinib) each in combination with

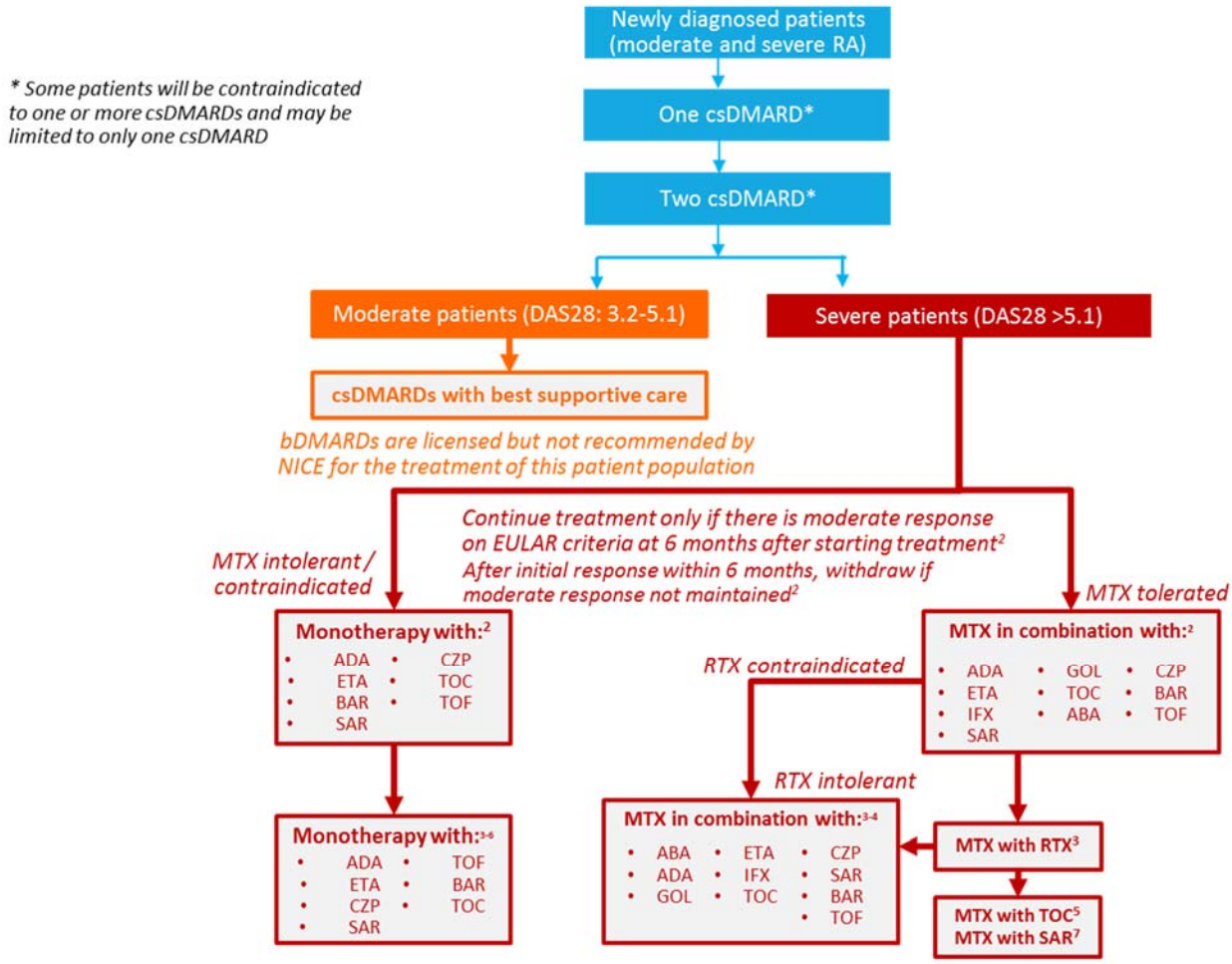
MTX are recommended as options (NICE Technology appraisal guidance 195, 198, 225, 247 ,415, 466, 480 and 485) (24-26, 31-33).

In patients who are MTX ineligible who have failed first line advanced therapy, advanced thearpies are recommended to be used as monotherapy (adalimumab, etanercept, certolizumab pegol, sarilumab, tocilizumab, tofacitinib and baricitinib), (NICE Technology appraisal guidance 195, 415, 466, 480 and 485)(24-26, 31, 34).

In patients who have responded inadequately to treatment with RTX and MTX, both tocilizumab and sarilumab in combination with MTX are recommended for use (NICE Technology Appraisal Guidance 198 and 485)(26, 32).

The clinical pathway of care is summarised in Figure 1.

Figure 1. NICE clinical pathway



Abbreviations: RA = rheumatoid arthritis, DMARD = disease-modifying antirheumatic drug, csDMARD = conventional DMARD, MTX = methotrexate, DAS28 = Disease Activity Score, bDMARD = biologic DMARD, ADA = adalimumab, CTZ =

certolizumab pegol, ETN = etanercept, TCZ = tocilizumab, GOL = golimumab, IFX = infliximab, ABA = abatacept, RTX = rituximab.

Sources: 1. NICE CG79, 2. NICE TA375, 3. NICE TA195, 4. NICE TA225, 5. NICE TA247, 6. NICE TA415, 7, NICE TA485

Limitation of current RA treatments

There is an unmet need for treatments in RA that have improved and sustained efficacy, including remission rates, which can also be used effectively as monotherapy to reduce the reliance on MTX. Limitations of current therapies include:

- Low rates of long-term, sustained clinical remission: There are a substantial number of patients with RA across all lines of therapy who are not achieving optimal therapeutic outcomes. Sustained clinical remission is only achieved by 20% to 40% of patients (35) and long term remission (>1 year) is only achieved by 3% to 14% of patients (36). Neither tofacitinib nor baricitinib, the only commercially available JAK inhibitors for RA treatment, have demonstrated superiority in clinical remission compared to adalimumab (37, 38).

- Inadequate inhibition of structural joint damage: The inhibition of structural joint damage is important in RA as this can help avoid permanent loss of function and disability (39).

- Poorly established efficacy when used as monotherapy without the need for concomitant MTX: Current biologics rely on the combination with MTX for optimal efficacy in some patients. However, about one-third of RA patients treated with TNFis in a real-life setting over a 2-year follow-up period experienced dose reduction/discontinuation of concomitant MTX because of intolerance/adverse events. A recent meta-analysis of 68 trials (6938 participants) showed the main AEs associated with low-dose methotrexate included nausea/vomiting, elevated transaminase levels, mucosal ulcerations, leukopenia, thrombogenic and infectious events (40). Approximately two thirds of patients discontinue MTX after 2 years of treatment due to insufficient response, intolerance, toxicity or dislike of MTX (41) (9, 42).

- Challenges in administration for intravenous (IV) and subcutaneous (SC) therapies, which ultimately decreases compliance: Current bDMARDs are administered intravenously or subcutaneously, placing a burden on both healthcare systems and patients, especially in those with limited mobility and patients who are needle-phobic or dislike injections. When asked what factors are important in choice of therapy, 49% to 79% patients with RA prefer the oral route of administration over parenteral (43-45).

- NICE recommendations for advanced treatments to date have been limited relative to their licences (restricted to severe RA in those who have failed intensive csDMARD treatment): One study which compared the percentage of RA patients receiving biologics across 12 countries identified a relationship between lower usage and poorer outcomes (for example in relation to mean DAS28 scores and remission rates). The UK was identified within this study as being a country with low use of bDMARDs with correspondingly poorer outcomes (46).

Need for the use of advanced therapies in moderate RA patients

Many other European countries follow the EULAR recommendations for the management of RA with synthetic and biological disease-modifying antirheumatic drugs which were last updated in 2016 (1, 23). In England and Wales these recommendations cannot be followed by clinicians due to the optimised NICE recommendations on the use of advanced therapies in moderate RA patients. Such limitations do not exist in many other European countries where advanced therapies are used to slow progression earlier in patients with moderate disease, before RA joints are structurally destroyed. Clinicians in England and Wales would, in the absence of such restrictions, use advanced therapies in line with EULAR recommendations (28). These guidelines recommend the use of advanced therapies after the failure of two lines of csDMARD treatment in both moderate and severe RA patients in those who do not possess prognostically unfavourable factors. In those that do possess prognostically unfavourable factors, the use of advanced therapies, for

both moderate and severe RA patients, is recommended earlier - after the failure of one line of csDMARD treatments.

Noted within the EULAR guidance is the critical importance of the rapid attainment of the targeted end point to achieve the treatment goal of remission or at least low disease activity within the time frame of 6 months (with at least 50% clinical improvement within 3 months being desirable) (47). This in line with NICE Clinical Guidelines for RA which state that patients should be treated with the aim of achieving a target of remission or low disease activity if remission cannot be achieved. The importance of poor prognostic factors in these patients is reflected by the NICE recommendation stipulating that the target of remission rather than low disease activity should be considered for people with an increased risk of radiological progression (presence of anti-CCP antibodies or erosions on X-ray at baselines assessment) (22).

The importance of achieving improved outcomes in moderate RA patients is supported by the following:

- In the UK a considerable proportion of moderate patients with RA (DAS28 >3.2 to ≤5.1) do not achieve a satisfactory clinical response to current therapies. Sustained clinical remission is only achieved by 20% to 40% of patients (35) and long term remission (>1 year) is only achieved by 3% to 14% of patients (36).

- Over time, sustained inflammation contributes to cartilage damage and bone erosion, affecting up to 80% of patients within one year of diagnosis (4, 48). Patients with persistent moderate disease (defined as a DAS28 3.2–5.1) in early RA have also been shown to experience functional decline (as measured by Health Assessment Questionnaire - Disability Index [HAQ-DI]), suggesting that these patients could benefit from more aggressive therapy (4, 48).

- In the UK the lack of flexibility allowed to clinicians to tailor the use of advanced therapy to the needs of patients may result in poorer long-term outcomes (49). Patients with moderate RA disease activity (DAS28 >3.2 to ≤5.1) may remain on csDMARDs rather than switching to more effective treatment strategies and thus are at risk of disease and radiographic progression (50). Advanced

therapies are licensed but not recommended by NICE for treatment of patients with moderate RA. Only patients with a DAS28 >5.1 are eligible for treatment with advanced therapies.

Positioning of upadacitinib

Based on the above and taking into account the views of clinicians in England and Wales, use of upadacitinib should be considered in line with its expected full marketing authorisation, the updated EULAR 2016 recommendations and the practice followed in other European countries for the use of advanced therapies (1). These guidelines recommend the use of advanced theraies after the failure of two lines of csDMARD treatment in both moderate and severe RA patients who do not possess prognostically unfavourable factors. In those that do possess prognostically unfavourable factors, the use of advanced therapies, for both moderate and severe RA patients, is recommended after the failure of one line of csDMARD treatments. Such unfavourable prognostic factors defined within the EULAR guidelines include high acute phase reactant levels, high swollen joint counts, the presence of RF and/or ACPA, especially at high levels and the presence of early erosions.

Based upon this, AbbVie's view is that upadacitinib will be used in line with its expected market authorisation namely in adults with moderate to severe, active RA whose disease has responded inadequately to, or who are intolerant of one or more disease modifying anti-rheumatic drugs (DMARDs), including conventional or biologic DMARDs. Upadacitinib may be used in the following patient groups:

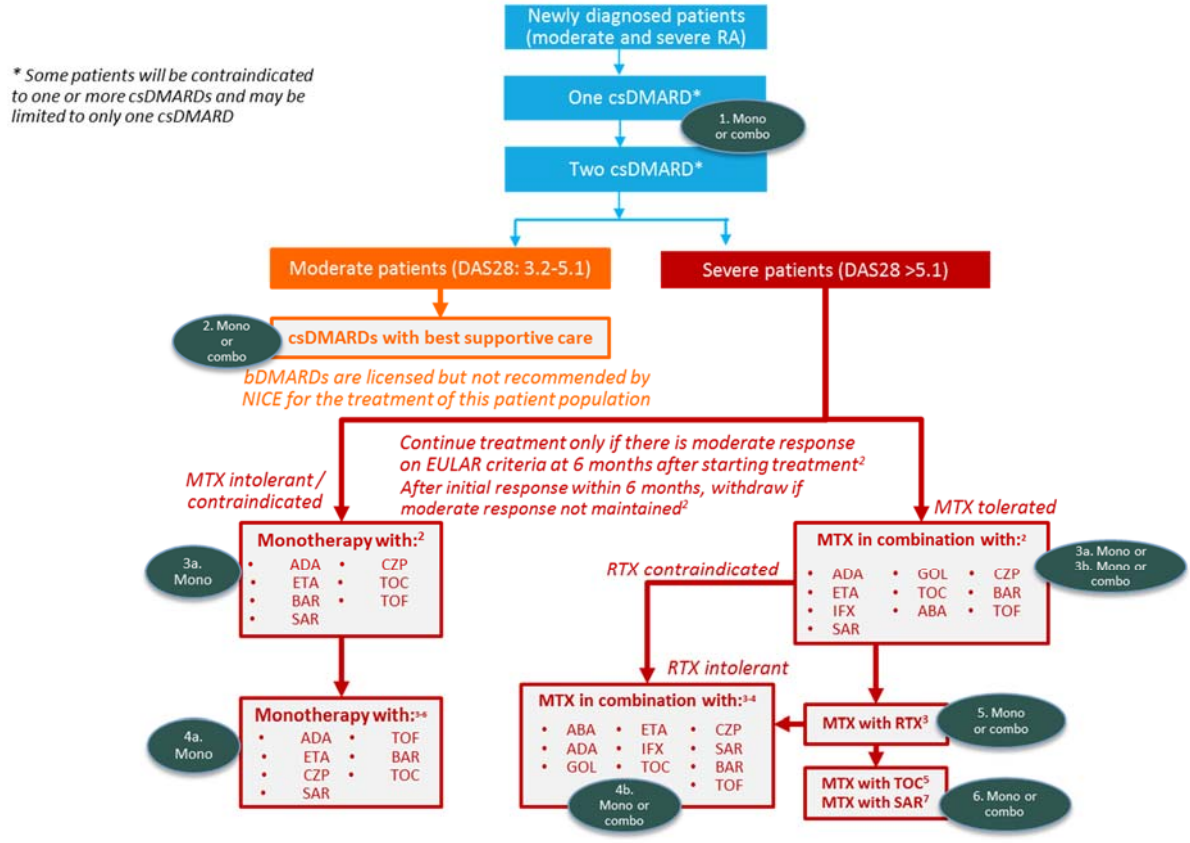
1. Moderate active RA that has not responded adequately to therapy with one csDMARD
    a. For patients with MTX intolerance/contraindication
    b. For patients who tolerate MTX and it is not contraindicated
2. Moderate active RA that has not responded adequately to therapy with two or more csDMARDs
    a. For patients with MTX intolerance/contraindication
    b. For patients who tolerate MTX and it is not contraindicated
3. Severe active RA that has not responded adequately to therapy with two or more csDMARDs:
    a. For patients with MTX intolerance/contraindication

b. For patients who tolerate MTX and it is not contraindicated

4. Severe active RA that has not responded adequately to therapy with advanced therapies:
    a. For patients with MTX intolerance/contraindication
    b. For patients who are rituximab (RTX) intolerant or contraindicated to RTX and who tolerate MTX and it is not contraindicated
5. Severe active RA that has not responded adequately to therapy with advanced and who are tolerant to MTX and RTX
6. Severe active RA that has not responded adequately to therapy with MTX+RTX.

The use of upadacitinib within the existing NICE pathway is outlined below.

Figure 2. Positioning of upadacitinib within the existing NICE pathway



Abbreviations: RA = rheumatoid arthritis, DMARD = disease-modifying antirheumatic drug, csDMARD = conventional DMARD, MTX = methotrexate, DAS28 = Disease Activity Score, bDMARD = biologic DMARD, ADA = adalimumab, CTZ = certolizumab pegol, ETN = etanercept, TCZ = tocilizumab, GOL = golimumab, IFX = infliximab, ABA = abatacept, RTX = rituximab.

B.1.4 Equality considerations

This technology is not likely to raise any equity issues.

B.2 Clinical effectiveness

Upadacitinib met all ranked primary and secondary endpoints in its comprehensive clinical trial programme demonstrating significant and consistently better rates of LDA and remission in comparison to adalimumab even without methotrexate and irrespective of line of therapy. In SELECT-COMPARE, upadacitinib combination therapy demonstrated superiority in rates of clinical remission relative to adalimumab. Upadacitinib further demonstrates a robust monotherapy profile with greater efficacy compared to MTX in patients who have not responded adequately to therapy with one or more csDMARD.

Moderate and severe patients

ACR20

In the two registration studies in moderate to severe RA patients who have experienced csDMARDs, upadacitinib combination therapy achieved its primary outcome of ACR20. In SELECT-MONOTHERAPY, in moderate to severe RA patients who have experienced csDMARDs, upadacitinib monotherapy achieved its primary outcome of ACR20. In the SELECT-BEYOND, patients with moderate to severe RA who had experienced bDMARDs, Upadacitinib combination therapy achieved its primary outcome of ACR20.

LDA and clinical remission

The primary outcome of low disease activity (LDA) and improved rates of remission were also achieved in all trials.

	SELECT-COMPARE			SELECT-NEXT		SELECT-MONOTHERAPY		SELECT-BEYOND	
Endpoints	**Week 12**			**Week 12**		**Week 14**		**Week 12**	
	PBO (+MTX)	**ADA (+MTX)**	**UPA 15 mg (+MTX)**	**PBO (+ csDMARDs)**	**UPA 15 mg (+ csDMARDs)**	**MTX**	**UPA 15 mg QD**	**PBO (+ csDMARDs)**	**UPA 15 mg (+ csDMARDs)**
	N=651	**N=327**	**N=651**	**N=221**	**N=221**	**N=216**	**N=217**	**N = 169**	**N = 164**
ACR20 response (%)	36.4	63***	70.5***#	35.7	63.8***	41.2	67.7***	28.4	64.6***
Clinical remission based on DAS28 (CRP) (%)	6.1	18.0***	28.7***##	10	30.8***	8.3	28.1***	9.5	28.7***
LDA DAS28(CRP) (%)	13.8	28.7***	45.0***##	17.2	48.4***	19.4	44.7***	14.2	43.3***

Abbreviations: ACR20 = American College of Rheumatology 20%, ADA = adalimumab; csDMARDs = conventional synthetic DMARDs; PBO = placebo; MTX = methotrexate; QD = once daily; UPA = upadacitinib
*** Statistically significant at 0.001 level for UPA vs placebo
#, ## Statistically significant at 0.05, and 0.001 level respectively for UPA vs ADA

Moderate patients

In a moderate subgroup analysis, efficacy results in terms of ACR, LDA, and clinical remission was [redacted] of moderate to severe RA patients.

	SELECT-COMPARE			SELECT-NEXT		SELECT-MONOTHERAPY		SELECT-BEYOND	
Endpoints	**Week 12**			**Week 12**		**Week 14**		**Week 12**	
	PBO (+MTX)	**ADA (+MTX)**	**UPA 15 mg (+MTX)**	**PBO (+ csDMARDs)**	**UPA 15 mg (+ csDMARDs)**	**MTX**	**UPA 15 mg QD**	**PBO (+ csDMARDs)**	**UPA 15 mg (+ csDMARDs)**
	[redacted]								
ACR20 response	[redacted]								
Clinical remission based on DAS28 (CRP)	[redacted]								
LDA DAS28(CRP)	[redacted]								

Abbreviations: ACR20 = American College of Rheumatology 20%, ADA = adalimumab; csDMARDs = conventional synthetic DMARDs; MTX = methotrexate; QD = once daily; UPA = Upadacitinib
*p<0.05; ** p<0.01; *** p<0.001 vs placebo

Safety

The safety profile of upadacitinib was comparable with placebo and adalimumab regardless of patient and disease characteristics in the extensive upadacitinib clinical development program. Across the four registration studies there were only two serious adverse event (SAE) reported by >0.5% of upadacitinib 15mg group.

Two deaths were reported among the four registration studies in the upadacitinib 15mg group, one due to haemorrhagic stroke and the other cardiac arrest. Mortality rates of Upadacitinib 15mg are comparable to comparator arms across the clinical trial programme.

Indirect comparison

Upadacitinib combination and monotherapy results in the csDMARD-IR NMA:

- Upadacitinib as combination therapy is ranked [redacted] in comparison to all other comparators based on EULAR response rates
- Upadacitinib as monotherapy has a [redacted]

Upadacitinib combination results in the bDMARD-IR NMA:

- Of nine advanced therapies based on EULAR response rates, upadacitinib combination was ranked [redacted] out of twelve comparators

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.

B.2.2 List of relevant clinical effectiveness evidence

The clinical efficacy of upadacitinib in patients with moderately to severely active RA with an inadequate response to, or who are intolerant of DMARDs, was assessed in four registrational Phase III studies in different RA patient populations. These four RCTs included more than 3,100 adult patients with moderate-to-severe active RA. The four trials are summarised in Table 3 with further details of their design provided in Section B.2.3.

SELECT-COMPARE was a phase III, randomised, double-blind, placebo-controlled and active comparator-controlled trial that included two periods. Period 1 provided the evidence of the clinical safety and efficacy of upadacitinib compared to adalimumab and placebo as measured at week 48 in adult patients with moderately to severely active RA, who were on a stable dose of MTX and had an inadequate response to MTX. Period 2 was a long-term extension (up to 5 years) conducted to evaluate the safety, tolerability, and efficacy of upadacitinib in patients who had completed Period 1 (51, 52). The primary efficacy endpoints, ACR20 response and clinical remission (defined by a 28-count DAS score based on CRP <2.6) versus placebo were evaluated at week 12. Secondary endpoints included, among others, HAQ-DI score, ACR50 response rate, and LDA achievement (based on CRP level) versus placebo and adalimumab at week 12, and pain assessment versus adalimumab at week 12, and LDA achievement (based on Clinical Disease Activity Index [CDAI]), change in morning stiffness severity, DAS28-CRP, SF-36 Physical Component Summary (PCS), Functional Assessment of Chronic Illness Therapy — Fatigue (FACIT-F), RA- Work Instability Scale (WIS) score and ACR-70 response rate versus placebo at week 12, and change in mTSS and achievement of no radiographic progression versus placebo at week 26.

SELECT-NEXT, was a phase III, randomised, double-blind, parallel-group, placebo-controlled trial, conducted in two periods. Period 1 compared the safety and efficacy

of upadacitinib and placebo at week 12 in patients with moderately to severely active RA who were on a stable dose of csDMARDs and had an inadequate response to csDMARDs. Period 2 was a blinded long-term extension (up to 5 years) conducted to evaluate the long-term safety, tolerability, and efficacy of upadacitinib in patients who had completed Period 1 (51, 53). The primary efficacy endpoints, ACR20 response and achievement of LDA versus placebo were evaluated at week 12. Secondary endpoints included ACR50/70 response rates, change in DAS28 CRP, HAQ-DI, SF-36 PCS, FACIT-F, RA-WIS, clinical remission and morning stiffness versus placebo evaluated at week 12.

SELECT-MONOTHERAPY was a phase III, randomised, double-blind, parallel-group, controlled trial, conducted in two periods. Period 1 compared the safety and efficacy of upadacitinib and MTX at week 14 in patients with moderately to severely active RA who despite stable doses of MTX had an inadequate response to MTX. Period 2 was a blinded long-term extension (up to week 226) conducted to evaluate the long-term safety, tolerability, and efficacy of upadacitinib in patients who had completed Period 1 (54, 55). The primary efficacy endpoints, ACR20 response and achievement of LDA versus MTX were evaluated at week 14. Secondary endpoints included ACR50/70 response rates, change in DAS28 CRP, HAQ-DI, SF-36 PCS, clinical remission and morning stiffness versus MTX evaluated at week 14.

SELECT-BEYOND was a phase III, randomised, double-blind, parallel-group, placebo-controlled trial, conducted in two periods. Period 1 compared the safety and efficacy of upadacitinib and placebo at week 24 in patients with moderately to severely active RA who were on a stable dose of csDMARDs and had an inadequate response to or intolerance to at least 1 bDMARD. Period 2 was a blinded long-term extension (up to week 216) conducted to evaluate the long-term safety, tolerability, and efficacy of upadacitinib in patients who had completed Period 1 (55, 56). The primary efficacy endpoints, ACR20 response and achievement of LDA versus placebo were evaluated at week 12. Secondary endpoints included ACR20 response rate versus placebo evaluated at week 1 and ACR20/50/70 response rates, change in DAS28 CRP, HAQ-DI, SF-36 PCS versus placebo evaluated at week 12.

Please note, data from SELECT-SUNRISE were available and included in the network meta-analyses (NMAs) as it met the NMA selection criteria. However, as this phase 3 trial was comprised entirely of Japanese patients, this was not an EMA registration trial and therefore the data are not presented in this section.

Table 3: List of relevant RCTs and long-term extension studies

Study	SELECT-COMPARE	SELECT-NEXT	SELECT-MONOTHERAPY	SELECT-BEYOND
Study Design	Phase III multicentre randomised, double-blind, parallel-group, placebo-controlled and active comparator-controlled trial	Phase III multicentre, randomised, double-blind, parallel-group, placebo-controlled trial	Phase III multicentre, randomised, double-blind, parallel-group, controlled trial	Phase III multicentre, randomised, double-blind, parallel-group, placebo-controlled period
Population	Subjects with moderately to severely active RA who are on a stable background of MTX and who have an inadequate response to MTX	Subjects with moderately to severely active RA who are on a stable dose of csDMARDs and had an inadequate response to csDMARDs	Subjects with moderately to severely active RA despite stable doses of MTX (inadequate response to MTX)	Subjects with moderately to severely active RA who are on a stable dose of csDMARDs and had an inadequate response to or intolerance to at least 1 bDMARD.
Intervention	Upadacitinib 15 mg orally QD (N=651) from Day 1 to Week 48 (Period 1) and thereafter up to 5 years (Period 2)	Upadacitinib 15 mg (N=221) and 30 mg (N=219) orally QD (N=200) from Day 1 to Week 12 (Period 1) and thereafter up to 5 years (Period 2)	Upadacitinib 15 mg (N=217) and 30 mg (N=215) orally QD (N=200) from Day 1 to Week 14 (Period 1) and thereafter up to Week 226 (Period 2)	Upadacitinib 15 mg (N=164) and 30 mg orally QD (N=165) from Day 1 to Week 24 (Period 1) and thereafter up to Week 216 (Period 2)
Comparators	Placebo (N=651) either orally QD or SC eow according to the matching drug (upadacitinib or adalimumab) from Day 1 to Week 26, followed by Upadacitinib 15 mg QD from Week 26 to Week 48 (Period 1) and thereafter up to 5 years (Period 2) Adalimumab 40 mg SC eow (N=327) from Day 1 to Week 48 (Period 1) and thereafter up to 5 years (Period 2)	Placebo (N=221) from Day 1 to Week 12, followed by Upadacitinib 15 mg or 30 mg orally QD (in two different randomised groups) at Week 12 and thereafter up to 5 years	MTX (N=216) once weekly from day 1 to Week 14 (Period 1), followed by Upadacitinib 15 mg or 30 mg orally QD at Week 14 and thereafter up to Week 226 (Period 2)	Placebo (N=169) from Day 1 to Week 12, followed by Upadacitinib 15 mg or 30 mg orally QD (in two different randomised groups) at Week 12 to Week 24 (Period 1) and thereafter up to Week 216 (Period 2)
Does trial support application for marketing authorization	Yes	Yes	Yes	Yes
Is trial used in model	Yes	Yes	Yes	Yes

Study	SELECT-COMPARE	SELECT-NEXT	SELECT-MONOTHERAPY	SELECT-BEYOND
Reported outcomes specified in the decision problem	• disease activity • physical function • joint damage, pain • fatigue • radiological progression • adverse effects of treatment • health-related quality of life	• disease activity • physical function • joint damage, pain • fatigue • adverse effects of treatment • health-related quality of life	• disease activity • physical function • joint damage, pain • adverse effects of treatment • health-related quality of life	• disease activity • physical function • joint damage, pain • adverse effects of treatment • health-related quality of life
Abbreviations: bDMARD: biological disease modifying anti-rheumatic drug; csDMARDs: Conventional synthetic disease modifying anti-rheumatic drug; eow: every other week; MTX: methotrexate; QD: once a day; RA: Rheumatoid Arthritis; SC: subcutaneous				

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

A comparative summary of the methodology of the four pivotal Phase III clinical trials are presented in Table 4.

SELECT-COMPARE

SELECT-COMPARE was a multicentre phase III study that was conducted in 2 periods. Period 1 was a 48-week randomised, double-blind, parallel-group, placebo-controlled and active comparator-controlled period.

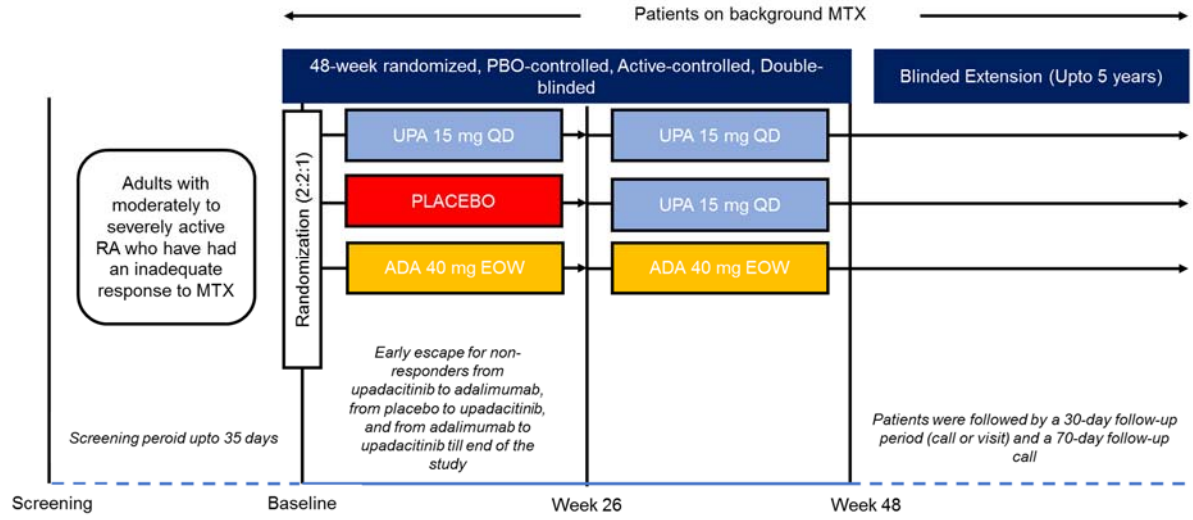
SELECT-COMPARE assessed the safety and efficacy of upadacitinib 15 mg QD versus placebo, and versus adalimumab, for the treatment of subjects with moderately to severely active RA who were on a stable dose of MTX and had an inadequate response to MTX.

Period 1 was also designed to compare the efficacy of upadacitinib 15 mg QD versus placebo for the prevention of structural progression. Period 2 is an ongoing long-term extension to evaluate the safety, tolerability, and efficacy of upadacitinib 15 mg QD in subjects with RA who had completed Period 1. Period 1 of the study began in December 2015, the primary completion date was April 2018 (initial 12-week treatment period), and final completion of Period 2 is expected in August 2020 (51, 52).

Patients were randomised in a 2:2:1 ratio to receive upadacitinib 15 mg QD, placebo, or SC adalimumab 40 mg every 2 weeks during the initial blinded treatment phase. All patients remained on their stable background dose of MTX. Following a 35-day screening period, patients entered a 48-week, active- and placebo-controlled treatment period (Period 1). Early escape for non-responders was provided from upadacitinib to adalimumab, from placebo to upadacitinib, and from adalimumab to upadacitinib. At week 26, patients receiving placebo were crossed over to the upadacitinib arm regardless of clinical response until week 48, while patients receiving upadacitinib or adalimumab continued their allocated treatment. After the initial 48-week study period, patients continued upadacitinib or adalimumab

treatment for up to 5 additional years in a long-term extension study (blinded until the last patient completed the last visit of Period 1) (Period 2). Patients were followed during a 30-day follow-up period (call or visit) and a 70-day follow-up call.(52) The schematic design of the trial is depicted in Figure 3.

Figure 3: SELECT-COMPARE trial design



Abbreviations: ABT: adalimumab; EOW every other week; QD: once daily; MTX: Methotrexate; RA: Rheumatoid Arthritis

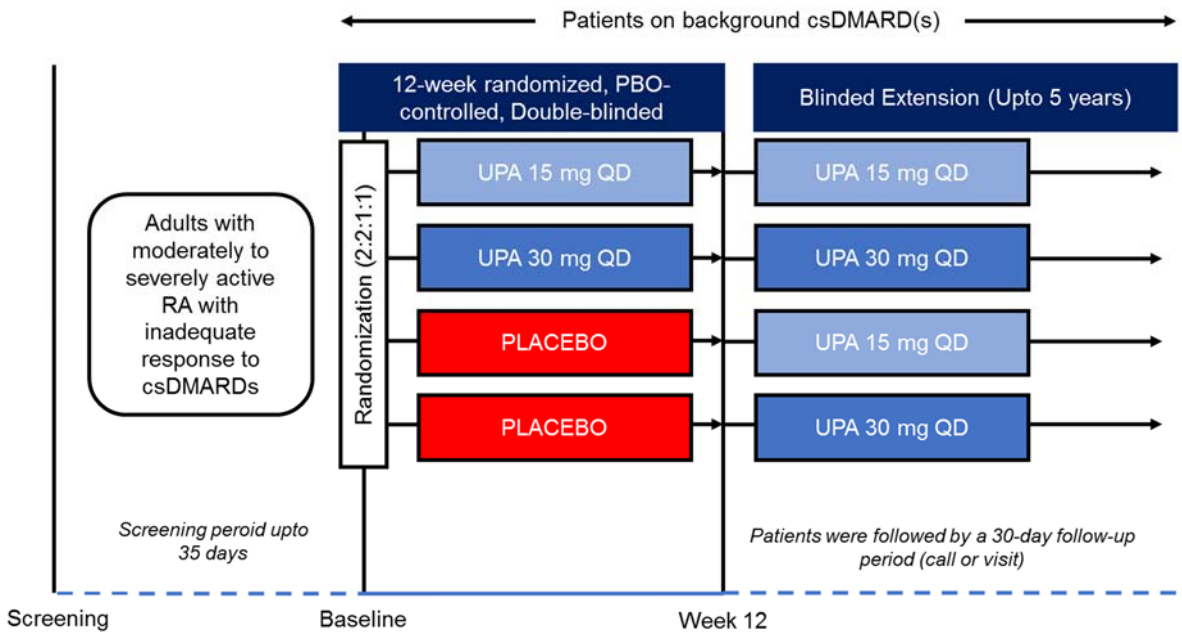
SELECT-NEXT

SELECT-NEXT was a multicentre phase III study that was conducted in 2 periods. Period 1 was a 12-week, randomised, double-blind, parallel-group, placebo-controlled period designed to compare the safety and efficacy of upadacitinib 30 mg QD and 15 mg QD versus placebo for the treatment of signs and symptoms of subjects with moderately to severely active RA who were on a stable dose of csDMARDs and had an inadequate response to csDMARDs. Period 2 is an ongoing blinded long-term extension period to evaluate the long-term safety, tolerability, and efficacy of upadacitinib 30 mg QD and 15 mg QD in subjects with RA who had completed Period 1.

This study began in December 2015, the primary completion date was June 2017 (initial 12-week treatment period) with completion of the long-term extension period expected in August 2020 (51, 53).

Patients were randomised in the 2:2:1:1 ratio to receive oral upadacitinib 15 mg QD, upadacitinib 30 mg QD, or placebo whilst maintaining their weekly stable background csDMARD. Following the initial 12-week study period (Period 1), patients receiving upadacitinib plus csDMARDs continued treatment for up to 5 additional years in a long-term extension study (Period 2); patients receiving placebo were crossed over to a pre-determined upadacitinib dose (15 mg or 30 mg) which was maintained for the duration of this extension phase. The study period also included a 30-day follow-up period (51, 53). The schematic design of the trial is depicted in Figure 4.

Figure 4: SELECT-NEXT trial design



Abbreviations: ACR20: American College of Rheumatology 20% response; BL: Baseline; csDMARDs: Conventional synthetic disease modifying anti-rheumatic drug; DAS28 = Disease Activity Score 28; QD: once daily; UPA: Upadacitinib

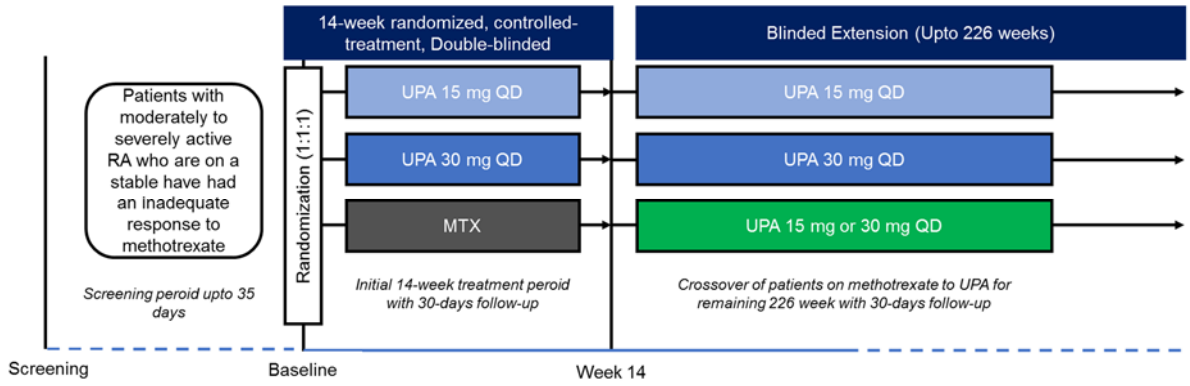
SELECT-MONOTHERAPY

SELECT-MONOTHERAPY was a multicentre phase III study that was conducted in 2 periods. Period 1 was a 14-week, randomised, double-blind, parallel-group, controlled period designed to compare the safety and efficacy of upadacitinib 30 mg QD monotherapy and 15 mg QD monotherapy versus continuing MTX monotherapy for the treatment of signs and symptoms of RA in subjects with moderately to severely active RA despite stable doses of MTX (inadequate response to MTX).

Period 2 is a blinded long-term extension period to evaluate the long-term safety, tolerability, and efficacy of upadacitinib 30 mg QD and 15 mg QD in subjects with RA who have completed Period 1. The study began in March 2016, the primary completion date was December 2017 (initial 14-week treatment period), and completion of the long-term extension period is expected in October 2020 (55, 57).

Patients were randomised 1:1:1 to receive either oral upadacitinib 15 mg QD, upadacitinib 30 mg QD, or to continue once-weekly oral MTX for the study duration of 14 weeks. Following a 35-day screening period, patients entered the initial 14-week, active-controlled study period. At week 14, patients receiving upadacitinib continued treatment for an additional 226 weeks in a long-term extension study; patients receiving MTX were crossed over to an upadacitinib arm for this extension phase. At the end of the study, patients were followed up for 30 days (call or visit) (55). The schematic design of the trials is depicted in Figure 5.

Figure 5: SELECT-MONOTHERAPY trial design



Abbreviations: QD: once daily; PO: per-os RA: Rheumatoid Arthritis

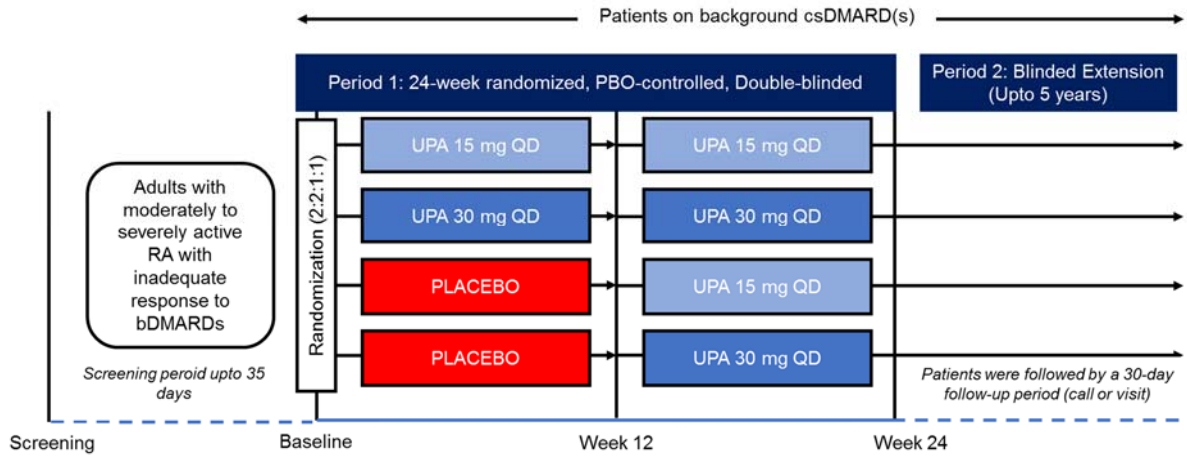
SELECT-BEYOND

SELECT-BEYOND was a multicentre phase III study that was conducted in 2 periods. Period 1 was a 24-week, randomised, double-blind, parallel-group, placebo-controlled period designed to compare the safety and efficacy of upadacitinib 30 mg QD and 15 mg QD versus placebo for the treatment of signs and symptoms of subjects with moderately to severely active RA who were on a stable dose of

csDMARDs and had an inadequate response to or intolerance to at least 1 prior bDMARD. Period 2 is a blinded long-term extension period to evaluate the long-term safety, tolerability, and efficacy of upadacitinib 30 mg QD and 15 mg QD in subjects with RA who had completed Period 1. The study began in March 2016, final data collection for primary outcome measures was conducted in April 2017 (initial 24-week trial design) and completion is expected in August 2020 (55, 56).

Patients in SELECT-BEYOND were randomised in a 2:2:1:1 ratio to receive upadacitinib 15 mg or 30 mg QD or placebo. Patients also continued their weekly stable background csDMARD. Following a 35-day screening period, patients entered an initial 12-week placebo-controlled treatment phase. After 12 weeks, patients receiving placebo were crossed over to receive upadacitinib 15 mg or 30 mg QD until week 24, while patients receiving upadacitinib continued their allocated dose (Figure 60). Following the initial 24-week period, patients continued treatment for up to 240 weeks in a long-term blinded extension study. Patients were followed up for 30 days after study completion (call or site visit). The schematic design of the trial is depicted in Figure 6 (55).

Figure 6: SELECT-BEYOND trial design



Abbreviations: ACR20: American College of Rheumatology 20% response; bDMARDs: biologic disease modifying anti-rheumatic drug; csDMARDs: Conventional synthetic disease modifying anti-rheumatic drug; DAS28: Disease Activity Score 28; PBO: Placebo; QD: once daily; RA: Rheumatoid Arthritis; UPA: Upadacitinib

Table 4: Comparative summary of trial methodology

Study	SELECT-COMPARE	SELECT-NEXT	SELECT-MONOTHERAPY	SELECT-BEYOND
Location where the data was collected	286 study sites located in 41 countries (Argentina, Australia, Belarus, Belgium, Bosnia and Herzegovina, Brazil, Bulgaria, Canada, Chile, Colombia, Croatia, Czech Republic, Estonia, France, Germany, Greece, Hong Kong, Hungary, Israel, Italy, Kazakhstan, Republic Of Korea, Latvia, Lithuania, Malaysia, Mexico, New Zealand, Poland, Portugal, Puerto Rico, Romania, Russian Federation, Serbia, Slovakia, South Africa, Spain, Taiwan [Province Of China], Turkey, Ukraine, United Kingdom, United States)	150 study sites located in 35 countries (Argentina, Australia, Austria, Belgium, Bosnia and Herzegovina, Bulgaria, Canada, Croatia, Czech Republic, Estonia, Finland, France, Germany, Greece, Hong Kong, Hungary, Ireland, Kazakhstan, Korea, Latvia, Lithuania, Mexico, New Zealand, Poland, Portugal, Romania, Russian Federation, Slovakia, South Africa, Spain, Switzerland, Taiwan, Ukraine, United Kingdom, United States)	138 study sites located in 24 countries (Argentina, Austria, Belgium, Bulgaria, Chile, Czech Republic, Estonia, Greece, Hungary, Israel, Italy, Japan, Mexico, Poland, Portugal, Puerto Rico, Romania, Russian Federation, Serbia, South Africa, Spain, Turkey, Ukraine, United States)	152 sites in 26 countries (Australia, Austria, Belgium, Canada, Czech Republic, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Israel, Korea, Latvia, New Zealand, Poland, Portugal, Puerto Rico, Russian Federation, Slovakia, Spain, Sweden, Turkey, United Kingdom, United States)
Trial Design	Phase III multicenter study that includes two periods. Period 1 is a 48-week randomised, double-blind, parallel-group, placebo-controlled and active comparator-controlled period designed to compare the safety and efficacy of upadacitinib 15 mg QD versus placebo, and versus adalimumab, for the treatment of signs and symptoms of subjects with moderately to severely active RA who were on a stable dose of MTX and had an inadequate response to MTX. Period 1 was also designed to compare the	Phase III multicenter study that includes two periods. Period 1 was a 12-week, randomised, double-blind, parallel-group, placebo-controlled period designed to compare the safety and efficacy of upadacitinib 30 mg QD and 15 mg QD versus placebo for the treatment of signs and symptoms of subjects with moderately to severely active RA who were on a stable dose of csDMARDs and had an inadequate response to csDMARDs. Period 2 is a blinded long-term extension period to evaluate the long-term	Phase III multicenter study that includes two periods. Period 1 was a 14-week, randomised, double-blind, parallel-group, controlled treatment period designed to compare the safety and efficacy of upadacitinib 30 mg QD alone and 15 mg QD alone versus continuing MTX alone for the treatment of signs and symptoms of RA in subjects with moderately to severely active RA despite stable doses of MTX (inadequate response to MTX). Period 2 is a blinded, long-term extension period to evaluate the long-term safety,	Phase III multicenter study that included two periods. Period 1 was a 24-week, randomised, double-blind, parallel-group, placebo-controlled period designed to compare the safety and efficacy of upadacitinib 30 mg QD and 15 mg QD versus placebo for the treatment of signs and symptoms of subjects with moderately to severely active RA who were on a stable dose of csDMARDs and had an inadequate response to or intolerance to at least 1 bDMARD. Period 2 is a blinded long-term extension period to

Study	SELECT-COMPARE	SELECT-NEXT	SELECT-MONOTHERAPY	SELECT-BEYOND
	efficacy of upadacitinib 15 mg QD versus placebo for the prevention of structural progression. Period 2 is a long-term extension to evaluate the safety, tolerability, and efficacy of upadacitinib 15 mg QD in subjects with RA who had completed Period 1.	safety, tolerability, and efficacy of upadacitinib 30 mg QD and 15 mg QD in subjects with RA who had completed Period 1.	tolerability, and efficacy of upadacitinib 30 mg QD and 15 mg QD in subjects with RA who have completed Period 1.	evaluate the long-term safety, tolerability, and efficacy of upadacitinib 30 mg QD and 15 mg QD in subjects with RA who had completed Period 1.
Eligibility criteria for participants	• Adult male or female, at least 18 years old. • Diagnosis of RA for ≥ 3 months, fulfilling the 2010 ACR/EULAR classification criteria for RA • Subjects must have been on oral or parenteral MTX therapy ≥ 3 months and on a stable prescription of 15 to 25 mg/week (or ≥ 10 mg/week in subjects intolerant of MTX at doses ≥ 15 mg/week) for ≥ 4 weeks prior to the first dose of study drug. In addition, all subjects should take a dietary supplement of folic acid or folinic acid throughout the study participation. • Participants are required to have: • at least 6 swollen joints and at least 6 tender joints at the screening and baseline visits as judged by joint counts • hsCRP ≥ 5 mg/L (central lab, ULN 2.87 mg/L) at screening visit • Patients are also required to	• Adult male or female, at least 18 years old • Diagnosis of RA for ≥ 3 months who also fulfil the 2010 ACR/EULAR classification criteria for RA • Subjects have been receiving csDMARD therapy ≥3 months and on a stable dose for ≥ 4 weeks prior to the first dose of study drug • Subjects must have failed at least one of the following: MTX, sulfasalazine, or leflunomide • Subject meets both of the following disease activity criteria: • ≥ 6 swollen joints (based on 66 joint counts) and ≥ 6 tender joints (based on 68 joint counts) at Screening and baseline Visits; and • hsCRP ≥ 3 mg/L (central lab) at Screening Visit • Subjects with prior exposure to at most one bDMARD may be enrolled if exposure ≤3 months OR if discontinued due to	• Adult male or female, at least 18 years old • Diagnosis of RA for ≥ 3 months who also fulfil the 2010 ACR/ EULAR classification criteria for RA • Subjects must have been on oral or parenteral MTX therapy ≥ 3 months and on a stable dose (15 to 25 mg/week; or ≥ 10 mg/week in subjects who are intolerant of MTX at doses ≥ 15 mg/week after complete titration) for ≥ 4 weeks prior to first dose of study drug • Must have discontinued all csDMARDs (other than MTX) ≥ 4 weeks prior to first dose of study drug • Subject has ≥ 6 swollen joints (based on 66 joint counts) and ≥ 6 tender joints (based on 68 joint counts) at Screening and baseline Visits; and hsCRP ≥ 3 mg/L (central lab) at Screening Visit	• Adult male or female, at least 18 years old • Diagnosis of RA for ≥ 3 months who also fulfil the 2010 ACR/EULAR classification criteria for RA • Subjects have been treated for ≥ 3 months prior to the screening visit with ≥ 1 bDMARD therapy, but continue to exhibit active RA or had to discontinue due to intolerability or toxicity, irrespective of treatment duration. • Subjects have been receiving csDMARD therapy ≥ 3 months and on a stable dose for ≥ 4 weeks prior to the first dose of study drug • Subject meets both of the following minimum disease activity criteria: o ≥ 6 swollen joints (based on 66 joint counts) and ≥ 6 tender joints (based on 68 joint counts) at Screening and baseline Visits o hsCRP ≥ 3 mg/L (central lab) at Screening Visit

Study	SELECT-COMPARE	SELECT-NEXT	SELECT-MONOTHERAPY	SELECT-BEYOND
	have: • ≥ 3 bone erosions on x-ray; or • ≥ 1 bone erosion and a positive rheumatoid factor; or • ≥ 1 bone erosion and a positive ACPA • Patients were required to discontinue all csDMARDs, with the exception of MTX	intolerability (up to 20% of study population)		
Trial drugs	Group 1: upadacitinib 15 mg QD (N = 600) Group 2: placebo (N = 600) Group 3: adalimumab (40 mg eow) (N = 300)	Group 1: upadacitinib 30 mg QD (N = 200) (Period 1) → upadacitinib 30 mg QD (Period 2) Group 2: upadacitinib 15 mg QD (N = 200) (Period 1) → upadacitinib 15 mg QD (Period 2) Group 3: Placebo (N = 100) (Period 1) → upadacitinib 30 mg QD (Period 2) Group 4: Placebo (N = 100) (Period 1) → upadacitinib 15 mg QD (Period 2)	Group 1: upadacitinib 30 mg QD (N = 200) (Period 1) → upadacitinib 30 mg QD (Period 2) Group 2: upadacitinib 15 mg QD (N = 200) (Period 1) → upadacitinib 15 mg QD (Period 2) Group 3: MTX (N = 100) (Period 1) → upadacitinib 30 mg QD (Period 2) Group 4: MTX (N = 100) (Period 1) → upadacitinib 15 mg QD (Period 2)	Group 1: upadacitinib 30 mg QD (N = 150) (Day 1 to Week 12) → upadacitinib 30 mg QD (Week 12 and thereafter) Group 2: upadacitinib 15 mg QD (N = 150) (Day 1 to Week 12) → upadacitinib 15 mg QD (Week 12 and thereafter) Group 3: Placebo (N = 75) (Day 1 to Week 12) → upadacitinib 30 mg QD (Week 12 and thereafter) Group 4: Placebo (N = 75) (Day 1 to Week 12) → upadacitinib 15 mg QD (Week 12 and thereafter)
Permitted and disallowed concomitant medication	Subjects should continue their stable background csDMARD therapy up to Week 24. Subjects taking MTX should take a dietary supplement of oral folic acid throughout study participation. Subjects should continue their stable doses of NSAIDs, acetaminophen/paracetamol, or inhaled corticosteroids. Prior exposure to JAK inhibitors is not allowed. Oral corticosteroids are not	Subjects should continue their stable background csDMARD therapy up to Week 24. Subjects taking MTX should take a dietary supplement of oral folic acid throughout study participation. Subjects should continue their stable doses of NSAIDs, acetaminophen/paracetamol, or inhaled corticosteroids. Prior exposure to JAK inhibitors is not allowed. Oral corticosteroids are not	Subjects taking MTX should take a dietary supplement of oral folic acid throughout study participation. Subjects should continue their stable doses of NSAIDs, acetaminophen/paracetamol, or inhaled corticosteroids. Prior exposure to JAK inhibitors is not allowed. Oral corticosteroids are not allowed during the first 24 weeks of the study. Subjects must have discontinued	Subjects should continue their stable background csDMARD therapy up to Week 24. Subjects taking MTX should take a dietary supplement of oral folic acid throughout study participation. Subjects should continue their stable doses of NSAIDs, acetaminophen/paracetamol, or inhaled corticosteroids. Prior exposure to JAK inhibitors is not allowed. Oral corticosteroids are not

Study	SELECT-COMPARE	SELECT-NEXT	SELECT-MONOTHERAPY	SELECT-BEYOND
	allowed during the first 24 weeks of the study. All biologic therapies are prohibited during the study (i.e., Periods 1 and 2). Systemic use of known strong CYP3A inhibitors or strong CYP3A inducers is excluded from the Screening Visit through the end of the study (i.e., end of Period 2). High potency opiates are not permitted during the study (i.e., Periods 1 and 2). Investigational drugs are also prohibited during the study. Live vaccines are not allowed within 4 weeks prior to the first dose of study drug and during the study (i.e., Periods 1 and 2). Oral traditional Chinese medicine is not permitted during the study.	allowed during the first 24 weeks of the study. All biologic therapies are prohibited during the study (i.e., Periods 1 and 2). Systemic use of known strong CYP3A inhibitors or strong CYP3A inducers is excluded from the Screening Visit through the end of the study (i.e., end of Period 2). High potency opiates are not permitted during the study (i.e., Periods 1 and 2). Investigational drugs are also prohibited during the study. Live vaccines are not allowed within 4 weeks prior to the first dose of study drug and during the study (i.e., Periods 1 and 2). Oral traditional Chinese medicine is not permitted during the study.	all csDMARDs (other than MTX) prior to the first dose of study drug as specified in the washout procedures. All biologic therapies are prohibited during the study (i.e., Periods 1 and 2). Systemic use of known strong CYP3A inhibitors or strong CYP3A inducers is excluded from the Screening Visit through the end of the study (i.e., end of Period 2). High potency opiates are not permitted during the study (i.e., Periods 1 and 2). Investigational drugs are also prohibited during the study. Live vaccines are not allowed within 4 weeks prior to the first dose of study drug and during the study (i.e., Periods 1 and 2). Oral traditional Chinese medicine is not permitted during the study.	allowed during the first 24 weeks of the study. All biologic therapies are prohibited during the study (i.e., Periods 1 and 2). Systemic use of known strong CYP3A inhibitors or strong CYP3A inducers is excluded from the Screening Visit through the end of the study (i.e., end of Period 2). High potency opiates are not permitted during the study (i.e., Periods 1 and 2). Investigational drugs are also prohibited during the study. Live vaccines are not allowed within 4 weeks prior to the first dose of study drug and during the study (i.e., Periods 1 and 2). Oral traditional Chinese medicine is not permitted during the study.
Primary outcome	• Proportion of patients achieving ACR20 response • Proportion achieving clinical remission (defined by a 28-count DAS score based on CRP <2.6)	• Proportion of patients achieving an ACR20 response • Proportion achieving LDA (defined by a 28-count DAS score based on CRP ≤3.2)	• Proportion of patients achieving an ACR20 response • Proportion achieving LDA (defined by a 28-count DAS score based on CRP ≤3.2)	• Proportion of patients achieving an ACR20 response • Proportion achieving LDA (defined by a 28-count DAS score based on CRP ≤3.2)

Study	SELECT-COMPARE	SELECT-NEXT	SELECT-MONOTHERAPY	SELECT-BEYOND
Major secondary outcomes	• Change in HAQ-DI score • Change in HAQ-DI score (superiority versus adalimumab) • Proportion of patients achieving LDA based on CDAI • Proportion of patients with no radiographic progression at week 26 • Change in morning stiffness severity • Change in DAS28 CRP • Change in SF-36 PCS from baseline • Change in FACIT-F from baseline • Change in mTSS at week 26 ACR50 response rates (superiority and non-inferiority versus adalimumab) • ACR50 response rates • ACR70 response rates • Proportion of patients achieving LDA (defined by a 28-count DAS score based on CRP ≤3.2) (non-inferiority versus adalimumab) • Proportion of patients achieving LDA (defined by a 28-count DAS score based on CRP ≤3.2) • Change from baseline in patients assessment of pain (superiority of upadacitinib versus adalimumab) • Change in RA-WIS score at baseline	• Change in DAS28 CRP • Proportion of patients achieving ACR50/70 response • Change in the HAQDI score from baseline • Change in SF-36 PCS from baseline • Proportion of patients achieving clinical remission (DAS28 CRP <2.6) • Change in FACIT-F from baseline • Change in RA-WIS score at baseline • Proportion of changes in morning stiffness severity	• Decrease in DAS28 CRP from baseline • Proportion of patients achieving an ACR50/70 response • Change in HAQ-DI score from baseline • Change in SF-36 PCS from baseline • Proportion of patients achieving clinical remission (DAS28 CRP <2.6) • Proportion of changes in morning stiffness severity	• Change in DAS28 CRP • Changes in the HAQ-DI score from baseline • Proportion of patients achieving ACR20/50/70 response • Change in SF-36 PCS score from baseline • ACR20 response rate at week 1

Study	SELECT-COMPARE	SELECT-NEXT	SELECT-MONOTHERAPY	SELECT-BEYOND
Pre-planned subgroups	The primary efficacy endpoints were examined in the following subgroups: • age (< 40, 40 to 64, ≥ 65); • sex (male or female), • weight (< 60 kg or ≥ 60 kg); • body mass index (BMI) (< 25 or ≥ 25); • race (white, non-white), • geographic region (North America, South/Central America, Western Europe, Eastern Europe, Asia, other); • RA disease duration (< 5 years or ≥ 5 years); • Baseline RF status (positive or negative); • Baseline anti-CCP antibody status (positive or negative); • Baseline RF and anti-CCP (at least one negative or double positive); • Baseline RF and anti-CCP (at least one positive or double negative); • Baseline DAS28 (hsCRP) (≤ 5.1 or > 5.1); and • prior bDMARD use (yes or no).	The primary efficacy endpoint was examined in the following subgroups: • age (< 40, 40 to 64, ≥ 65); • sex (male or female), • weight (< 60 kg or ≥ 60 kg); • BMI (< 25 or ≥ 25); • race (white, non-white), geographic region (North America, Western Europe, Eastern Europe, other); • duration of RA diagnosis (< 5 years or ≥ 5 years); • baseline RF status (positive or negative); • baseline anti-CCP antibody status (positive or negative); • baseline both RF positive and anti-CCP positive (yes or no); • baseline both RF negative and anti-CCP negative (yes or no); • baseline DAS28 (CRP) (≤ 5.1 or > 5.1); and • prior bDMARD use (yes or no).	The primary efficacy endpoints were examined in the following subgroups: • age (< 40, 40 to 64, ≥ 65); • sex (male or female), • weight (< 60 kg or ≥ 60 kg); • body mass index (BMI) (< 25 or ≥ 25); • race (white, non-white), • geographic region (North America, South/Central America, Western Europe, Eastern Europe, Asia, other); • RA disease duration (< 5 years or ≥ 5 years); • Baseline RF status (positive or negative); • Baseline anti-CCP antibody status (positive or negative); • Baseline RF and anti-CCP (at least one negative or double positive); • Baseline RF and anti-CCP (at least one positive or double negative); • Baseline DAS28 (hsCRP) (≤ 5.1 or > 5.1).	The primary efficacy endpoint was examined in the following subgroups: • age (< 40, 40 to 64, ≥ 65); • sex (male or female), • weight (< 60 kg or ≥ 60 kg); • BMI (< 25 or ≥ 25); • race (white, non-white), geographic region (North America, South/Central America, Western Europe, Eastern Europe, other); • duration of RA diagnosis (< 10 years or ≥ 10 years); • Baseline RF status (positive or negative); • Baseline anti-CCP antibody status (positive or negative); • Baseline RF and anti-CCP (at least one negative or double positive); • Baseline RF and anti-CCP (at least one positive or double negative); • baseline DAS28 (hsCRP) (≤ 5.1 or > 5.1); • prior failed bDMARD; and failed anti-IL6 due to lack of efficacy.

Abbreviations: ACR: American College of Rheumatology; ACR20/50/70: American College of Rheumatology 20%, 50%, 70% response; bDMARD: biologic disease-modifying anti-rheumatic drug; BMI: body mass index; CCP: cyclic citrullinated peptide; CDAI: Clinical Disease Activity Index; CRP: C-reactive protein; csDMARDs: conventional synthetic disease-modifying anti-rheumatic drug(s); DAS28: Disease Activity Score 28; eow: every other week; FACIT-F: Functional Assessment of Chronic Illness Therapy — Fatigue; HAQ-DI: Health Assessment Questionnaire — Disability Index; hsCRP: high-sensitivity C-reactive protein; JAK: Janus kinase; LDA: low disease activity; mTSS: modified Total Sharp Score; MTX: methotrexate; NSAIDs: non-steroidal anti-inflammatory drugs; PCS: physical component summary; QD: once daily; RA: rheumatoid arthritis; RF: rheumatoid factor; SF-36: Short Form-36; ULN: upper limit of normal; WIS: Work Instability Scale

Baseline characteristics

The baseline demographics and clinical characteristics of patients were well balanced between the treatment groups in each trial and were generally similar across studies. The baseline characteristics from all four phase III clinical trials (SELECT-COMPARE, SELECT-NEXT, SELECT-MONOTHERAPY and SELECT-BEYOND) are summarised in Table 5 with a brief overview presented below.

Across the four RCTs, the mean age of patients ranged between 53.6 to 57.6 years. The mean DAS-28 score ranged from 5.6 (SELECT-NEXT) to 5.8 (SELECT-COMPARE) and mean CDAI score was between 37.8 and 41.7. The mean TJC68 and SJC66 were similar across studies, ranging between 24.7 and 28.5, and between 15.4 and 17.2, respectively. The mean HAQ-DI score ranged from 1.4 to 1.7 and the mean CRP level ranged from 16.0 to 19.8 mg/L. These baseline characteristics demonstrate that, upon entering the study, patients were considered to have moderate to severe active RA. The duration of diagnosis amongst patients enrolled in SELECT-COMPARE and SELECT-NEXT trials ranged between 7.2 and 8.3, while that of patients enrolled in SELECT-BEYOND trial ranged between 12.4 and 14.5.

With regard to treatment history, 60.3% patients in the SELECT-COMPARE trial were receiving oral corticosteroids. In SELECT-NEXT, 12.7% patients reported prior bDMARD use, while 60.5%, 20.5% and 19.0% reported MTX, MTX and other csDMARDs, and csDMARD other than MTX concomitant use, respectively. There were 46.1% patients who were taking oral steroids. In SELECT-BEYOND, 69.1% and 30.9% patients were failed with <2 and >2 bDMARDs use respectively, 90.3% reported at least 1 failed anti-TNF agent use. The majority of patients were concomitantly using MTX (73.8%), followed by csDMARDs other than MTX (16.6%) and MTX and other csDMARDs (9.5%).

Table 5: Baseline characteristics of trial population

Study	SELECT-COMPARE			SELECT-NEXT			SELECT-MONOTHERAPY			SELECT-BEYOND		
Treatment	PBO (N=651)	ADA (N=327)	UPA (N=651)	PBO (N=221)	UPA 15 mg (N=221)	UPA 30 mg (N=219)	MTX (N=216)	UPA 15 mg QD (N=217)	UPA 30 mg QD (N=215)	PBO (N=169)	UPA 15 mg (N=164)	UPA 30 mg (N=165)
Sex, n (%)												
Male	139 (21.4)	68 (20.8)	130 (20.0)	55 (24.9)	39 (17.6)	47 (21.5)	37 (17.1)	43 (19.8)	45 (20.9)	26 (15.4)	27 (16.5)	27 (16.4)
Female	512 (78.6)	259 (79.2)	521 (80.0)	166 (75.1)	182 (82.4)	172 (78.5)	179 (82.9)	174 (80.2)	170 (79.1)	143 (84.6)	137 (83.5)	138 (83.6)
Age (years) Mean (SD)	53.6 (12.24)	53.7 (11.70)	54.2 (12.08)	56.0 (12.22)	55.3 (11.47)	55.8 (11.29)	55.3 (11.12)	54.5 (12.20)	53.1 (12.72)	57.6 (11.39)	56.3 (11.34)	57.3 (11.55)
Race, n (%)												
White	561 (86.2)	292 (89.3)	576 (88.5)	187 (84.6)	188 (85.1)	186 (84.9)	176 (81.5)	173 (79.7)	180 (83.7)	143 (84.6)	142 (86.6)	148 (89.7)
Black or African American	38 (5.8)	17 (5.2)	33 (5.1)	10 (4.5)	13 (5.9)	8 (3.7)	11 (5.1)	15 (6.9)	9 (4.2)	21 (12.4)	17 (10.4)	10 (6.1)
American Indian/Alaska Native	2 (0.3)	1 (0.3)	1 (0.2)	1 (0.5)	0	1 (0.5)	3 (1.4)	4 (1.8)	3 (1.4)	0	3 (1.8)	4 (2.4)
Native Hawaiian or other Pacific Islander	1(0.2)	0	0							0	0	1 (0.6)
Asian	39 (6.0)	15 (4.6)	31 (4.8)	19 (8.6)	19 (8.6)	21 (9.6)	24 (11.1)	24 (11.1)	21 (9.8)	5 (3.0)	2 (1.2)	2 (1.2)
Multiple	10 (1.5)	2 (0.6)	10 (1.5)	4 (1.8)	1 (0.5)	3 (1.4)	2 (0.9)	1 (0.5)	2 (0.9)			
Ethnicity (Hispanic or Latino), n (%)	206 (31.6)	106 (32.4)	215 (33.0)	27 (12.2)	23 (10.4)	30 (13.7)	50 (23.1)	52 (24.0)	54 (25.1)	24 (14.2)	34 (20.7)	28 (17.0)
BMI (kg/m^2), Mean (SD)	28.7 (6.20)	28.6 (6.53)	29.2 (7.00)	29.6 (6.60)	29.7 (7.56)	29.9 (7.42)	29.1 (7.00)	28.2 (6.32)	28.5 (6.73)	29.7 (7.36)	31.2 (7.3)	29.7 (6.2)
Duration of RA diagnosis (years) – continuous, Mean (SD)	8.3 (8.00)	8.3 (8.41)	8.1 (7.73)	7.2 (7.45)	7.3 (7.89)	7.3 (7.86)	5.8 (6.63)	7.5 (8.88)	6.5 (6.98)	14.5 (9.22)	12.4 (9.38)	12.7 (9.65)
RF – categorical, n (%)	517 (79.4)	265 (81.0)	521 (80.0)	164 (74.2)	163 (73.8)	146 (66.7)	151 (69.9)	155 (71.4)	151 (70.2)	113 (66.9)	119 (73.0)	113 (68.5)
Anti-CCP – categorical, n (%)	529 (81.5)	264 (80.7)	525 (80.6)	167 (75.9)	174 (79.1)	155 (70.8)	153 (70.8)	159 (73.3)	151 (70.6)	117 (69.2)	119 (72.6)	120 (72.7)
RF and anti-CCP, n (%)	475 (73.2)	241 (73.7)	480 (73.7)	150 (67.9)	153 (69.5)	137 (62.6)	135 (62.5)	142 (65.4)	131 (60.9)	102 (60.4)	107 (65.6)	101 (61.2)
DAS28 (CRP) – continuous, Mean (SD)	5.8 (0.94)	5.9 (0.96)	5.8 (0.97)	5.6 (0.84)	5.7 (0.97)	5.7 (0.9)	5.6 (1.04)	5.6 (0.92)	5.6 (1.06)	5.8 (1)	5.9 (0.95)	5.8 (0.89)

Study	SELECT-COMPARE			SELECT-NEXT			SELECT-MONOTHERAPY			SELECT-BEYOND		
Treatment	PBO (N=651)	ADA (N=327)	UPA (N=651)	PBO (N=221)	UPA 15 mg (N=221)	UPA 30 mg (N=219)	MTX (N=216)	UPA 15 mg QD (N=217)	UPA 30 mg QD (N=215)	PBO (N=169)	UPA 15 mg (N=164)	UPA 30 mg (N=165)
CDAI – continuous, Mean (SD)	40.0 (12.73)	39.8 (13.18)	39.7 (12.92)	37.8 (11.81)	38.3 (11.86)	38.6 (12.72)	37.8 14.39)	38.0 (13.12)	38.4 (13.77)	41 (13.3)	41.7 (13.28)	40.1 (12.25)
TJC68, Mean (SD)	26.0 (14.30)	26.4 (15.16)	26.4 (15.15)	24.7 (14.96)	25.2 (13.8)	26.2 (14.26)	25.2 (15.99)	24.5 (15.10)	24.8 (15.19)	28.5 (15.27)	27.8 (16.31)	27.3 (15.23)
SJC66, Mean (SD)	16.2 (8.97)	16.3 (9.19)	16.6 (10.31)	15.4 (9.24)	16 (10.04)	16.2 (10.55)	16.9 (11.52)	16.4 (10.94)	16.9 (10.23)	16.3 (9.58)	17 (10.75)	17.2 (11.37)
HAQ-DI Mean (SD)	1.6 (0.61)	1.6 (0.59)	1.6 (0.64)	1.4 (0.63)	1.5 (0.61)	1.5 (0.61)	1.5 (0.66)	1.5 (0.66)	1.5 (0.65)	1.6 (0.6)	1.7 (0.64)	1.6 (0.59)
CRP (mg/L), Mean (SD)	18.0 (21.52)	19.8 (21.51)	17.9 (22.49)	12.6 (13.96)	16.6 (19.17)	14.8 (16.86)	14.5 (17.33)	14.0 (16.49)	16.3 (20.77)	16.3 (21.1)	16.2 (18.62)	16.0 (21.23)
Baseline mTSS, Mean (SD)	35.9 (51.66)	34.5 (47.06)	34 (50.08)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Baseline joint erosion score Mean (SD)	17.0 (27.43)	15.4 (23.10)	16.5 (26.42)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Baseline JSN score, Mean (SD)	18.9 (26.12)	19.2 (25.84)	17.5 (25.1)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Morning stiffness duration (minutes), Mean (SD)	142.4 (169.78)	146.1 (184.93)	141.5 (187.61)	138.9 (213.97)	152.4 (241.9)	128.6 (155.98)	153.0 (21.72)	144.2 (215.05)	133.9 (152.73)	138.4 (178.59)	140.4 (189.72)	184.5 (284.89)
MTX dose at Baseline (mg), Mean (SD)	16.8 (3.82)	17.1 (3.76)	17 (4.17)	NR	NR	NR	16.7 (4.41)	16.8 (4.21)	16.5 (4.56)	NR	NR	NR
Oral corticosteroid dosing at Baseline, n (%)	392 (60.2)	202 (61.8)	388 (59.6)	NR	NR	NR	115 (53.2)	114 (52.5)	98 (45.6)	NR	NR	NR
Oral corticosteroid dose (mg), Mean (SD)	6.3 (2.41)	6.5 (2.44)	6.2 (2.27)	NR	NR	NR	6.2 (2.56)	6.1 (2.52)	5.9 (2.48)	NR	NR	NR
Prior biologic DMARD use, n (%)	63 (9.7)	34 (10.4)	54 (8.3)	29 (13.1)	27 (12.2)	28 (12.8)	NR	NR	NR	169 (100)	164 (100)	164 (99.4)
Concomitant csDMARD at baseline, n (%)												
MTX alone	NR	NR	NR	141 (64.1)	122 (55.5)	136 (62.1)	NR	NR	NR	122 (72.6)	118 (73.3)	124 (75.6)
MTX and other csDMARD	NR	NR	NR	49 (22.3)	47 (21.4)	39 (17.8)	NR	NR	NR	17 (10.1)	19 (11.8)	11 (6.7)
csDMARD other than MTX	NR	NR	NR	30 (13.6)	51 (23.2)	44 (20.1)	NR	NR	NR	29 (17.3)	24 (14.9)	29 (17.7)
Missing	NR	NR	NR	1	1	0	NR	NR	NR	NR	NR	NR

Study	SELECT-COMPARE			SELECT-NEXT			SELECT-MONOTHERAPY			SELECT-BEYOND		
Treatment	PBO (N=651)	ADA (N=327)	UPA (N=651)	PBO (N=221)	UPA 15 mg (N=221)	UPA 30 mg (N=219)	MTX (N=216)	UPA 15 mg QD (N=217)	UPA 30 mg QD (N=215)	PBO (N=169)	UPA 15 mg (N=164)	UPA 30 mg (N=165)
Oral steroid dosing at baseline, n (%)	NR	NR	NR	106 (48.0)	96 (43.4)	103 (47.0)	NR	NR	NR	NR	NR	NR
Oral steroid dose (mg), Mean (SD)	NR	NR	NR	6.3 (2.55)	6 (2.36)	6.3 (2.6)	6.2 (2.56)	6.1 (2.52)	5.9 (2.48)	6.3 (2.42)	5.7 (2.37)	6.4 (5.75)
MTX dose (mg), Mean (SD)	NR	NR	NR	16.3 (4.89)	17 (4.87)	16.8 (4.33)	16.7 (4.4)	16.8 (4.21)	16.5 (4.6)	NR	NR	NR
Prior failed bDMARDs, n (%)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Stratum 1:1 MOA and ≤ 2 prior bDMARDs	NR	NR	NR	NR	NR	NR	NR	NR	NR	117 (69.2)	116 (70.7)	111 (67.3)
Stratum 2:> 1 MOA and/or > 2 prior bDMARDs	NR	NR	NR	NR	NR	NR	NR	NR	NR	52 (30.8)	48 (29.3)	54 (32.7)
Failed at least 1 anti-TNF, n (%)	NR	NR	NR	NR	NR	NR	NR	NR	NR	152 (89.9)	146 (89.0)	151 (92.1)

Abbreviations: ADA: Adalimumab; bDMARD: biological Disease Modifying Anti-Rheumatic Drugs; BMI: Body Mass Index; CDAI: Crohn's Disease Activity Index; CRP: C-Reactive Protein; DAS28: Disease Activity Score version 28; csDMARD: conventional synthetic Disease Modifying Anti-Rheumatic Drugs; DMARD: Disease Modifying Anti-Rheumatic Drugs; HAQ-DI: Health Assessment Questionnaire Disability Index; JSN: Joint Space Narrowing; mTSS: modified Total Sharp Score; MOA: Mechanism of Action; MTX: Methotrexate; PBO: Placebo; RA: Rheumatoid Arthritis; RF: Rheumatoid Factor; SD: Standard deviation; SJC66: Swollen joint count based on 66 joints; TJC68: Tender joint count based on 68 joints; TNF: Tumor Necrosis Factor; UPA: Upadacitinib;

Generalisability to the UK RA patient population

The four RCTs were conducted across Australia, Asia, Europe and North America, with 11 trial sites in the UK. Additionally, an analysis was conducted to compare the baseline characteristics of a subgroup of patients with severe RA in these trials with those of the UK RA adult population eligible for advanced therapy using data from the British Society of Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR) (58). The baseline characteristics of the patient cohort about to initiate treatment with a TNFi in the BSRBR registry are depicted in Table 6.

The BSRBR registry data depicts the baseline characteristics of patients about to initiate treatment with a TNFi in the UK. This therefore represents adult patients in the UK with severe RA as patients are only eligible for treatment with advanced therapy once they have severe RA. This was compared to a subgroup analysis of baseline characteristics of patients from the upadacitinib RCTs with severe RA.

The analysis demonstrated that the baseline characteristics of the patients in the upadacitinib RCTs are broadly similar to those eligible for advanced therapies in the BSRBR registry (please refer to Table 6 for more details). This indicates that the patients in the upadacitinib trials are representative of adult patients in the UK with severe RA who are eligible for treatment with advanced therapy.

Compared with the bDMARD patient cohort in the BSRBR registry, the mean age at baseline in the four RCTs was similar, the mean baseline DAS-28 was also similar (6.0.-6.2 vs. 6.5) and baseline HAQ-DI score was comparable (1.6-1.8 vs. 2.0) (58).

This comparison would suggest that it is reasonable to expect that the results achieved in these RCTs would be applicable to patients treated for RA in clinical practice in the UK.

Table 6. Baseline characteristics of the eligible for bDMARDs patient cohort in the BSRBR registry compared to severe RA patient subgroup in upadacitinib trials

Characteristic	SELECT-COMPARE			SELECT-NEXT		SELECT-MONOTHERAPY		SELECT-BEYOND		BSRBR registry
	PBO	ADA	UPA	PBO	UPA 15 mg	MTX	UPA 15 mg	PBO	UPA 15 mg	Eligible for bDMARDs
	(N=519)	(N=254)	(N=498)	(N=152)	(N=151)	(N=143)	(N=144)	(N=128)	(N=124)	(N = 11,798)
Age, mean (S.D.), years	53.4 (12.21)	53.7 (11.72)	54.6 (11.66)	56.3 (12.26)	55.7 (11.17)	55.8 (10.94)	55.4 (11.13)	57.6 (10.87)	56.4 (11.52)	56 (12)
Gender, female (%)	401 (77.3)	198 (78.0)	403 (80.9)	116 (76.3)	126 (83.4)	120 (83.9)	120 (83.3)	111 (86.7)	103 (83.1)	8777 (76)
DAS-28, mean (S.D.)	6.2 (0.70)	6.2 (0.71)	6.2 (0.70)	6.0 (0.56)	6.1 (0.68)	6.2 (0.71)	6.1 (0.70)	6.2 (0.7)	6.2 (0.8)	6.5 (1.0)
HAQ score, mean (S.D.)	1.7 (0.57)	1.8 (0.52)	1.8 (0.57)	1.6 (0.57)	1.6 (0.55)	1.7 (0.58)	1.7 (0.59)	1.7 (0.6)	1.8 (0.6)	2.0 (0.6)

Abbreviations: ADA: Adalimumab; DAS28: Disease Activity Score version 28; DMARD: Disease Modifying Anti-Rheumatic Drugs; HAQ: Health Assessment Questionnaire; MTX: Methotrexate; PBO: Placebo; SD: Standard deviation; TNF: tumor necrosis factor; UPA: Upadacitinib;

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

The efficacy analyses conducted were based on a modified intent-to-treat (mITT) principle on populations which comprised all patients who were randomised and received at least one dose of study drug during the trial (Full Analysis Set). Safety analyses are based on the actual treatment received at the randomisation visit. This set of patients is called the safety set (SAF) (53).

The type I error rate for comparisons of the primary and secondary endpoints for each upadacitinib dose was strongly controlled using a graphical multiple testing procedure (53).

For binary endpoints, pairwise comparisons between each upadacitinib arm and the MTX/placebo arm were conducted using the Cochran-Mantel-Haenszel test, adjusting for the main stratification factors. For continuous endpoints, pairwise comparisons between treatment arms were conducted using the analysis of covariance (ANCOVA) model. For mTSS, linear extrapolation was the primary analysis approach; with sensitivity analysis conducted using Observed Case analysis (24-week endpoint) and the As-Observed approach (48-week endpoint). For other endpoints, non-responder imputation (NRI) served as the primary analysis method for binary endpoints and multiple imputations were used for continuous endpoints; sensitivity analysis was also conducted based on the observed cases and last observation carried forward (LOCF) approaches for key endpoints (53).

SELECT-COMPARE was powered to show a benefit of the upadacitinib group over adalimumab and placebo in terms of the primary efficacy endpoints, ACR20 response and clinical remission based on DAS28 (CRP), at week 12.

SELECT-NEXT was powered to show a benefit of the upadacitinib group over placebo in terms of the primary efficacy endpoints, ACR20 response and LDA based on DAS28 (CRP), at 12 weeks. The study was also powered to assess the benefit-risk profile of both doses of upadacitinib (15 mg and 30 mg) based on efficacy and safety.

SELECT-MONOTHERAPY was powered to show a benefit of the upadacitinib group over MTX in terms of the primary efficacy endpoints, ACR20 response and LDA based on DAS28 (CRP), at 14 weeks. The study was also powered to assess the benefit of upadacitinib as favourable based on overall efficacy and safety through week 48.

SELECT-BEYOND was powered to show a benefit of the upadacitinib group over placebo in terms of the primary efficacy endpoints, ACR20 response and LDA based on DAS28 (CRP), at 12 weeks. The study was also powered to assess the benefit-risk profile of both doses of upadacitinib (15 mg and 30 mg) based on efficacy and safety.

Further details of the statistical methods applied and sample size calculations in SELECT-COMPARE, SELECT-NEXT, SELECT-MONOTHERAPY and SELECT-BEYOND are presented in Appendix D, Section 1.4.

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

A summary of the quality assessment for the four phase III clinical trials is presented in Appendix D, Section 1.17. Overall, the four RCTs are considered of high quality. Randomisation in the trials was carried out appropriately such that baseline characteristics were well balanced across treatment groups. Patients and investigators remained blinded throughout the study, all outcome assessments were based on the mITT principle. For the primary endpoint analysis in all the trials, non-responder imputation (NRI) was used. For secondary endpoint analysis of ACR20 response and LDA based on DAS28 (CRP) in SELECT-COMPARE trial, the superiority of upadacitinib versus adalimumab was tested using the Cochran-Mantel-Haenszel test adjusting for stratification factor prior bDMARD use. In all trials, for the analysis of major RA continuous endpoints (DAS28 and HAQ-DI change from baseline), the statistical inference was conducted using analysis of covariance (ANCOVA) coupled with Multiple Imputation (MI) for missing data handling. For other continuous endpoints, the statistical inference was conducted using the Mixed Effect Model Repeat Measurement (MMRM) model with the main stratification factor being prior bDMARD use. Further details of the methodologies used are reported in

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

B.2.6 Clinical effectiveness results of the relevant trials

B.2.6.1 SELECT-COMPARE

SELECT-COMPARE assessed the efficacy of upadacitinib 15 mg QD versus placebo, and versus adalimumab, for the treatment of subjects with moderately to severely active RA who were on a stable dose of MTX and had an inadequate response to MTX.

The clinical effectiveness results demonstrated the superiority of upadacitinib vs placebo, as assessed by the proportion of patients who achieved an ACR20 response at Week 12, as well as proportion of patients achieving clinical remission DAS28 score (CRP <2.6). Additionally, this study demonstrated that upadacitinib had clinically meaningful improvements when compared to adalimumab, in terms of ACR responses and clinical remission.

The following secondary outcomes are also presented: ACR50/70 response, DAS28(CRP) and LDA based on DAS28(CRP), HAQ-DI, mTSS, LDA CDAI, RA-WIS, SF-36 PCS, EQ-5D, and FACIT-F.

A summary of the outcomes is presented in Table 7.

Table 7: Summary of clinical effectiveness results for SELECT-COMPARE

Endpoints	Week 12			Week 26		
	PBO (+MTX) (N=651)	ADA (+MTX) (N=327)	UPA 15 mg (+MTX) (N=651)	PBO (+MTX) (N=651)	ADA (+MTX) (N=327)	UPA 15 mg (+MTX) (N=651)
ACR20 response	36.4	63***	70.5***#	35.6	57.2**	67.4***
ACR50 response	14.9	29.1***	45.2***##	20.9	41.9***	53.9***
ACR70 response	4.9	13.5***	24.9***##	9.5	22.9***	34.7***
Clinical remission based on DAS28 (CRP)	6.1	18.0***	28.7***##	9.2	26.9***	40.9***
DAS28 (CRP) CFB	–1.1	–2.0***	–2.5***	–1.2	–2.3***	–2.8***
EQ-5D-5L CFB	0.1	0.2*	0.2***	0.1	0.2*	0.2***
FACIT-F CFB	4.8	7.4*	9.0***	5.48	8.24*	9.68***
HAQ-DI CFB	–0.3	–0.5**	–0.6***	–0.3	–0.6**	–0.7***

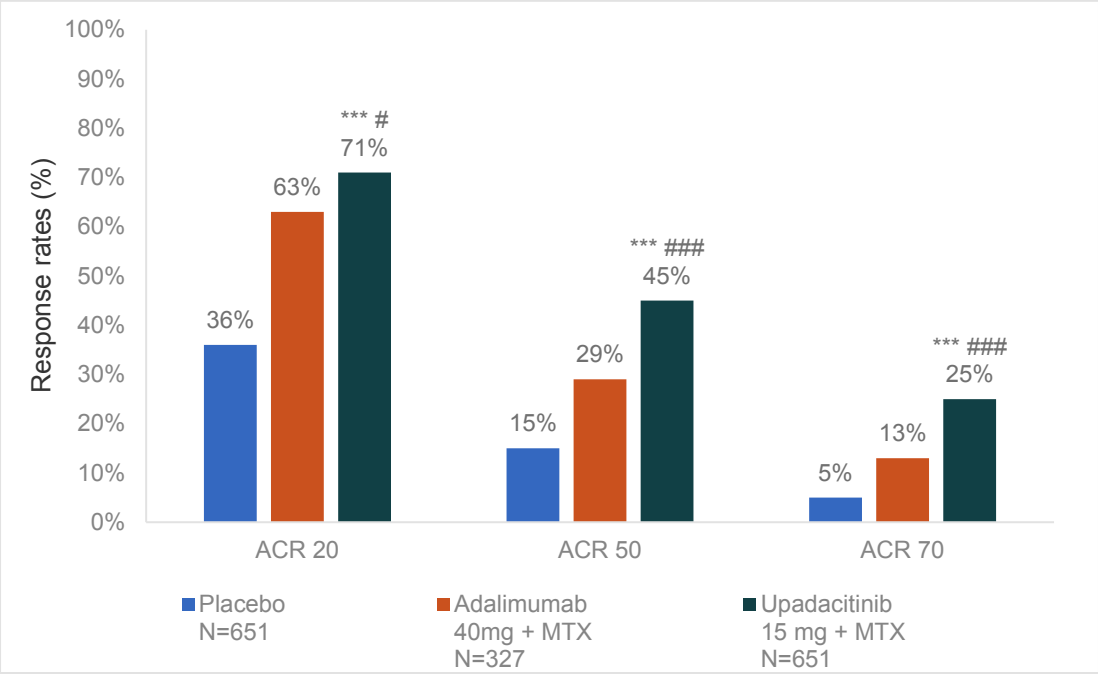
Endpoints	Week 12			Week 26		
	PBO (+MTX) (N=651)	ADA (+MTX) (N=327)	UPA 15 mg (+MTX) (N=651)	PBO (+MTX) (N=651)	ADA (+MTX) (N=327)	UPA 15 mg (+MTX) (N=651)
LDA CDAI	16.3	30**	40.4***	22.1	38.2	52.7***
LDA DAS28(CRP)	13.8	28.7***	45.0***##	18.0	38.5***	54.7***
LDA DAS28(CRP) - Non -Inferiority	13.8	28.7	45.0	NA	NA	NA
Morning stiffness duration (minutes) change	–48.6	-82.7	–92.6***	-53.88	-91.36	-100.25***
mTSS CFB	NA	NA	NA	0.9	0.1	0.2***
Patient's global assessment of pain change	-15.5	–25.3***	–31.8***	NA	NA	NA
Proportion of subjects with no radiographic progression	NA	NA	NA	76	86.8	83.5
RA-WIS score CFB	-2.0	-4.5	-5.2	NA	NA	NA
SF-36 PCS CFB	3.6	6.3**	7.9***	NA	NA	NA

Abbreviations: ACR20/50/70 = American College of Rheumatology 20%, 50%, 70% response; CDAI = Clinical Disease Activity Index; CFB = Change From Baseline; CRP = C-reactive protein; DAS28 = Disease Activity Score 28; FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue; HAQ-DI = Health Assessment Questionnaire – Disability Index; LDA = low disease activity; PCS = physical component summary; QD = once daily; SF-36 = Short Form-36
***, **, * Statistically significant at 0.001, 0.01, and 0.05 level, respectively UPA vs placebo
#, ## Statistically significant at 0.05, and 0.001 level respectively for UPA vs ADA

B.2.6.1.1 Primary endpoints

The primary outcomes showed that at week 12, a significantly greater proportion of patients receiving upadacitinib combination therapy achieved an ACR20 response compared with patients receiving placebo + MTX (70.5% versus 36.4% respectively, p<0.001); as well as adalimumab 40 mg + MTX (70.5% versus 63.0%, p<0.05) (Figure 7) (59). Similarly, a significantly greater proportion of patients receiving upadacitinib combination therapy achieved clinical remission (based on DAS28 CRP <2.6) compared with placebo + MTX (28.7% versus 6.1%, respectively, p<0.05); as well as adalimumab 40 mg + MTX (28.7% versus 18.0%, p<0.001) (see Figure 8) (59).

Figure 7: ACR response rates at week 12 in SELECT-COMPARE†



Source: (59)

†Primary endpoints included ACR20 and clinical remission based on DAS28 (CRP) for upadacitinib versus placebo (superiority). Ranked secondary endpoints included ACR50 versus adalimumab (both non-inferiority and superiority) and LDA versus adalimumab (non-inferiority) and versus placebo (superiority). All other comparisons were not adjusted for multiplicity. Not all ranked secondary endpoints shown.

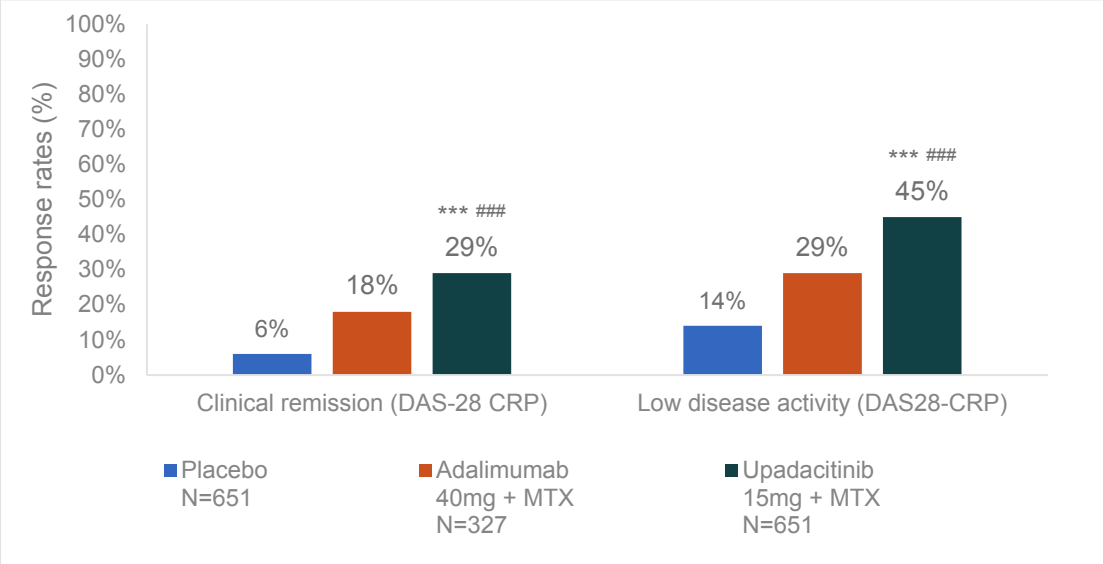
***Denotes statistical significance at the 0.001 level for comparison versus placebo.

#Denotes statistical significance at the 0.05 level for comparison versus adalimumab.

###Denotes statistical significance at the 0.001 level for comparison versus adalimumab.

Abbreviations: ACR20/50/70 = American College of Rheumatology 20%, 50%, 70% response; MTX = Methotrexate

Figure 8: Clinical remission and LDA at week 12 in SELECT-COMPARE†,a,b



Source: (59)

[†]Primary endpoints included ACR20 and clinical remission based on DAS28 (CRP) for upadacitinib versus placebo (superiority). Ranked secondary endpoints included ACR50 versus adalimumab (both non-inferiority and superiority) and LDA versus adalimumab (non-inferiority) and versus placebo (superiority). All other comparisons were not adjusted for multiplicity. Not all ranked secondary endpoints shown.

[a]Clinical remission was based on DAS28[CRP] less than 2.6.

[b]LDA was defined by a clinical response DAS28 CRP less than or equal to 3.2.

***Denotes statistical significance at the 0.001 level for comparison versus placebo.

###Denotes statistical significance at the 0.001 level for comparison versus adalimumab.

Abbreviations: DAS28 = Disease Activity Score 28; MTX = Methotrexate

B.2.6.1.2 Secondary endpoints

Study findings demonstrated the superiority of upadacitinib + MTX over both placebo + MTX and adalimumab + MTX for all ranked secondary endpoints that compared both groups (59).

Clinical remission

A significantly greater proportion of patients receiving upadacitinib 15 mg QD + MTX achieved clinical remission compared with placebo + MTX (28.7% versus 6.1%, respectively at week 12 and 40.9% versus 9.2% at week 26, p<0.05).

A significantly greater proportion of patients receiving upadacitinib 15 mg QD + MTX achieved clinical remission compared with patients receiving adalimumab 40 mg EOW (every other week) + MTX at week 12 (28.7% versus 18.0%, p<0.001). Similarly, at week 26, a significantly greater proportion of patients receiving upadacitinib 15 mg QD + MTX achieved clinical remission compared with patients receiving adalimumab 40 mg EOW + MTX (40.9% versus 26.9%, p<0.001) (59).

ACR50 and ACR70

At week 12, a significantly greater proportion of patients receiving upadacitinib 15 mg QD + MTX achieved an ACR50 response compared with patients receiving placebo + MTX (45.2% versus 14.9% respectively, p<0.001) and compared to adalimumab (29.1%, p<0.001). Similarly, a significantly greater proportion of patients receiving upadacitinib 15 mg QD + MTX achieved an ACR70 response compared with patients receiving placebo + MTX (24.9% versus 4.9% respectively, p<0.001) and compared to adalimumab + MTX (13.5%, p<0.001) (see Figure 7) (59).

LDA (based on DAS28(CRP)≤3.2)

At week 12, a significantly greater proportion of patients receiving upadacitinib 15 mg QD + MTX achieved LDA (based on DAS28(CRP)≤3.2) compared with patients receiving placebo + MTX (45.0% versus 13.8% respectively, p<0.001) and compared to adalimumab + MTX (28.7%, p<0.001). Similarly, at week 26, a significantly greater proportion of patients receiving upadacitinib 15 mg QD + MTX achieved LDA (based on DAS28(CRP)≤3.2) compared with patients receiving placebo + MTX (54.7% versus 18.0% respectively, p<0.001) and compared to adalimumab + MTX (38.5%, p<0.001) (59).

Patient's Assessment of Pain

At week 12, a greater proportion of patients receiving upadacitinib + MTX achieved the reduction of pain as measured by the Patient's Assessment of Pain (based on the Visual Analog Scale [VAS] compared with patients receiving adalimumab + MTX (-31.8 versus -15.5, p=0.001) (59).

HAQ-DI

At week 12, a greater proportion of patients receiving upadacitinib + MTX achieved improvements in physical function, as measured by the HAQ-DI compared with patients receiving adalimumab + MTX (-0.6 versus -0.5) (59).

EQ-5D-5L

At Week 12, a greater proportion of patients receiving upadacitinib + MTX achieved greater increase (improvement) from baseline in mean current health status as measured by EQ-5D-5L index compared to placebo and with patients receiving adalimumab + MTX (0.21 versus 0.10 and 0.17, respectively, p=0.001). Similarly, at Week 12, a greater proportion of patients receiving upadacitinib + MTX achieved greater increase (improvement) from baseline in mean current health status as measured by EQ-5D-5L index compared to placebo and with patients receiving adalimumab + MTX (0.22 versus 0.11 and 0.20, respectively, p=0.001).

B.2.6.2 SELECT-NEXT

SELECT-NEXT compared efficacy of upadacitinib 15 mg QD versus placebo for the treatment of signs and symptoms of subjects with moderately to severely active RA who were on a stable dose of csDMARDs and had an inadequate response to csDMARDs.

The clinical effectiveness results demonstrated the superiority of upadacitinib vs placebo, as assessed by the proportion of patients who achieved an ACR20 response at Week 12, as well as LDA (DAS28 - CRP ≤3.2) at Week 12. The following secondary outcomes are also presented: ACR50/70 response, clinical remission based on DAS28 (CRP), and HAQ-DI. A summary of the outcomes is presented in Table 8 (51).

Table 8: Summary of clinical effectiveness results for SELECT-NEXT

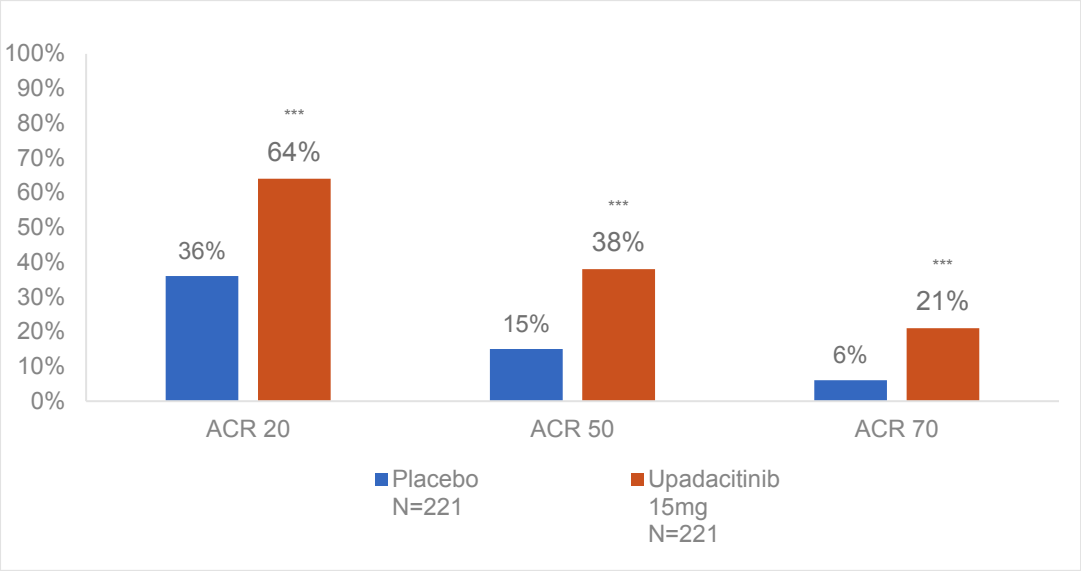
Endpoints	Week 12	
	PBO (+csDMARDs) (N=221)	UPA 15 mg (+ csDMARDs) (N=221)
ACR20 response	35.7	63.8***
ACR50 response	14.9	38.0***
ACR70 response	5.9	20.8***
Clinical remission based on DAS28 (CRP)	10.0	30.8***
DAS28 (CRP) CFB	–1.0	–2.2***
EQ-5D-5L CFB	0.1	0.2***
FACIT-F CFB	3.0	7.9***
HAQ-DI CFB	–0.3	–0.6***
LDA CDAI	19.0	40.3***
LDA DAS28(CRP)	17.2	48.4***
Morning stiffness duration (minutes) change	–34.3	–85.3***
RA-WIS CFB	–1.6	–4.3
SF-36 PCS CFB	3.0	7.6***

Abbreviations: ACR20/50/70 = American College of Rheumatology 20%, 50%, 70% response; CDAI = Clinical Disease Activity Index; CFB = Change From Baseline; CRP = C-reactive protein; DAS28 = Disease Activity Score 28; FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue; HAQ-DI = Health Assessment Questionnaire – Disability Index; LDA = low disease activity; PCS = physical component summary; QD = once daily; SF-36 = Short Form-36
*** Statistically significant at 0.001 level

B.2.6.2.1 Primary outcomes

The primary outcome measure demonstrated that a greater proportion of patients receiving upadacitinib 15 mg QD + csDMARDs achieved an ACR20 response compared with patients receiving placebo + csDMARDs (63.8% versus 35.7% respectively, p<0.001). The onset of activity was rapid, with significantly more patients achieving an ACR20 response on upadacitinib 15 mg + csDMARDs versus placebo + csDMARDs as early as week 1: 22% versus 9% (p<0.001 for both upadacitinib + csDMARD arms versus placebo + csDMARDs). The ACR responses rates are depicted in Figure 9 (60).

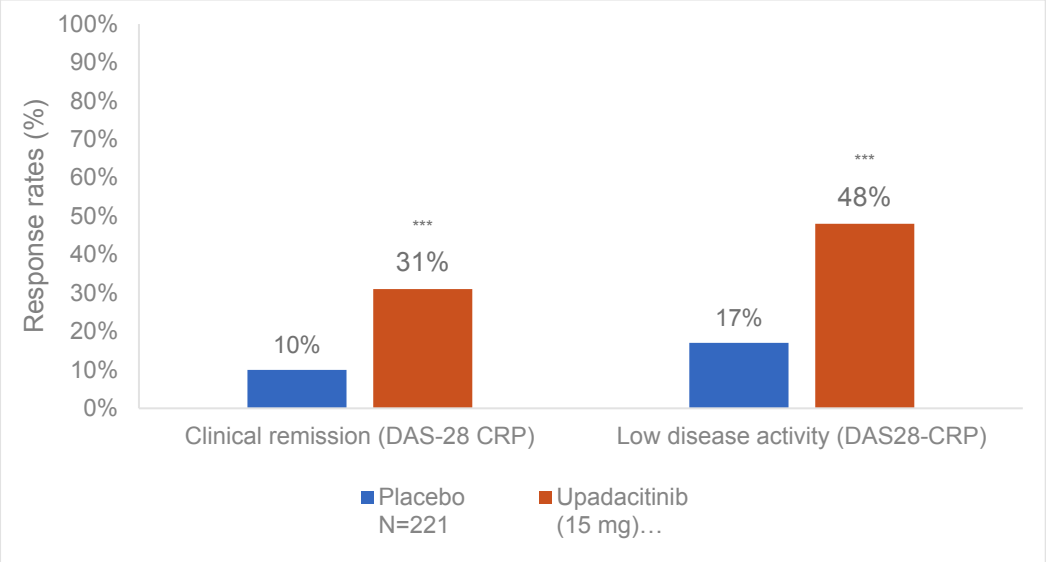
Figure 9: ACR response rates at week 12 in SELECT-NEXT



Source: (60)
Responses for ACR20, ACR50, and ACR70 over 12 weeks, with non-responder imputation.
******Denotes statistical significance at the p<0.001 for comparison versus placebo.***
Abbreviations: ACR20/50/70 = American College of Rheumatology 20%, 50%, 70% response

At week 12, a significantly greater proportion of patients receiving upadacitinib 15 mg QD + csDMARDs LDA (DAS28 - CRP ≤3.2) compared with patients receiving placebo + csDMARDs (47.9% versus 17.2% respectively, p<0.001) (See Figure 10) (51).

Figure 10: Clinical remission and LDA at week 12 in SELECT-NEXT[†,a,b]



Source: (60)

[†]Patients achieving DAS28(CRP) of ≤3·2 or DAS28(CRP) <2·6 with non-responder imputation.

[a]Clinical remission was based on DAS28-CRP less than 2.6.

[b]LDA was defined by a clinical response DAS28 CRP less than or equal to 3.2.

***Denotes statistical significance p<0.001 versus placebo for both doses.

Abbreviations: DAS28 = Disease Activity Score 28

B.2.6.2.2 Secondary Outcomes

Study findings demonstrated the superiority of upadacitinib + csDMARDs versus placebo + csDMARDs for doses 15 mg dose (60). The changes from baseline and percentage of responders for minimal clinically important differences (MCID) and for normative values at week 12 after upadacitinib initiation are shown in Table 8.

ACR50 and ACR70

In addition to results achieved for ACR20, upadacitinib 15 mg QD consistently demonstrated efficacy across the ACR50 and ACR70 outcomes at Week 12. A significantly greater proportion of patients receiving upadacitinib 15 mg QD + csDMARDs achieved an ACR50 response compared with patients receiving placebo + csDMARDs (38.0% versus 14.9% respectively, p<0.001) at week 12. Similarly, a significantly greater proportion of patients receiving upadacitinib 15 mg + csDMARDs achieved an ACR70 response compared with patients receiving placebo + csDMARDs (20.8% versus 5.9% respectively, p<0.001) (Table 8).

Clinical Remission

At week 12, a significantly greater proportion of patients receiving upadacitinib 15 mg + csDMARDs achieved clinical remission (DAS28(CRP)<2.6) compared to patients receiving placebo + csDMARDs (30.8% versus 10.0% respectively, p<0.001) (Figure 8). Furthermore, significantly more patients receiving upadacitinib at 15 mg QD + csDMARDs versus placebo + csDMARDs achieved remission by the CDAI and Simplified Disease Activity Index (SDAI) criteria. Boolean remission was achieved by 10.0% (22 of 221 patients [p=0.0085]) of patients receiving upadacitinib 15 mg QD + csDMARDs versus 3.6% of patients receiving placebo + csDMARDs (60). Improvements from baseline in DAS28(CRP) and CDAI were significantly greater for patients receiving upadacitinib at both doses + csDMARDs compared to placebo + csDMARDs, as early as week 1 and at every time point thereafter, including week 12 (60).

HAQ-DI

At week 12, significantly greater proportions of patients receiving upadacitinib 15 mg QD + csDMARDs achieved the HAQ-DI MCID and normative values compared to placebo + csDMARDs (Table 9) (60).

EQ-5D-5L

At Week 12, a greater proportion of patients receiving upadacitinib 15 mg QD + csDMARDs achieved greater increase (improvement) from baseline in mean current health status as measured by EQ-5D-5L index compared to placebo (0.2 versus 0.1, p=0.001).

Medical Outcomes Study 36-Item Short Form Health Survey

At week 12, patients receiving upadacitinib 15 mg QD + csDMARDs had significant improvements in QoL, as measured by SF-36 PCS compared with patients receiving placebo + csDMARDs (mean change from baseline of 7.6 and 8.0 versus 3.0 respectively, p≤0.001 versus placebo + csDMARDs) (Table 8). Similarly, significantly greater proportions of patients receiving upadacitinib 15 mg + csDMARDs achieved the SF-36 PCS MCID and normative values compared with patients receiving placebo + csDMARDs (p<0.05) (Table 9) (61).

Patient's Assessment of Pain

At week 12, patients receiving upadacitinib 15 mg QD + csDMARDs had significant improvements in pain, as measured by the Pain VAS, compared with patients receiving placebo + csDMARDs (mean change from baseline of -29.2 versus -10.26 respectively; $p<0.05$) (Table 8). Similarly, significantly greater proportions of patients receiving upadacitinib 15 mg and QD + csDMARDs reported improvements in the Pain VAS ≥MCID compared with patients receiving upadacitinib + csDMARDs ($p<0.05$) (Table 9) (61).

FACIT-F

At week 12, patients receiving upadacitinib 15 mg QD + csDMARDs had significant improvements in fatigue, as measured by FACIT-F compared with patients receiving placebo + csDMARDs (mean change from baseline of 7.9 versus 3.0 respectively, $p\leq0.001$]) (Table 8). Similarly, significantly greater proportions of patients receiving upadacitinib 15 mg QD + csDMARDs reported improvements in FACIT-F ≥MCID and normative values compared with patients receiving upadacitinib + csDMARDs ($p<0.05$) (Table 9) (61).

Duration and severity of morning joint stiffness

At week 12, patients receiving upadacitinib 15 mg QD + csDMARDs had significant improvements in the duration of morning stiffness (mean change from baseline of -85.3 minutes versus -34.3 minutes respectively, $p<0.001$), with significant improvements noted at many earlier visits. By week 1, a significantly greater proportion of patients receiving upadacitinib 15 mg + csDMARDs reported improvements in the severity of morning stiffness compared with patients receiving placebo + csDMARDs ($p\leq0.001$), and improvements continued over the 12 weeks (Table 9) (60). Similarly, significantly greater proportions of patients receiving upadacitinib 15 mg QD + csDMARDs reported improvements in duration of morning stiffness ≥MCID compared with patients receiving placebo + csDMARDs ($p<0.05$) (61).

Table 9. Least squared mean (LSM) changes from baseline and percentage of responders for MCID and for normative values at week 12 after upadacitinib initiation

PRO	Change from baseline		% responders			
	LSM		Reporting scores ≥MCID, n (%)		Reporting scores ≥normative values, n (%)	
	PBO N=221	UPA 15 mg N=221	PBO N=221	UPA 15 mg N=221	PBO N=221	UPA 15 mg N=221
HAQ-DI	-0.26	-0.61*	109 (49.3)	156 (72.2) *	30 (13.6)	56 (25.9) *
Tag	-10.36	-29.67*	94 (42.5)	153 (70.5) *	32 (14.5)	78 (35.9) *
Pain VAS	-10.26	-29.92*	97 (43.9)	158 (72.8) *	-	-
FACIT-F	2.96	7.91*	91 (41.2)	138 (63.9) *	35.8 (15.8)	60 (27.8) *
Duration morning stiffness[a]	-34.27	-85.28*	29 (13.4)	57 (26.3) *, [b]	-	-
Severity morning stiffness[b]	-1.38	-2.88*	130 (60.2)	165 (76.0) *, [b]	-	-
SF-36 PCS	3.03	7.58*	106 (48.0)	152 (69.4) *	18 (8.1)	39 (17.8) *
SF-36 MCS	2.58	4.69*	91 (41.2)	120 (54.8) *	102 (46.2)	114 (52.1)

Abbreviations: HAQ-DI = Health Assessment Questionnaire – Disability Index; MCID = minimum clinically important differences; MCS= Mental component summary; PCS = physical component summary; PtGA = Patient's Global Assessment of Disease Activity QD = once daily; SF-36 = Short Form-36; VAS = Visual Analogue Scale

Source: (61) *p<0.05 for upadacitinib versus placebo.

[a]Duration in minutes.

[b]% responders reporting scores minimal important difference.

[c]Assessed on a numeric scale of 1–10, 10 being the worst level.

B.2.6.3 SELECT-MONOTHERAPY

SELECT-MONOTHERAPY compared efficacy of upadacitinib 15 mg QD monotherapy versus continuing MTX monotherapy for the treatment of signs and symptoms of RA in subjects with moderately to severely active RA despite stable doses of MTX (inadequate response to MTX).

The clinical effectiveness results demonstrated the superiority of upadacitinib 15 mg vs continuing methotrexate (cMTX), as assessed by the proportion of patients who achieved an ACR20 response at Week 14, as well as proportion of patients with LDA based on DAS28 score (CRP <3.2). The following secondary outcomes are also presented: ACR50/70 response, DAS28(CRP), HAQ-DI, and SF-36 PCS. A summary of the outcomes is presented in

Table **10**.

Table 10: Summary of clinical effectiveness results for SELECT-MONOTHERAPY

Endpoints	Week 14	
	cMTX (N=216)	UPA 15 mg QD (N=217)
ACR20 response	41.2	67.7***
ACR50 response	15.3	41.9***
ACR70 response	2.8	22.6***
Clinical remission based on DAS28 (CRP)	8.3	28.1***
DAS28 (CRP) CFB	–1.20	–2.29***
EQ-5D-5L CFB	0.1	0.2***
HAQ-DI CFB	–0.32	–0.65***
LDA DAS28(CRP)	19.4	44.7***
Morning stiffness duration (minutes) change	–53.03	–94.56**
SF-36 PCS CFB	4.32	8.28***

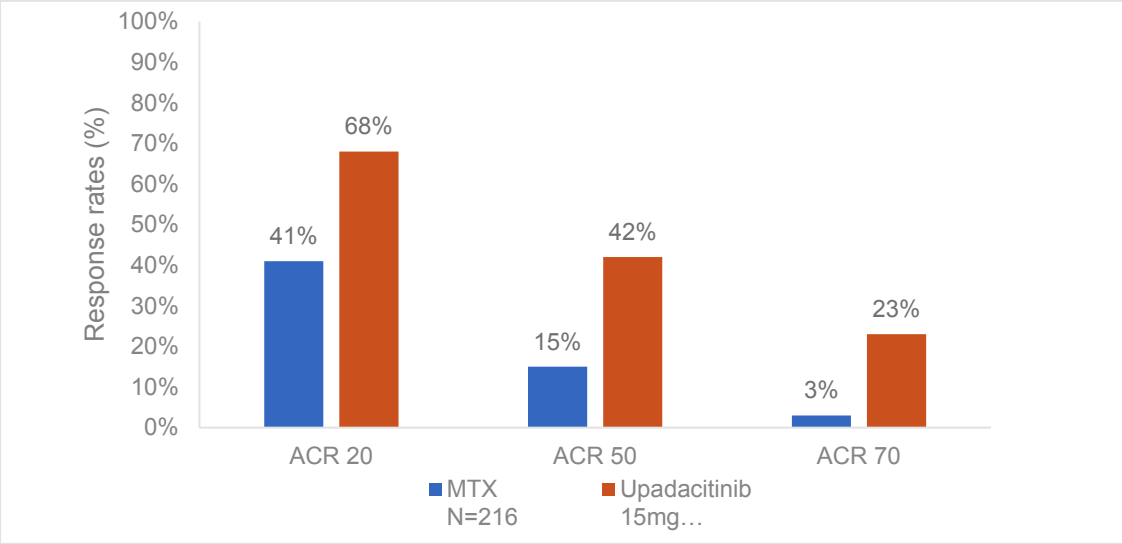
Abbreviations: ACR20/50/70 = American College of Rheumatology 20%, 50%, 70% response; CFB = Change From Baseline; CRP = C-reactive protein; DAS28 = Disease Activity Score 28; HAQ-DI = Health Assessment Questionnaire – Disability Index; LDA = low disease activity; PCS = physical component summary; PBO =Placebo; QD = once daily; SF-36 = Short Form-36; UPA = Upadacitinib
** Statistically significant at 0.01 level
*** Statistically significant at 0.001 level

B.2.6.3.1. Primary outcomes

The primary outcomes demonstrated that at week 14, a significantly greater proportion of patients receiving upadacitinib 15 mg QD achieved an ACR20 response compared with patients receiving MTX monotherapy (67.7% versus 41.2% respectively, p<0.001) (see Figure 11) (62). Also, a significantly greater proportion of patients receiving upadacitinib 15 mg QD achieved LDA (DAS28(CRP) ≤3.2) compared with patients receiving MTX monotherapy (44.7% versus 19.4% respectively, p<0.001) (see

Figure **12**) (62).

Figure 11: ACR response rates at week 12 in SELECT-MONOTHERAPY[†]

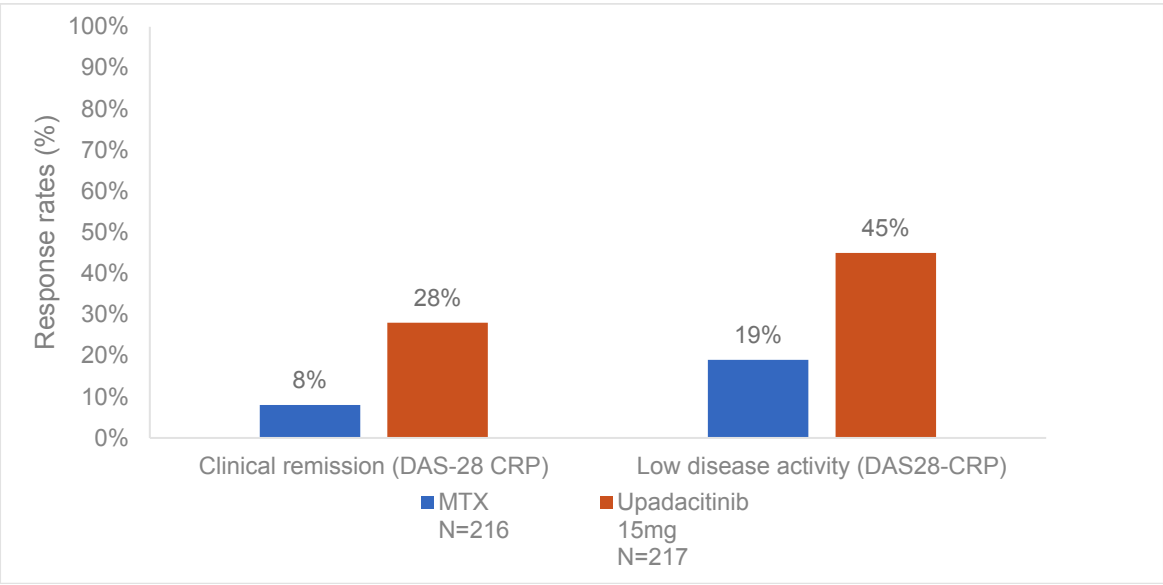


Source: (56)

[†]All week 14 endpoints shown in the table achieved p-values of <0.001 versus MTX for both doses. Not all ranked secondary endpoints shown. ACR50 and ACR70 were not ranked secondary endpoints. MTX patients shown are patients who continued on their baseline MTX dose in a blinded manner.

Abbreviations: ACR20/50/70 = American College of Rheumatology 20%, 50%, 70% response; MTX = Methotrexate

Figure 12: Clinical remission and LDA results at week 12 in SELECT-MONOTHERAPY[a,b]



Source: (62)

[†]All week 14 endpoints shown in the table achieved p-values of <0.001 versus MTX for both doses. Not all ranked secondary endpoints shown. MTX patients shown are patients who continued on their baseline MTX dose in a blinded manner.

[a]Clinical remission was based on DAS28 CRP less than 2.6.

[b]LDA was defined by a clinical response DAS28 CRP less than or equal to 3.2.

Abbreviations: DAS28 = Disease Activity Score 28; CRP = C-reactive protein; MTX: Methotrexate

B.2.6.3.2. Secondary outcomes

Study findings showed the superiority of upadacitinib at either dose versus MTX for all ranked secondary endpoints that compared both groups.

ACR 50 and ACR70 response

At week 14, a significantly greater proportion of patients receiving upadacitinib 15 mg QD monotherapy achieved an ACR50 response compared with patients receiving MTX monotherapy (42% versus 15% respectively, p<0.001). Similarly, a significantly greater proportion of patients receiving upadacitinib 15 mg QD monotherapy achieved an ACR70 response compared to patients receiving MTX monotherapy 23% versus 3% respectively, p<0.001) (62).

Clinical Remission

At week 14, a significantly greater proportion of patients receiving upadacitinib 15 mg QD monotherapy achieved clinical remission (based on DAS28(CRP)<2.6) compared with patients receiving MTX monotherapy (28% versus 8% respectively, p<0.001) (63).

HAQ-DI

At week 14, patients receiving upadacitinib 15 mg QD monotherapy had significant improvements in HAQ-DI, compared with patients receiving MTX monotherapy (mean change from baseline of -0.65 versus -0.32 respectively; p<0.001 versus MTX monotherapy) (60).

EQ-5D-5L

At Week 12, a greater proportion of patients receiving upadacitinib 15 mg QD monotherapy achieved greater increase (improvement) from baseline in mean current health status as measured by EQ-5D-5L index compared with patients receiving MTX monotherapy (0.2 versus 0.1, p=0.001).

SF-36 PCS

At week 14, patients receiving upadacitinib 15 mg QD monotherapy had significant improvements in QoL, as measured by SF-36 PCS compared with patients receiving

MTX monotherapy (mean change from baseline of 8.28 versus 4.32 respectively, p<0.001 versus MTX monotherapy) (63).

Duration of morning stiffness

At week 14, patients receiving upadacitinib 15 mg QD monotherapy had significant improvements in the duration of morning stiffness (mean change from baseline of -94.6 minutes versus -53.0 minutes respectively, p<0.01 versus MTX monotherapy) (60).

B.2.6.4 SELECT-BEYOND

SELECT-BEYOND compared the efficacy of upadacitinib 15 mg QD versus placebo for the treatment of signs and symptoms of subjects with moderately to severely active RA who were on a stable dose of csDMARDs and had an inadequate response to or intolerance to at least 1 prior bDMARD.

The clinical effectiveness results demonstrated the superiority of upadacitinib 15 mg vs placebo, as assessed by the proportion of patients who achieved an ACR20 response at Week 12, as well as proportion of patients with LDA based on DAS28 score (CRP <2.6). The following secondary outcomes are also presented: ACR50/70 response, DAS28(CRP), HAQ-DI, mTSS, LDA CDAI, RA-WIS, and SF-36 PCS. A summary of the outcomes is presented in Table 11.

Table 11: Summary of clinical effectiveness results for SELECT-BEYOND

Endpoints	Week 12		Week 24
	PBO (+ csDMARDs)	UPA 15 mg (+ csDMARDs)	UPA 15 mg (+ csDMARDs)
	n = 169	n = 164	n = 164
ACR20 response	28.4	64.6***	61.6
ACR20 response at Week 1	10.7	27.4***	NA
ACR50 response	11.8	34.1***	42.7
ACR70 response	6.5	11.6*	22.0
Clinical remission (DAS28- CRP ≤2.6)	9.5	28.7***	32.3
CDAI CFB	-13.3	-24.4***	-27.5
DAS28 (CRP) CFB	-1.0	-2.3***	-2.6
EQ-5D-5L CFB	0.1	0.2**	0.52
HAQ-DI change from baseline	-0.2	-0.4***	-0.4

Endpoints	Week 12		Week 24
	PBO (+ csDMARDs)	UPA 15 mg (+ csDMARDs)	UPA 15 mg (+ csDMARDs)
LDA based on DAS28 (CRP) ≤ 3.2	14.2	43.3***	52.4
SDAI CFB	-13.5	-25.6***	-28.4
SF-36 PCS CFB	2.4	5.8***	5.7

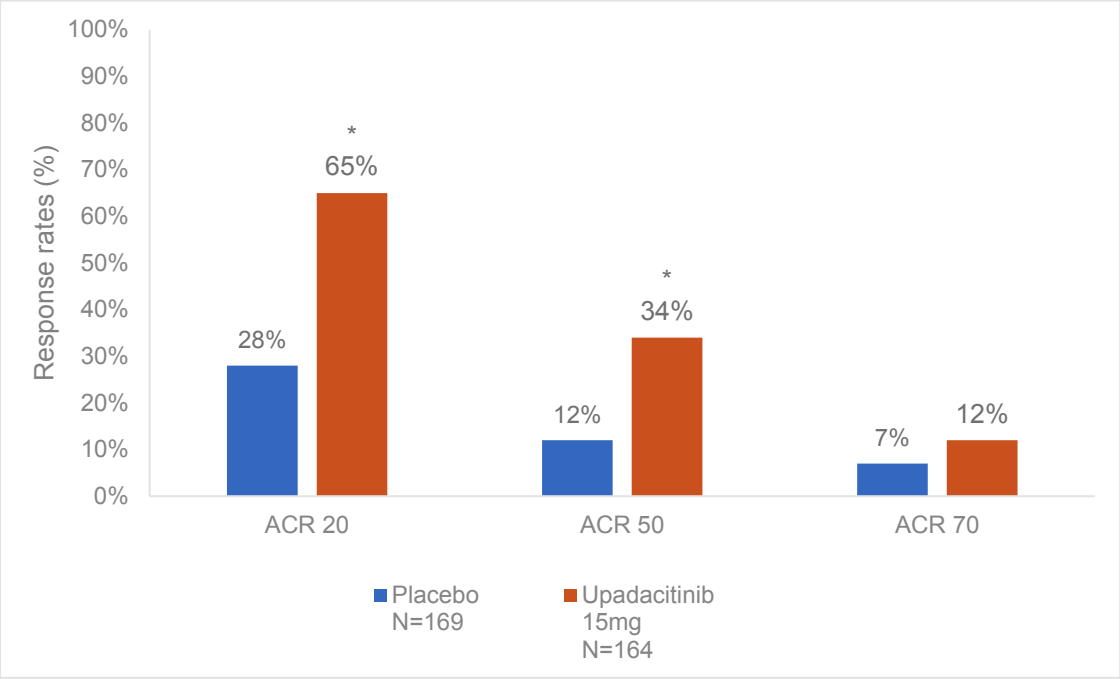
Abbreviations: ACR20/50/70 = American College of Rheumatology 20%, 50%, 70% response; CDAI = Clinical Disease Activity Index; CFB = Change From Baseline; CRP = C-reactive protein; DAS28 = Disease Activity Score 28; FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue; HAQ-DI = Health Assessment Questionnaire – Disability Index; LDA = low disease activity; PCS = physical component summary; QD = once daily; SF-36 = Short Form-36
*** Statistically significant at 0.001 level

B.2.6.4.1 Primary outcomes

The primary outcomes demonstrated that at week 12, a significantly greater proportion of patients receiving upadacitinib 15 mg + csDMARDs achieved an ACR20 response compared with patients receiving placebo + csDMARDs (64.6% versus 28.4% respectively, p<0.001) (see Figure 13) (63). At week 24, ACR20 response was achieved in 61.6% of patients treated with upadacitinib 15 mg QD + csDMARDs from study entry.

At week 12, a significantly greater proportion of patients receiving upadacitinib 15 mg QD + csDMARDs achieved LDA (DAS28(CRP) ≤3.2) compared with patients receiving placebo + csDMARDs (43.3% versus 14.2% respectively, p<0.001) (see Figure 16) (63). At week 24, LDA (DAS28(CRP) ≤3.2) was achieved by 52.4 of patients receiving dose of upadacitinib 15mg QD + csDMARDs. Comparisons to placebo + csDMARDs cannot be made at week 24, since all placebo patients received either upadacitinib 15 mg QD + csDMARDs beginning at week 12 (see Figure 14) (56).

Figure 13: ACR response rates at week 12 in SELECT-BEYOND[a]



Source: (63)

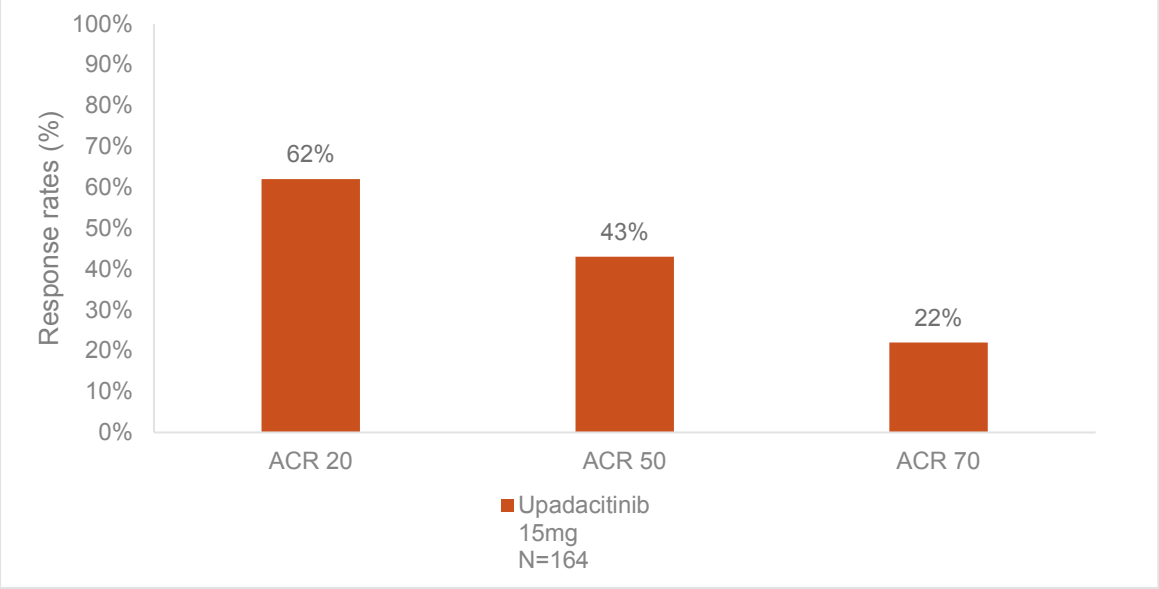
*All week 12 endpoints shown in the bar graph achieved p-values of <0.001 versus placebo for both doses except for the 15 mg ACR70 value.

ACR50 and ACR70 were not ranked secondary endpoints. Not all ranked and non-ranked secondary endpoints shown.

[a]ACR20/50/70 is defined as American College of Rheumatology 20 percent/50 percent/70 percent improvements in tender and swollen joint counts, patient assessments of pain, global disease activity and physical function, physician global assessment of disease activity and acute phase reactant.

Abbreviations: ACR20/50/70 = American College of Rheumatology 20%, 50%, 70% response

Figure 14: ACR response rates at week 24 in SELECT-BEYOND

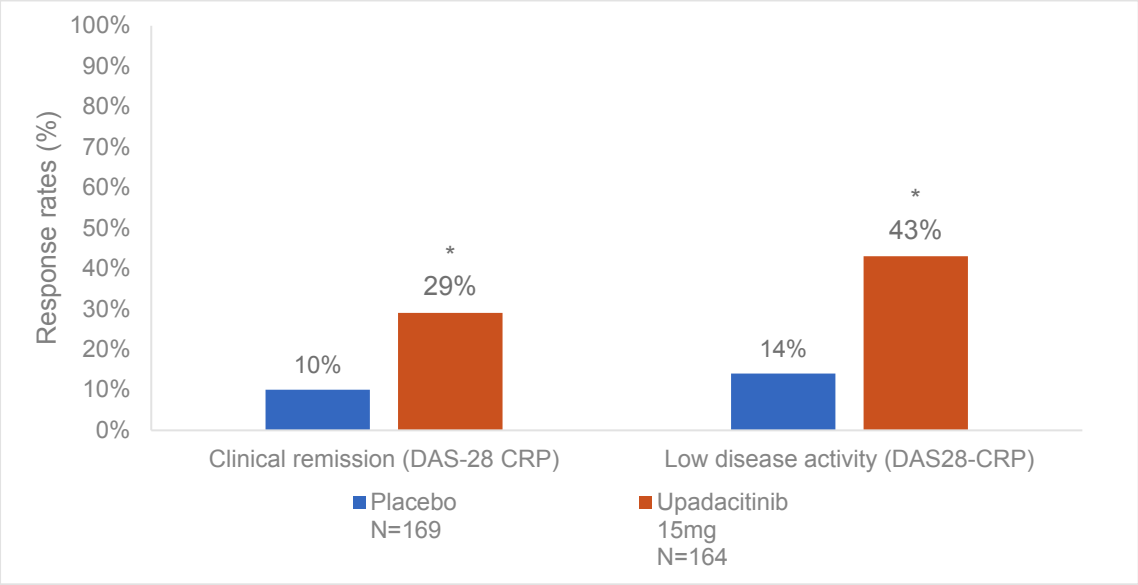


Source: (56)

Statistical comparisons to placebo were not conducted for week 24 values since no patients received placebo beyond week 12. Data for week 24 only shown for patients treated with upadacitinib from study entry.

Abbreviations: ACR20/50/70 = American College of Rheumatology 20%, 50%, 70% response

Figure 15: Clinical remission and LDA results at week 12 in SELECT-BEYOND[a,b]



Source: (63)

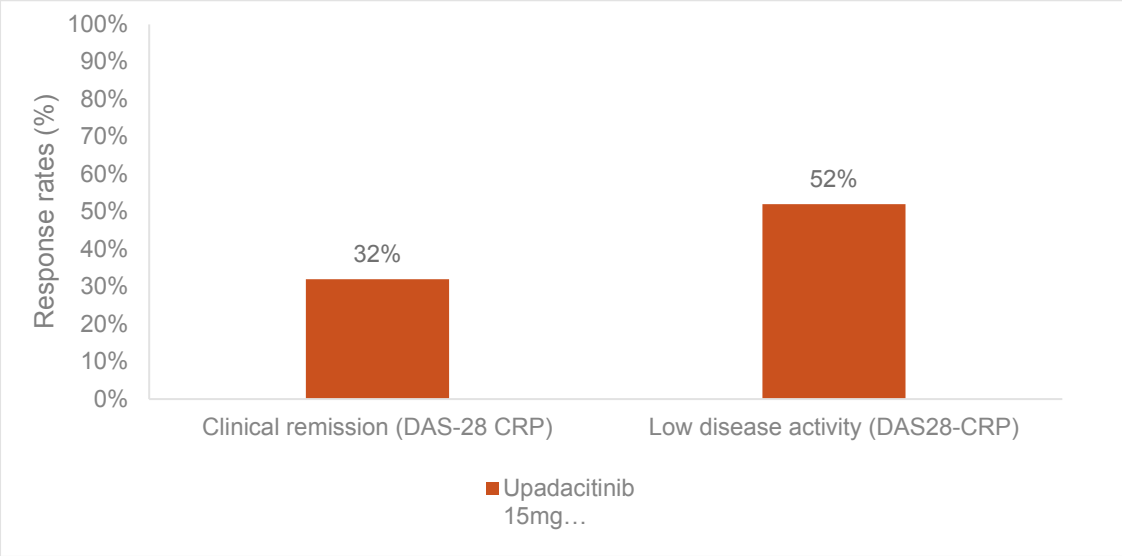
*All week 12 endpoints shown in the bar graph achieved p-values of <0.001 versus placebo for both. Not all ranked and non-ranked secondary endpoints shown

[a]LDA was defined by a clinical response DAS28 CRP less than or equal to 3.2

[b]Clinical remission was based on DAS28 (CRP) less than 2.6.

Abbreviations: DAS28 = Disease Activity Score 28; MTX = Methotrexate

Figure 16: Clinical remission and LDA results at week 24 in SELECT-BEYOND[*,a,b]



Source: (56)

*Statistical comparisons to placebo were not conducted for week 24 values since no patients received placebo beyond week 12. Data for week 24 only shown for patients treated with upadacitinib from study entry.

[a]LDA was defined by a clinical response DAS28 CRP less than or equal to 3.2

[b]Clinical remission was based on DAS28 (CRP) less than 2.6.

Abbreviations: DAS28 = Disease Activity Score 28

B.2.6.4.2 Secondary endpoints

Study findings showed the superiority of upadacitinib at either dose + csDMARDs versus placebo + csDMARDs for all ranked secondary endpoints that compared both groups.

ACR50 and ACR70

At week 12, a significantly greater proportion of patients receiving upadacitinib 15 mg QD + csDMARDs achieved an ACR50 response compared with patients receiving placebo + csDMARDs (34% versus 12%, respectively, p<0.001). A similar proportion of patients receiving upadacitinib 15 mg QD + csDMARDs achieved an ACR70 response compared with patients receiving placebo + csDMARDs (12% versus 7% respectively, p=0.1104). At week 24, ACR50 response was maintained in patients receiving upadacitinib 15 mg QD + csDMARDs from study entry (43.0%). Similarly, ACR70 response was maintained in patients receiving upadacitinib 15 mg QD + csDMARDs from study entry (22.0%). For patients receiving upadacitinib through week 24, ACR20 and ACR50 responses were maintained over time, with week 24 responses similar amongst those who switched from placebo + csDMARDs to upadacitinib + csDMARDs at week 12. Among patients with inadequate response/intolerance to bDMARDs, the percentages of patients who achieved an ACR20 response by week 12 on upadacitinib were comparable (63).

Clinical Remission

At week 12, a significantly greater proportion of patients receiving upadacitinib 15 mg QD + csDMARDs achieved clinical remission (DAS28(CRP)<2.6) compared with patients receiving placebo + csDMARDs (28.7% versus 9.5%, respectively p<0.001)(56). Significant improvements from baseline in DAS28(CRP) were observed as early as week 1, and at every visit through week 12 with either dose of upadacitinib + csDMARDs versus placebo + csDMARDs (p<0.001); further improvements were observed through week 24 (63). Clinical remission was achieved by 32.3% of patients in the 15 mg QD + csDMARDs groups (see Figure 16). In patients who switched from placebo to upadacitinib 15 mg QD + csDMARDs, clinical remission was achieved by 39% of patients.

CDAI and SDAI

At week 12, significantly more patients receiving upadacitinib 15 mg QD + csDMARDs versus placebo + csDMARDs achieved CDAI ≤10 ($p<0.01$) and SDAI ≤11 ($p<0.001$)(63). In patients who switched from placebo to upadacitinib 15 mg QD + csDMARDs at week 12, CDAI≤10 was achieved 34% of patients at week 24. In these patients, SDAI≤11 was achieved by 37% of patients. Comparisons to placebo + csDMARDs cannot be made at week 24, since all placebo + csDMARD patients received either upadacitinib 15 mg QD + csDMARDs beginning at week 12 (see Figure 14) (56).

SELECT-BEYOND demonstrated that even in difficult-to-treat bDMARD-IR patients with active RA, treatment with upadacitinib + csDMARDs resulted in significantly more patients with clinically meaningful improvements in patient reported outcomes (PROs) or responses that approached normative values (64).

Health Assessment Questionnaire-Disability Index

At week 12, patients receiving upadacitinib 15 mg + csDMARDs had significant improvements in HAQ-DI based on change from baseline (-0.41; $p<0.001$) versus placebo + csDMARDs (-0.16). The percentage of patients achieving the HAQ-DI MCID (≥0.22) was significantly greater for upadacitinib 15 mg QD + csDMARDs versus placebo + csDMARDs at all visits from week 1 through week 12. Similarly, a greater proportion of patients receiving upadacitinib 15 mg QD + csDMARDs achieved the HAQ-DI normative values compared with patients receiving placebo + csDMARDs ($p<0.05$) (see Table 12) (63).

Duration and severity of morning joint stiffness

Improvements were also observed in other PROs. Specifically, significant improvements from baseline in the duration and severity of morning stiffness were observed from week 1. At week 12, patients receiving upadacitinib 15 mg QD + csDMARDs had significant improvements in the duration of morning stiffness compared with patients receiving placebo + csDMARDs (mean change in baseline of -81.5 minutes versus -15.1 minutes, respectively, $p<0.05$). Similarly, significantly

greater proportions of patients receiving upadacitinib 15 mg QD + csDMARDs reported improvements in duration of morning stiffness ≥MCID compared with patients receiving placebo + csDMARDs (see Table 12) (63).

Patient's Assessment of Pain

At week 12, patients receiving upadacitinib 15 mg QD + csDMARDs had significant improvements in pain, as measured by the Pain VAS, compared with patients receiving placebo + csDMARDs (mean change from baseline of -25.91 versus -10.38 respectively, $p<0.05$ versus placebo + csDMARDs). Similarly, significantly greater proportions of responders reported scores ≥MCID 74% versus 46% respectively, $p<0.05$). Similarly, significantly more patients receiving upadacitinib 15 mg QD + csDMARDs reported improvements in pain ≥MCID compared with patients receiving upadacitinib + csDMARDs ($p<0.05$) (see Table 12) (64).

Medical Outcomes Study 36-Item Short Form Health Survey

Treatment with upadacitinib + csDMARDs versus placebo + csDMARDs resulted in an improved quality of life (SF-36 PCS) at week 12, with improvements maintained out to week 24 (see Table 12).

EQ-5D-5L

At Week 12, a greater proportion of patients receiving upadacitinib + csDMARDs achieved greater increase (improvement) from baseline in mean current health status as measured by EQ-5D-5L index compared to upadacitinib + csDMARDs (0.1 versus 0.2, $p=0.01$).

Table 12: Least squares mean (LSM) changes from baseline and percentage of responders for MCID and normative values at week 12

PRO	Change from baseline		% responders			
	LSM		Reporting scores ≥MCID, n (%)		Reporting scores ≥normative values, n (%)	
	PBO N=169	UPA 15 mg N=164	PBO N=169	UPA 15 mg N=164	PBO N=169	UPA 15 mg N=164
HAQ-DI	-0.16	-0.41*	61 (36.6)	102 (62.6) *	11 (6.6)	26 (16.0) *
PtGA	-10.03	-26.04*	71 (42.8)	1119 (73.0) *	25 (15.5)	46 (28.2) *
Pain VAS	-10.38	-25.91*	76 (45.8)	120 (73.6) *	-	-
Duration AM stiffness[a]	-15.07	81.47*	17 (10.1)	33 (20.1) *, [b]	-	-
Severity AM stiffness[b]	-1.57	-2.86*	95 (56.2)	131 (79.9) *, [b]	-	-
SF-36 PCS	2.39	5.83*	65 (39.2)	98 (60.1) *	9 (5.4)	18 (11.0)
SF-36 MCS	3.01	4.54	72 (43.4)	88 (54.0)	73 (44.0)	88 (54.0)

Abbreviations: HAQ-DI = Health Assessment Questionnaire – Disability Index; MCS= Mental component summary; PCS = physical component summary; PtGA = Patient's Global Assessment of Disease Activity QD = once daily; SF-36 = Short Form-36; VAS = Visual Analogue Scale

Source: (64)

*p<0.05 for upadacitinib versus placebo

[a]Duration in minutes

[b]% responders reporting scores minimal important difference

[c]Assessed on a numeric scale of 1–10, 10 being the worst level

B.2.7 Subgroup analysis

Across the four RCTs, post-hoc subgroup analyses were conducted for moderate patients and severe patient separately compared with the corresponding subgroups of patients receiving comparator treatments. Baseline characteristics for the moderate RA group are presented in Table 13.

Based upon the primary outcomes of the associated registration studies (ACR20 and LDA) and clinical remission these subgroup analyses show that [redacted] (Table 14). Furthermore, when compared to the respective full trial data sets of moderate to severe RA, the upadacitinib arm

amongst the moderate subgroup provides numerically similar or higher results (as shown initially in Table 7, Table 8,

Table **10**, Table 11 and summarised in

Table **15** for ease of comparison):

Table 13: Baseline characteristics for the moderate RA subgroup across all four registration trials.

Study	SELECT-COMPARE			SELECT-NEXT		SELECT-MONOTHERAPY		SELECT-BEYOND	
Treatment	PBO	ADA	UPA 15 mg	PBO	UPA 15 mg	MTX	UPA 15 mg	PBO	UPA 15mg
Total N moderate subgroup	[redacted]								
Sex, n (%)									
Male	[redacted]								
Female	[redacted]								
Age (years) Mean (SD)	[redacted]								
Duration of RA diagnosis (years) – continuous, Mean (SD)	[redacted]								
TJC68, Mean (SD)	[redacted]								
SJC66, Mean (SD)	[redacted]								
HAQ-DI Mean (SD)	[redacted]								
DAS 28 based on CRP	[redacted]								
Number of prior csDMARD use, Mean	[redacted]								

Abbreviations: ADA: Adalimumab; bDMARD: biological Disease Modifying Anti-Rheumatic Drugs; BMI: Body Mass Index; CDAI: Crohn's Disease Activity Index; CRP: C-Reactive Protein; DAS28: Disease Activity Score version 28; csDMARD: conventional synthetic Disease Modifying Anti-Rheumatic Drugs; DMARD: Disease Modifying Anti-Rheumatic Drugs; HAQ-DI: Health Assessment Questionnaire Disability Index; JSN: Joint Space Narrowing; mTSS: modified Total Sharp Score; MOA: Mechanism of Action; MTX: Methotrexate; PBO: Placebo; RA: Rheumatoid Arthritis; RF: Rheumatoid Factor; SD: Standard deviation; SJC66: Swollen joint count based on 66 joints; TJC68: Tender joint count based on 68 joints; TNF: Tumor Necrosis Factor; UPA: Upadacitinib.

Table 14: Efficacy results for the moderate RA subgroup across all four registration trials

Study	SELECT-COMPARE			SELECT-NEXT		SELECT-MONOTHERAPY		SELECT-BEYOND	
Treatment	PBO	ADA	UPA 15 mg	PBO	UPA 15 mg	MTX	UPA 15 mg	PBO	UPA 15mg
Total N (moderate)	[redacted]								
	Week 12			Week 12		Week 14		Week 12	
ACR20 response rate (% week 12)	[redacted]								
Clinical remission (DAS28- CRP ≤2.6) (responder %)	[redacted]								
LDA based on DAS28 (CRP) ≤ 3.2 (responder %)	[redacted]								

Abbreviations: ADA: Adalimumab; bDMARD: biological Disease Modifying Anti-Rheumatic Drugs; BMI: Body Mass Index; CDAI: Crohn's Disease Activity Index; CRP: C-Reactive Protein; DAS28: Disease Activity Score version 28; csDMARD: conventional synthetic Disease Modifying Anti-Rheumatic Drugs; DMARD: Disease Modifying Anti-Rheumatic Drugs; HAQ-DI: Health Assessment Questionnaire Disability Index; JSN: Joint Space Narrowing; mTSS: modified Total Sharp Score; MOA: Mechanism of Action; MTX: Methotrexate; PBO: Placebo; RA: Rheumatoid Arthritis; RF: Rheumatoid Factor; SD: Standard deviation; SJC66: Swollen joint count based on 66 joints; TJC68: Tender joint count based on 68 joints; TNF: Tumor Necrosis Factor; UPA: Upadacitinib;
*p<0.05; ** p<0.01; *** p<0.001 vs placebo

Table 15: Efficacy results for the full trial data set across all four registration studies

Study	SELECT-COMPARE			SELECT-NEXT		SELECT-MONOTHERAPY		SELECT-BEYOND	
Treatment	PBO	ADA	UPA 15 mg	PBO	UPA 15 mg	MTX	UPA 15 mg	PBO	UPA 15mg
Total N	N=651	N=327	N=651	N=221	N=221	N=216*	N=217*	N = 169	N = 164
ACR20 response rate (% week 12)	[redacted]								
Clinical remission (DAS28- CRP ≤2.6) (responder %)	[redacted]								
LDA based on DAS28 (CRP) ≤ 3.2 (responder %)	[redacted]								

Abbreviations: ADA: Adalimumab; bDMARD: biological Disease Modifying Anti-Rheumatic Drugs; BMI: Body Mass Index; CDAI: Crohn's Disease Activity Index; CRP: C-Reactive Protein; DAS28: Disease Activity Score version 28; csDMARD: conventional synthetic Disease Modifying Anti-Rheumatic Drugs; DMARD: Disease Modifying Anti-Rheumatic Drugs; HAQ-DI: Health Assessment Questionnaire Disability Index; JSN: Joint Space Narrowing; mTSS: modified Total Sharp Score; MOA: Mechanism of Action; MTX: Methotrexate; PBO: Placebo; RA: Rheumatoid Arthritis; RF: Rheumatoid Factor; SD: Standard deviation; SJC66: Swollen joint count based on 66 joints; TJC68: Tender joint count based on 68 joints; TNF: Tumor Necrosis Factor; UPA: Upadacitinib; * assessed at week 14

In SELECT-COMPARE, the primary outcomes of the subgroup analysis with only moderate patients showed that at week 12, [redacted]

In SELECT-NEXT, the primary outcomes of the subgroup analysis with only moderate patients demonstrated a [redacted]

In SELECT-MONOTHERAPY, the primary outcomes of the subgroup analysis with only moderate patients showed a [redacted]

In SELECT-BEYOND, the primary outcomes of the subgroup analysis with only moderate patients showed that at week 12, [redacted]

[redacted]

Results were also explored within both moderate and severe patient populations combined, stratified by rheumatoid factor status, anti-CCP status and after one and two or more csDMARD failures in order to understand the efficacy of upadacitinib in patients who could be classified as moderate RA displaying poor prognostic factors as determined by EULAR criteria. Table 16 summarises the ACR20 response at week 12 and Table 17 shows efficacy stratified by previous exposure to csDMARDs.

[redacted]

Table 16: Efficacy (% responders) for patients with poor prognostic factors* and after one and two or more csDMARD failures

	SELECT-COMPARE			SELECT-NEXT		SELECT-MONOTHERAPY		SELECT-BEYOND	
Treatment	PBO	ADA	UPA 15 mg	PBO	UPA 15 mg	MTX	UPA 15 mg	PBO	UPA 15 mg
N Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rheumatoid factor status (responder %)									
Positive	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Negative	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-CCP antibody status (responder %)									
Positive	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Negative	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA: Adalimumab; bDMARD: biological Disease Modifying Anti-Rheumatic Drugs; BMI: Body Mass Index; CDAI: Crohn's Disease Activity Index; CRP: C-Reactive Protein; DAS28: Disease Activity Score version 28; csDMARD: conventional synthetic Disease Modifying Anti-Rheumatic Drugs; DMARD: Disease Modifying Anti-Rheumatic Drugs; HAQ-DI: Health Assessment Questionnaire Disability Index; JSN: Joint Space Narrowing; mTSS: modified Total Sharp Score; MOA: Mechanism of Action; MTX: Methotrexate; PBO: Placebo; RA: Rheumatoid Arthritis; RF: Rheumatoid Factor; SD: Standard deviation; SJC66: Swollen joint count based on 66 joints; TJC68: Tender joint count based on 68 joints; TNF: Tumor Necrosis Factor; UPA: Upadacitinib; * assessed at week 14

*poor prognostic factors were measured by levels of biomarkers such as Rheumatoid factor, and Anti-CCP antibody

Table 17 Efficacy results stratified by previous csDMARD use

Study	**SELECT-COMPARE**		**SELECT-NEXT**		**SELECT-MONOTHERAPY**	
Treatment	PBO	UPA 15 mg	PBO	UPA 15 mg	MTX	UPA 15 mg
	Week 12		**Week 12**		**Week 14**	
Prior exposure to 1 csDMARD (N total)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ACR20 response rate (% week 12)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical remission (DAS28- CRP ≤2.6) (responder %)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LDA based on DAS28 (CRP) ≤ 3.2 (responder %)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior exposure to ≥ 2 csDMARDs (N total)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ACR20 response rate (% week 12)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical remission (DAS28- CRP ≤2.6) (responder %)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LDA based on DAS28 (CRP) ≤ 3.2 (responder %)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Study	SELECT-COMPARE		SELECT-NEXT		SELECT-MONOTHERAPY	
Treatment	PBO	UPA 15 mg	PBO	UPA 15 mg	MTX	UPA 15 mg
	Week 12		Week 12		Week 14	

Abbreviations: ADA: Adalimumab; bDMARD: biological Disease Modifying Anti-Rheumatic Drugs; BMI: Body Mass Index; CDAI: Crohn's Disease Activity Index; CRP: C-Reactive Protein; DAS28: Disease Activity Score version 28; csDMARD: conventional synthetic Disease Modifying Anti-Rheumatic Drugs; DMARD: Disease Modifying Anti-Rheumatic Drugs; HAQ-DI: Health Assessment Questionnaire Disability Index; JSN: Joint Space Narrowing; mTSS: modified Total Sharp Score; MOA: Mechanism of Action; MTX: Methotrexate; PBO: Placebo; RA: Rheumatoid Arthritis; RF: Rheumatoid Factor; SD: Standard deviation; SJC66: Swollen joint count based on 66 joints; TJC68: Tender joint count based on 68 joints; TNF: Tumor Necrosis Factor; UPA: Upadacitinib;

B.2.8 Meta-analysis

Whilst a meta-analysis of RCTs was theoretically feasible, the fact that a comprehensive network meta-analysis of all relevant comparators was conducted and and allowed for more precise estimates of treatment effects to be calculated meant that this approach was favoured instead of a meta-analysis of these RCT studies.

B.2.9 Indirect and mixed treatment comparisons

B.2.9.1 Analysis Scope

As head-to-head RCTs between all comparators specified in the NICE scope have not been conducted, network meta-analyses (NMA) were performed to assess the relative efficacy of upadacitinib compared with the relevant comparators in csDMARD-IR or bDMARD-IR patients with moderate-to-severe RA. The methodology of the systemic literature review (SLR) that identified studies to inform the NMAs is described in Appendix D.

B.2.9.2 Study selection for the NMA

As reported in Appendix D, a total of 55 unique studies from 207 publications were included in the NMA for csDMARD failed population studies. The list of studies excluded from NMA is available in Table 5 (Appendix D). Furthermore, a total of 12 unique studies from 68 publications were included in the NMA for bDMARD failed population studies (See Appendix D). Characteristics of studies included in the NMA are shown in Appendix D (Section D.1.1.12). The list of studies excluded from the NMA is available in Table 6 (Appendix D).

Comparators

The interventions and doses of interest included in the NMAs for the csDMARD-IR population and bDMARD-IR population are shown in Table 18. For each of the interventions included in the NMAs, only licensed doses were included in the analysis.

Table 18: Summary table of treatments included in each NMA

csDMARD experienced population	bDMARD experienced population
• csDMARD • ABA IV 10 mg/kg Q4W + csDMARD • ABA SC 125 mg QW + csDMARD • ADA SC 40 mg Q2W • ADA SC 40 mg Q2W + csDMARD • BAR oral 2 mg QD + csDMARD • BAR oral 4 mg QD + csDMARD • CTZ SC 200 mg Q2W + csDMARD • ETN SC 25 mg BIW • ETN SC 25 mg BIW + csDMARD • GOL SC 50 mg Q4W + csDMARD • IFX IV 3 mg/kg Q8W + csDMARD • Intensive csDMARD • PBO • RTX IV 2x1000 mg days 1 and 15 + csDMARD • SAR SC 200 mg Q2W • SAR SC 150 mg Q2W + csDMARD • SAR SC 200 mg Q2W + csDMARD • TCZ IV 8 mg/kg Q4W • TCZ IV 8 mg/kg Q4W + csDMARD • TCZ SC 162 mg Q2W + csDMARD • TOF oral 5 mg BID • TOF oral 5 mg BID + csDMARD • TOF oral 10 mg BID + csDMARD • UPA oral 15 mg QD • UPA oral 15 mg QD + csDMARD	• csDMARD • ABA IV 10 mg/kg Q4W + csDMARD • BAR oral 2 mg QD + csDMARD • BAR oral 4 mg QD + csDMARD • CTZ SC 200 mg Q2W + csDMARD • GOL SC 50 mg Q4W + csDMARD • RTX IV 2x1000 mg days 1 and 15 + csDMARD • SAR SC 150 mg Q2W + csDMARD • SAR SC 200 mg Q2W + csDMARD • TCZ IV 8 mg/kg Q4W + csDMARD • TCZ SC 162 mg Q2W + csDMARD • TOF oral 5 mg BID + csDMARD • TOF oral 10 mg BID + csDMARD • UPA oral 15 mg BID + csDMARD
Abbreviations: ABA = abatacept, ADA = adalimumab, BAR = baricitinib, BID = twice daily, BIW = twice weekly, CTZ = certolizumab pegol, ETN = etanercept, GOL = golimumab, IFX = infliximab, IV = intravenous, PBO = placebo, QD = once daily, QW = every week, Q2W = every two weeks, Q4W = every four weeks, Q8W = every eight weeks, RTX = rituximab, SAR = sarilumab, SC = subcutaneous, TCZ = tocilizumab, TOF = tofacitinib, UPA = upadacitinib	

B.2.9.3 Summary of trials included in the NMA

A summary of the trials included in the base case NMA and in the sensitivity analysis NMAs are described in Appendix D for the csDMARD-IR and bDMARD-IR populations, respectively. The reporting of outcomes from each study considered for inclusion is also detailed in Appendix D.

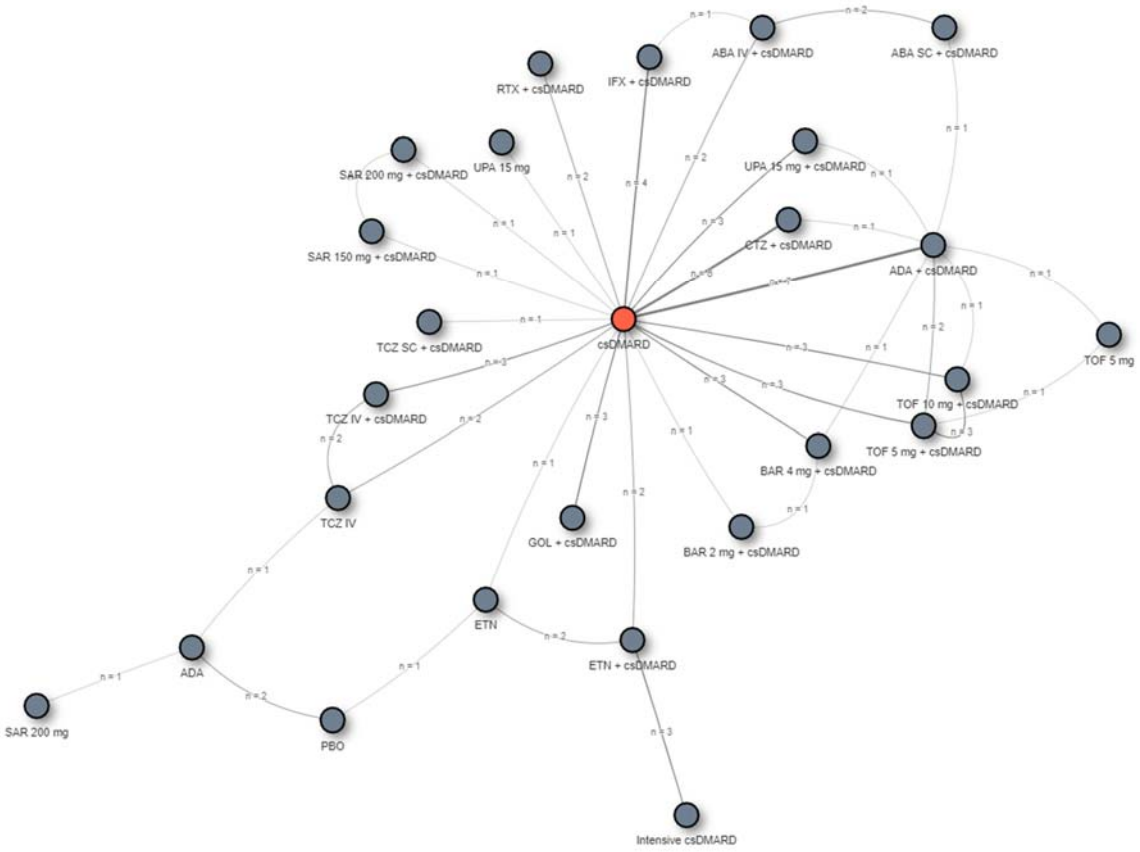
Network diagrams

The treatment networks for the RCTs included in the base case analyses for the csDMARD-IR and bDMARD-IR populations are presented below.

csDMARD-IR population

The treatment network for ACR response for the three and six month combined model in the csDMARD-IR population is presented in Figure 17.

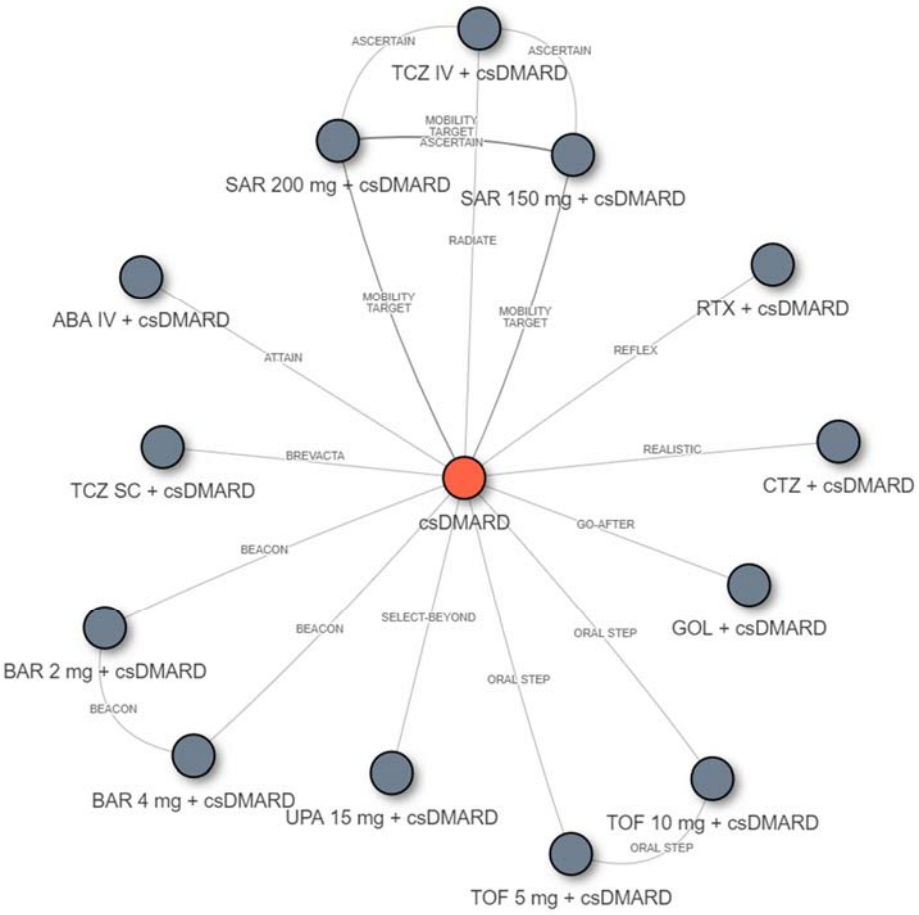
Figure 17: Network diagram of studies contributing to ACR outcomes in the three and six month combined model in the csDMARD experienced population (N=55)



bDMARD-IR population

The treatment network for ACR response for the three and six month combined model in the bDMARD-IR population is presented in Figure 18.

Figure 18: Network diagram of studies contributing to ACR outcomes in the three and six month combined model in the bDMARD experienced population (N=12)



B.2.9.4 Excluded studies

Trials identified in the clinical SLR that were not included in the NMA analyses are listed in Appendix D with the reason for exclusion.

B.2.9.6 Risk of bias

Quality assessment of included randomised controlled trials (RCTs) was conducted using the seven-criteria checklist provided in section 2.5 of the NICE single technology appraisal (STA) user guide (65). This approach is based on guidance provided by the Centre for Reviews and Disseminations for assessing the quality of studies included in systematic reviews and assesses the likelihood of selection, performance, attrition and detection bias (4). Details of the critical appraisal can be found in Table 29 and Table 30 (Appendix D).

B.2.9.7 NMA Methodology

A Bayesian NMA was conducted using an ordered multinomial likelihood with a probit link to estimate the probabilities of achieving different levels of ACR response.

The ordered probit model is designed to model a discrete dependent variable that takes ordered multinomial outcomes, such as ACR 20, 50 and 70. The probability of an outcome was calculated by estimating a latent variable as a linear function of the independent variable (randomized treatment) plus a set of threshold/cut-off points. This can be interpreted as the individual's underlying percentage change in ACR from baseline. The higher the value of the latent variable, the more likely they are to report a higher category of ACR response. For trials reporting ACR 20, 50, and 70 endpoints, patients may be in one of four mutually exclusive categories: less than ACR 20, ACR 20 to ACR 49, ACR 50 to ACR 69, or ACR 70 to 100. Hence, the range of the latent variable is divided into four intervals corresponding to these categories.

Trials report r_{ikj}, the number of patients in arm *k* of trial *i* belonging to different thresholds *j* (e.g., 20%, 50% or 70% improvement), on a common underlying continuous scale (e.g., ACR). The responses for each arm *k* of each trial *i* in category *j* will follow a multinomial distribution with probabilities p_{ijk}.

The model can be written as:

$$p_{ijk} = \Phi(\mu_i + z_j + \delta_{i,bk} I_{\{k \neq 1\}})$$

where *j* represents the different ACR response thresholds, *k* is an arm of a trial *i*, and p_{ijk} is the probability that a patient in arm *k* of trial *i* belongs to category *j*. Φ represents the standard normal cumulative distribution function, and is used to map onto the real line. The term μ_i specifies the trial-specific probability on the probit scale for achieving <20% improvement in ACR response with the reference treatment. The terms z_j specify the average differences in the probability of achieving <50% vs. <20% improvement and in achieving <70% vs. <20% improvement on the probit scale. Finally, $\delta_{i,bk}$ are the trial-specific treatment effect of the treatment arm k relative to the control treatment arm b. In other words, the pooled effect of taking the experimental treatment versus the control arm is to change the probit score of the

control arm by $\delta_{i,bk}$. This model allows inclusion of trials using different thresholds, or trials reporting different numbers of thresholds. This is the case in the current analysis, as not all included studies reported all ACR outcomes.

Using the ordered probit model makes efficient use of categorical data and guarantees coherent prediction of the probability that a patient will achieve the different levels of response on scales like ACR. By contrast, if each ACR response category was analysed separately, it would be possible to end up with a model that makes impossible predictions, for example that more patients experience a 50% improvement in ACR score than experience a 70% improvement.

To facilitate modelling, the following assumptions were made:

- Treatment effects can be considered exchangeable between trials
- Treatment effects are consistent between direct evidence and indirect evidence (i.e., the consistency equations hold)
- Category cut-offs/thresholds on the probit scale were assumed to be fixed across trials

All analyses were implemented using the statistical software R and WinBUGS, with 50,000 burn-in iterations, a thinning factor of 10, and 3 chains each with 50,000 posterior iterations. The probabilities of achieving each level of ACR response were summarized using posterior medians and their associated 95% credible intervals.

Results were generated using both random- and fixed-effects models with non-informative priors and compared for goodness of fit to the data calculated using the posterior median residual deviance. For the bDMARD experienced population, an informative prior for the between-study standard deviation (log normal with mean -2.56 and variance 1.74*1.74, which was proposed by Turner et al. 2012 (66)) was used due to the small network sample size, consistent with the recommendation provided in TA485(26). The models were also evaluated using the Deviance Information Criterion (DIC), which is a measure combining model fit and model

complexity. The model with the lowest DIC is generally considered the model with the best fit to the data.

Networks were assessed for inconsistency, through comparison of the standard consistency model with an inconsistency model as outlined in the NICE Decision Support Unit (DSU) Technical Support Document 4 (67). Posterior summaries of contrasts between treatments on the probit scale, residual deviance, the leverage or the effective number of parameters (pD) and DIC were compared from random-effects consistency and inconsistency models to assess fit and validity of consistency assumptions.

Combined three and six month ACR response model

To accommodate the breadth of data provided at the six month time point for comparators and at the 3 month time point for upadacitinib, a combined model was considered as a sensitivity analysis. In the combined NMA model, results at three and six month time points were included in the same network. Analyses were conducted using an ordered probit model using random effects with one additional parameter, $\zeta_{i,l}$, to account for the change in treatment effect from the three to six month time point across all treatments. The model can be written as:

$$p_{ijkl} = \Phi(\mu_i + z_j + \delta_{i,bk} I_{\{k \neq 1\}} + \zeta_l I_{\{l=24\}} + \eta_{i,k} I_{\{Ti=2\}})$$

where j represents the different ACR response thresholds, k is an arm of a trial i, and l is 12 or 24 representing the three or six month time points, respectively. p_{ijkl} is the probability that a patient in arm k of trial i at time point l belongs to category j. Φ represents the standard normal cumulative distribution function. The term μ_i specifies the trial-specific probability on the probit scale for achieving <20% improvement in ACR response with the reference treatment at three month time point. The terms z_j specify the average differences in the probability of achieving <50% vs. <20% improvement and in achieving <70% vs. <20% improvement on the probit scale. The term ζ_l specifies the average difference in six month vs. three month time point on the probit scale. T_i represents whether trial i has 1 or 2 time points reported (i.e., whether or not the trial reports results at both three month and six month time

points). If a trial *i* has both three and six month time points (T_i=2), the term $\underline{\eta_{i,k}}$ is a random-effects term for trial *i* in treatment arm *k* for achieving <20% improvement in ACR, which captures the correlations that arise from the fact that trial *i* contributes two time points of data. Finally, $\delta_{i,bk}$ are the trial-specific treatment effects of the treatment arm k relative to the control treatment arm b in trial i. In other words, the pooled effect of taking the experimental treatment versus the control arm is to change the probit score of the control arm by $\delta_{i,bk}$. This model allows inclusion of trials reporting outcomes at different time points.

Summary of analyses conducted

The results for the following NMA models are presented for ACR outcomes in the csDMARD experienced population:

- Base case: A random effects model combining data from the three and six month time points including an adjustment term for time point

- Sensitivity analysis 1: A random effects model conducted at the six month time point including data from SELECT-COMPARE, SELECT-NEXT and SELECT-MONOTHERAPY using an optimistic imputation approach. The optimistic approach utilized ACR response outcomes observed at six months for upadacitinib but uses data at three months for the csDMARD control arm (as data on this treatment arm was unavailable at week 24). This approach is considered optimistic since patients receiving active treatment with upadacitinib had six months to achieve response while patients on csDMARD only had three months to achieve response. It is line with the approach accepted by the NICE Appraisal Committee in the tofactinib appraisal which faces the same challenge as upadacitinib with regard to extrapolating three months trial data to six months.

- Sensitivity analysis 2: A random effects model conducted at the six month time point including data from SELECT-COMPARE, SELECT-NEXT and SELECT-MONOTHERAPY using a conservative imputation approach. In the conservative approach, data from three months was used for all treatment

arms. This approach is considered conservative since patients receiving upadacitinib had only three months to achieve response compared to 20-30 weeks for patients evaluated in other RCTs included in the NMA. It is line with the approach accepted by the NICE Appraisal Committee in the tofactinib appraisal which faces the same challenge as upadacitinib with regard to extrapolating three months trial data to six months.

The results for the following NMA models are presented for ACR outcomes in the bDMARD experienced population:

- Base case: A random effects model combining data from the three and six month time points including an adjustment term for time point
- Sensitivity analysis 1: A random effects model conducted at the six month time point including data from SELECT-BEYOND using an optimistic imputation approach
- Sensitivity analysis 2: A random effects model conducted at the six month time point including data from SELECT-BEYOND using a conservative imputation approach

B.2.9.9 Statistical assessment of heterogeneity

To assess heterogeneity and model fit across base-case and sensitivity analyses for both the csDMARD experienced population and the bDMARD experienced populations, tau, the Deviance Information Criterion (DIC), and the residual deviance are utilized. Tau measures the variance between studies. Thus, tau quantifies between study heterogeneity (i.e., a lower tau indicates a lower between-study heterogeneity). The total residual deviance assesses goodness of fit or how well the model fits the data, while the leverage, pD, provides further information on whether poorly fitting data have an effect on the model parameters. A model was considered a good fit if the total residual deviance was approximately equal to the number of data points available. The DIC is the sum of the posterior mean of the residual deviance and the leverage, pD. DIC is often considered a measure of model fit - lower values of DIC suggest a more parsimonious and better fit model.

csDMARD-IR population

Table 19 summarizes the tau heterogeneity parameter, the total residual deviance, and DIC, for base-case and sensitivity analyses.

As shown in Table 19, the 95% CrI of the tau heterogeneity parameter was estimated to be 15.3 to 52.6 in the basecase (combined three and six month model). The narrow intervals suggest that there is high probability that heterogeneity in the networks is indeed low. The total residual deviance for the base-case, was 1252.6 which can be compared with the number of data points in the model (351). The DIC for the base-case was 4214.7.

Evidence for low heterogeneity was also found in the six month networks used in sensitivity analyses 1 and 2 as shown also in Table 19.

Table 19: Heterogeneity and model fit statistics for ACR response models in csDMARD experienced RA

Analysis			Tau		Total residual deviance		DIC
	Time Point	Data Points	Posterior Median	(95% CrI)	Posterior Median	(95% CrI)	
Base case	Combined	596	28.4	(15.3, 52.6)	1252.6	(1220.2, 1290.4)	4214.7
Sensitivity Analysis 1 (Optimistic approach)	Six months	331	32.0	(14.6, 81.8)	564.6	(536.4, 598.3)	2251.0
Sensitivity Analysis 2 (Conservative approach)	Six months	331	28.9	(13.6, 68.5)	503.6	(475.6, 536.9)	2191.1

Abbreviations: CrI, credible interval; DIC, Deviance information criterion.

In addition to the heterogeneity assessment, inconsistency was tested for the NMA network by a comparison between the data in the three month NMA and an inconsistency model. In the consistency model a network that has x treatments has x-1 parameters dAB, dAC, etc. that estimate the effects of all treatments relative to treatment A. All other treatment contrasts, such as dBC, can be derived using the consistency assumption, dBC = dAC - dAB. In the inconsistency model each treatment contrast, where direct evidence is available is represented by a separate

parameter to be estimated by the model (i.e., no consistency is assumed). While this comparison is drastically underpowered for detection of inconsistency, evaluated the estimates of treatment contrasts and model fit statistics between the consistency and inconsistency models is the preferred method for evaluating inconsistency as recommended by NICE DSU 4.

Comparing the posterior estimates of the treatment effects in both three month random effects meta-analysis model, the consistency and inconsistency posterior medians are very similar. In all cases, there are overlaps in the 95% credible intervals. The consistency model has slightly smaller posterior mean of the residual deviance, effective parameters, and DIC compared to the inconsistency model.

Regarding the six month results, the consistency model has slightly smaller posterior mean of the residual deviance, effective parameters, and DIC compared to the inconsistency model. Therefore, there is no evidence that the NMA estimates are internally inconsistent at either three or six months.

For the details of the inconsistency models, please refer to Appendix D.

bDMARD-IR population

Table 20 summarizes the tau heterogeneity parameter, the total residual deviance, and DIC, for base-case and sensitivity analyses.

The posterior median estimates for tau suggest that there was low heterogeneity across the networks. In addition, the 95% CrI of the tau heterogeneity parameter was estimated to be from 6.5 to 331.1 in the base-case (combined three and six month model) and 5.8 to 305.8 in sensitivity analysis 1 (optimistic approach), and 5.6 to 304.4 in sensitivity analysis 2 (conservative approach). The total residual deviance for the base-case and sensitivity analysis 1-2 was 179.0, 98.7, and 107.3, respectively, which can be compared to the number of data points in each model (87, 72 and 72). The DIC for the base-case and sensitivity analysis 1-2 were 780.8, 439.4, and 447.9, respectively.

Table 20: Heterogeneity and model fit statistics for ACR response models in bDMARD experienced RA

Analysis	Time Point	Data Points	Tau		Total residual deviance		
			Posterior Median	(95% CrI)	Posterior Median	(95% CrI)	DIC
Base case	Combined	129	44.3	(6.5, 331.1)	179.0	(165.9, 196.8)	780.8
Sensitivity Analysis 1 (Optimistic approach)	Six months	72	38.2	(5.8, 305.8)	98.7	(87.6, 114.6)	439.4
Sensitivity Analysis 2 (Conservative approach)	Six months	72	38.2	(5.6, 304.4)	107.3	(96.3, 123.3)	447.9
Abbreviations: CrI, credible interval; DIC, Deviance information criterion							

In addition to the heterogeneity assessment, inconsistency was also tested for the bDMARD-IR NMA network. However, there were no head-to-head trials for the biologic experienced RA population. Thus, by definition, there cannot be any inconsistency between indirect and direct evidence.

B.2.9.10 Justification of Fixed Effects or Random Effects Analyses

Fixed- and random-effects Bayesian models were fitted for all populations for all the base-case models. The fixed effects model assumes that all studies have the same true effect, while the random effects model assumes that the studies differ from each other and should individually impact the treatment effect. Statistical measures including total residual deviance and DIC were used to assess the goodness of fit for fixed- and random-effect models. The total residual deviance assesses goodness of fit or how well the model fits the data (68). A model was considered a good fit if the total residual deviance was approximately equal to the number of data points available. The DIC is the sum of the posterior mean of the residual deviance and the leverage, pD. DIC is often considered a measure of model fit - lower values of DIC suggest a more parsimonious model, thus a better fit one (69). For the csDMARD population, the residual deviance and DIC are much lower for the random effects model, and thus it can be safely concluded that the random effects model is

preferable to the fixed effects model. For the bDMARD population, the random effects model has slightly lower residual deviance and slightly higher for the DIC compared with the fixed effects model. Given the similarity in values between the random effects and fixed effects model, either model is justifiable, and random effects is preferred because it is more robust to potential heterogeneity.

csDMARD-IR population

Goodness of fit diagnostics for the random effects and fixed effects models for the base-case network in csDMARD experienced RA are provided in Table 21. The random effects model had lower total residual deviance and DIC compared with the fixed effects model and therefore random effects model is the preferred model.

Table 21: Fixed- and random-effect model fit statistics in csDMARD experienced RA base-case analysis (combined three and six month)

Analysis	Time Point	Data Points	Total residual deviance		DIC
			Posterior Median	(95% CrI)	
Random effects	Combined	596	1252.6	(1220.2, 1290.4)	4214.7
Fixed effects	Combined	596	1415.9	(1407.6, 1444.7)	4331.7
Abbreviations: CrI, credible interval; DIC, Deviance information criterion					

bDMARD-IR population

Goodness of fit diagnostics for the random effects and fixed effects models for the base-case network in bDMARD experienced RA are provided in Table 22. The random effects model had similar total residual deviance and DIC compared with the fixed effects model. The random effects model was chosen based on similar fit due to its ability to estimate between trial deviations appropriately.

Table 22: Fixed- and random-effect model fit statistics in bDMARD experienced RA base-case analysis (combined three and six month)

Analysis	Time Point	Data Points	Total residual deviance		DIC
			Posterior Median	(95% CrI)	
Random effects (base case)	Combined	129	179	(165.9, 196.8)	780.8
Fixed effects (base case)	Combined	129	183.6	(182.8, 191.7)	777.3
Abbreviations: CrI, credible interval; DIC, Deviance information criterion					

B.2.9.8 Results of the NMA

B.2.9.8.1 Base Case analyses

csDMARD-IR: Combined three and six month ACR response model

ACR 20 response rates

In csDMARD-IR patients, a significant difference in ACR 20 response rates was observed in upadacitinib combination therapy and upadacitinib monotherapy compared to placebo [redacted] Similarly, a significant difference in ACR 20 response rates were observed in upadacitinib combination therapy and upadacitinib monotherapy compared to csDMARDs [redacted] However, no significant difference in ACR 20 response rates was observed in upadacitinib combination therapy, upadacitinib monotherapy versus other comparators.

ACR 50 and 70 response rates

A significant difference in ACR 50 response rates was observed in upadacitinib combination therpy and upadacitinib monotherapy compared to placebo [redacted] and [redacted]. Similarly, a significant difference in ACR 50 response rates were observed in upadacitinib combination therapy and upadacitinib monotherapy compared to csDMARD [redacted] However, no significant

difference was observed in ACR 50 response rates for upadacitinib combination therapy and upadacitinib monotherapy versus other comparators.

Similarly, a significant difference in ACR 70 response rates was observed in upadacitinib combination therapy and upadacitinib monotherapy compared to placebo [redacted] and [redacted] versus [redacted] A significant difference in ACR 70 response rates was also observed in upadacitinib combination therapy and upadacitinib monotherapy compared to csDMARD [redacted] However, no significant difference was observed in ACR 70 response rates for upadacitinib combination therapy, upadacitinib monotherapy versus other comparators.

ACR 20, 50 and 70 response rates at Week 24 for the csDMARD-IR population are presented in Table 23.

Table 23: Base case: Combined model with random effects in csDMARD experienced RA: absolute probabilities of achieving ≥20, ≥50 or ≥70 ACR response for each treatment – week 24

	ACR 20		ACR 50		ACR 70	
Treatment	**Posterior Median**	**(95% CrI)**	**Posterior Median**	**(95% CrI)**	**Posterior Median**	**(95% CrI)**
csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abatacept 10 mg/kg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abatacept 125 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab 40 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab 40 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baricitinib 2 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baricitinib 4 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Certolizumab 200 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept 50 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept 50 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	ACR 20		ACR 50		ACR 70	
Treatment	**Posterior Median**	**(95% CrI)**	**Posterior Median**	**(95% CrI)**	**Posterior Median**	**(95% CrI)**
Golimumab 50 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab 3 mg/kg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Intensive csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rituximab 2000 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sarilumab 150 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sarilumab 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sarilumab 200 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tocilizumab 8 mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tocilizumab 8 mg/kg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tocilizumab 162 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tofacitinib 10 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tofacitinib 5 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tofacitinib 5 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Upadacitinib 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Upadacitinib 15 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ACR, American College of Rheumatology; csDMARD, conventional synthetic disease modifying antirheumatic drug; CrI, credible interval; RA, rheumatoid arthritis.

[redacted]

[redacted]

EULAR response rates

EULAR response is a classified response criteria which classifies the patients as non-, moderate or good responders dependent on both the absolute DAS28 score at endpoint and the improvement in DAS28 (70). A detailed definition can be found in Table 24.

Table 24: Definition of EULAR response

DAS28 at endpoint	Improvement in DAS28 ≤ 1.2	Improvement in DAS28 > 0.6 and ≤ 1.2	Improvement in DAS28 ≤ 0.6
≤3.2	good	moderate	none
>3.2 and ≤5.1	moderate	moderate	none
>5.1	moderate	none	none

EULAR response rates at six months for the csDMARD-IR population are presented in Table 25.

Table 25: Base case: Treatment comparison of six month estimated EULAR response mapped from the network meta-analysis ACR outcomes in csDMARD-experienced RA from combined three/six month network

Treatment	No Response (95% CrI)	Moderate Response (95% CrI)	Good Response (95% CrI)
Placebo	[redacted]	[redacted]	[redacted]
csDMARD	[redacted]	[redacted]	[redacted]

Treatment	No Response (95% CrI)	Moderate Response (95% CrI)	Good Response (95% CrI)
Intensive csDMARD	[redacted]	[redacted]	[redacted]
Etanercept 50 mg	[redacted]	[redacted]	[redacted]
Adalimumab 40 mg	[redacted]	[redacted]	[redacted]
Tofacitinib 5 mg	[redacted]	[redacted]	[redacted]
Sarilumab 150 mg + csDMARD	[redacted]	[redacted]	[redacted]
Sarilumab 200 mg	[redacted]	[redacted]	[redacted]
Rituximab 2000 mg + csDMARD	[redacted]	[redacted]	[redacted]
Infliximab 3 mg/kg + csDMARD	[redacted]	[redacted]	[redacted]
Abatacept 125 mg + csDMARD	[redacted]	[redacted]	[redacted]
Abatacept 10 mg/kg + csDMARD	[redacted]	[redacted]	[redacted]
Etanercept 50 mg + csDMARD	[redacted]	[redacted]	[redacted]
Baricitinib 2 mg + csDMARD	[redacted]	[redacted]	[redacted]
Adalimumab 40 mg + csDMARD	[redacted]	[redacted]	[redacted]
Upadacitinib 15 mg	[redacted]	[redacted]	[redacted]
Tofacitinib 5 mg + csDMARD	[redacted]	[redacted]	[redacted]
Baricitinib 4 mg + csDMARD	[redacted]	[redacted]	[redacted]
Tocilizumab 162 mg + csDMARD	[redacted]	[redacted]	[redacted]
Golimumab 50 mg + csDMARD	[redacted]	[redacted]	[redacted]
Sarilumab 200 mg + csDMARD	[redacted]	[redacted]	[redacted]
Tocilizumab 8 mg/kg + csDMARD	[redacted]	[redacted]	[redacted]
Tocilizumab 8 mg/kg	[redacted]	[redacted]	[redacted]
Tofacitinib 10 mg + csDMARD	[redacted]	[redacted]	[redacted]
Upadacitinib 15 mg + csDMARD	[redacted]	[redacted]	[redacted]
Certolizumab 200 mg + csDMARD	[redacted]	[redacted]	[redacted]

Abbreviations: ACR, American College of Rheumatology; csDMARD, conventional synthetic disease modifying antirheumatic drug; CrI, credible interval; EULAR, European League Against Rheumatism; RA, rheumatoid arthritis.

Since the EULAR response data is mapped from the ACR20/50/70 estimates the treatments show a similar ranking to those seen for the ACR NMAs.

[redacted]

[redacted]

bDMARD-IR: Combined three and six month ACR response model

ACR 20 response rates

In bDMARD-IR patients, a significant difference in ACR 20 response rates was observed in upadacitinib combination therapy compared to csDMARDs [redacted]

However, no significant difference in ACR 20 response rates was observed in upadacitinib combination therapy, upadacitinib monotherapy versus other comparators.

ACR 50 and 70 response rates

Similar to the difference in ACR 20 response rates, a significant difference in ACR 50, and 70 response rates was also observed in upadacitinib combination therapy compared to csDMARDs:

- ACR 50 response rates: [redacted]
- ACR 70 response rates: [redacted]

However, no significant difference was in ACR 50 and 70 response rates observed in upadacitinib combination therapy and other comparators.

[redacted]

[redacted]

Table 26: Base case: Combined model with random effects in bDMARD experienced RA: absolute probabilities of achieving ≥20, ≥50 or ≥70 ACR response for each treatment – six months

	ACR 20		ACR 50		ACR 70	
Treatment	**Posterior Median**	**(95% CrI)**	**Posterior Median**	**(95% CrI)**	**Posterior Median**	**(95% CrI)**
csDMARD	[redacted]					
Abatacept 10 mg/kg + csDMARD						
Baricitinib 2 mg + csDMARD						
Baricitinib 4 mg + csDMARD						
Certolizumab 200 mg + csDMARD						
Golimumab 50 mg + csDMARD						
Rituximab 2000 mg + csDMARD						
Sarilumab 150 mg + csDMARD						
Sarilumab 200 mg + csDMARD						
Tocilizumab 8 mg/kg + csDMARD						
Tocilizumab 162 mg + csDMARD						
Tofacitinib 10 mg + csDMARD						
Tofacitinib 5 mg + csDMARD						
Upadacitinib 15 mg + csDMARD						

Abbreviations: ACR, American College of Rheumatology; csDMARD, conventional synthetic disease modifying antirheumatic drug; CrI, credible interval; RA, rheumatoid arthritis.

EULAR response rates

There are were no statistical differences between the treatments. Since the EULAR response data is mapped from the ACR20/50/70 estimates the treatments show a similar ranking to those seen for the ACR NMAs. EULAR response rates at six months for the bDMARD-IR population are presented in Table 27.

[redacted]

Table 27: Base case: Treatment comparison of six month estimated EULAR response mapped from the network meta-analysis ACR outcomes in bDMARD-experienced RA from combined three/six month network

Treatment	No Response (95% CrI)[1]	Moderate Response (95% CrI)[1]	Good Response (95% CrI)[1]
csDMARD	[redacted]	[redacted]	[redacted]
Certolizumab 200 mg + csDMARD	[redacted]	[redacted]	[redacted]
Baricitinib 2 mg + csDMARD	[redacted]	[redacted]	[redacted]
Golimumab 50 mg + csDMARD	[redacted]	[redacted]	[redacted]
Tofacitinib 5 mg + csDMARD	[redacted]	[redacted]	[redacted]
Sarilumab 150 mg + csDMARD	[redacted]	[redacted]	[redacted]
Baricitinib 4 mg + csDMARD	[redacted]	[redacted]	[redacted]
Tofacitinib 10 mg + csDMARD	[redacted]	[redacted]	[redacted]
Sarilumab 200 mg + csDMARD	[redacted]	[redacted]	[redacted]
Abatacept 10 mg/kg + csDMARD	[redacted]	[redacted]	[redacted]
Upadacitinib 15 mg + csDMARD	[redacted]	[redacted]	[redacted]
Rituximab 2000 mg + csDMARD	[redacted]	[redacted]	[redacted]
Tocilizumab 162 mg + csDMARD	[redacted]	[redacted]	[redacted]
Tocilizumab 8 mg/kg + csDMARD	[redacted]	[redacted]	[redacted]

Abbreviations: ACR, American College of Rheumatology; csDMARD, conventional synthetic disease modifying antirheumatic drug; EULAR, European League Against Rheumatism; RA, rheumatoid arthritis.

B.2.9.8.2 Sensitivity analyses

In addition to the base case analyses, two sensitivity analyses (SA) were performed for both csDMARD-IR and bDMARD-IR populations.

In the csDMARD experienced population:

- Sensitivity analysis 1: A random effects model conducted at the six month time point including data from SELECT-COMPARE, SELECT-NEXT and SELECT-MONOTHERAPY using an optimistic imputation approach

- Sensitivity analysis 2: A random effects model conducted at the six month time point including data from SELECT-COMPARE, SELECT-NEXT and SELECT-MONOTHERAPY using a conservative imputation approach

In the bDMARD experienced population:

- Sensitivity analysis 1: A random effects model conducted at the six month time point including data from SELECT-BEYOND using an optimistic imputation approach

- Sensitivity analysis 2: A random effects model conducted at the six month time point including data from SELECT-BEYOND using a conservative imputation approach

B.2.9.8.2.1 csDMARD-IR

Optimistic imputation SA compared to base case – csDMARD-IR NMA

Comparing the percentage of total EULAR responders (both good and moderate) between the base case (three/six month combined model) csDMARD-IR NMA and the optimistic imputation SA NMA shows:

- Upadacitinib combination therapy has one percentage point less total responders in the optimistic SA. [redacted]
- Upadacitinib monotherapy has the same total percentage responders in both NMAs and has the same ranking in both as well [redacted]
- All comparators have the same or reduced percentage points of total responders in the optimistic SA (with the highest reduction being 5% points).

Conservative imputation SA compared to base case – csDMARD-IR NMA

The conservative imputation SA NMA was used as the basis of efficacy in scenario analysis 4 presented in Table 83.

Comparing the percentage of total EULAR responders (both good and moderate) between the base case (three/six month combined model) csDMARD-IR NMA and the conservative imputation SA NMA shows:

- Upadacitinib combination therapy has one percentage point less total responders in the conservative SA. [redacted]
- Upadacitinib monotherapy has three percentage points less total responders in thew conservative NMA and [redacted]
- All comparators have the same or a reduced percentage points of total responders in the conservative SA (with the highest reduction being 5% points).

ACR 20, 50 and 70, and EULAR response rates at three and six months for the csDMARD-IR population are presented in Appendix D.

B.2.9.8.2.2 bDMARD-IR

Optimistic imputation SA compared to base case – bDMARD-IR NMA

Comparing the percentage of total EULAR responders (both good and moderate) between the base case (three/six month combined model) bDMARD-IR NMA and the optimistic imputation SA NMA shows:

- Upadacitinib combination therapy has one percentage point more total responders in the optimistic SA. [redacted]

- All comparators show a slight improvement to a small reduction in the percentage points of total responders in the optimistic SA (1% point improvement to a 4% percentage point reduction).

Conservative imputation SA compared to base case – bDMARD-IR NMA

Comparing the percentage of total EULAR responders (both good and moderate) between the base case (three/six month combined model) bDMARD-IR NMA and the conservative imputation SA NMA shows:

- Upadacitinib combination therapy has three percentage points fewer total responders in the conservative SA. [redacted]
- All comparators show a slight improvement to a small reduction in the percentage points of total responders in the conservative SA (1% point improvement to a 4% percentage point reduction).

ACR 20, 50 and 70 and EULAR response rates at three months and six months for the bDMARD-IR population are presented in Appendix D.

The conservative imputation NMA has been used as the basis of one of the scenario analyses shown in Table 86.

B.2.9.11 Uncertainties in the indirect and mixed treatment comparisons

The presence and extent of between-study heterogeneity among studies included in the NMA was explored for key patient baseline characteristics as well as the statistical assessment of heterogeneity across base-case and sensitivity analyses (See section 2.9.9). This did not point to major between-study heterogeneity. The model fit measures to identify the most reliable estimates of treatment effect suggested that the baseline risk-adjusted NMA provided the best fit for the ACR20/50/70 response, and therefore was selected as the base-case analysis. Supported by the assessment on risk of bias and heterogeneity, the results of this NMA appear to be relatively robust.

B.2.9.12 Conclusion

In the csDMARD experience RA population, the EULAR base case NMA [redacted] Relative treatment rankings from the base-case model are mostly preserved in the sensitivity analyses.

For the biologic experienced RA population, the EULAR base case NMA results show that [redacted] Relative treatment rankings from the base-case model are mostly preserved in the sensitivity analyses.

B.2.10 Adverse reactions

The safety profile of upadacitinib was comparable with placebo and adalimumab regardless of patient and disease characteristics in the extensive upadacitinib clinical development program. Across the four registration studies there were only two serious adverse event (SAE) reported by >0.5% of upadacitinib 15mg group.

Two deaths were reported among the four registration studies in the upadacitinib 15mg group, one due to haemorrhagic stroke and the other cardiac arrest. Mortality rates of Upadacitinib 15mg are comparable to comparator arms across the clinical trial programme.

- Upadacitinib 15 mg has a favourable safety and tolerability profile in patients with moderate to severe active RA: frequencies of serious AEs <7.5% were observed throughout the Phase III clinical trial programs, serious infections were reported in similar frequencies to bDMARD comparators, while malignancies and major adverse cardiovascular events (MACE) events were uncommon.

- Upadacitinib 15 mg was generally well tolerated by patients. Across all the four pivotal trials of upadacitinib, it showed comparable safety as compared to placebo and/or other active comparators (adalimumab and methotrexate).

- Upadacitinib did not show many serious AEs in more than 0.5% of patients in any of the four trials. The frequency of the serious AEs was below 7.5% in patients throughout all the trials. The incidence of any serious infections was similar to the active comparators. Incidence of malignancies and MACE events was uncommon. There were no new safety concerns.

- The most commonly reported adverse events reactions events occurring in ≥ 2% of patients treated with upadacitinib were upper respiratory tract infections, nausea, cough and increased blood creatine phosphokinase (CPK). Additional details on the adverse reactions reported during SELECT-COMPARE, SELECT-NEXT, SELECT-MONOTHERAPY and SELECT-BEYOND are presented in Appendix F in section 2.2.

B.2.10.1 Summary of safety data from SELECT-COMPARE

A summary of the safety events reported during the placebo-controlled and active-comparator period up to Week 26 for the SELECT-COMPARE study is outlined in Table 28.

Upadacitinib, at a dose of 15mg, generally showed a safety profile consistent with previously reported results from Phase II clinical trials, with no new safety signals detected. Through week 14 the serious AEs reported were similar across all groups and were observed in 2.8% patients receiving upadacitinib 15 mg QD + MTX, 2.4% patients receiving adalimumab 40 mg + MTX, and 2.1% patients receiving placebo + MTX. Through week 26, serious AEs were observed in 3.7% patients receiving upadacitinib 15 mg QD + MTX, 4.3% patients receiving adalimumab 40 mg + MTX, and 2.9% patients receiving placebo + MTX. Severe AE (Grade 3 or above) of any type were observed in 4.5% patients receiving upadacitinib 15 mg QD + MTX, 4.6% patients receiving adalimumab 40 mg + MTX, and 4.0% patients receiving placebo + MTX. A small proportion of patients discontinued treatment due to AEs at week 26, with the rate of discontinuation reported in the upadacitinib group (3.7%) lower than

that reported in the adalimumab group (6.1%). There were no deaths reported in the upadacitinib group while there were two deaths in the adalimumab group (0.6%) and two deaths in the placebo group (0.3%) through week 26 (59).

Table 28: Summary of key safety events from SELECT-COMPARE

	SELECT-COMPARE					
	Week 14			Week 26		
	PBO (N=651)	ADA (N=327)	UPA (N=651)	PBO (N=651)	ADA (N=327)	UPA (N=651)
Any AE, n (%)	303 (46.5)	158 (48.3)	348 (53.5)	347 (53.2)	197 (60.2)	417 (64.2)
Any SAE, n (%)	14 (2.1)	8 (2.4)	18 (2.8)	19 (2.9)	14 (4.3)	24 (3.7)
Any AE leading to discontinuation of study drug, n (%)	12 (1.8)	16 (4.9)	18 (2.8)	15 (2.3)	20 (6.1)	24 (3.7)
Any severe AE[a], n (%)	22 (3.4)	10 (3.1)	20 (3.1)	26 (4.0)	15 (4.6)	29 (4.5)
Any AE with reasonable possibility of being related to study drug[b], n (%)	119 (18.3)	74 (22.6)	174 (26.8)	144 (22.1)	94 (28.7)	212 (32.6)
Any AE leading to death, n (%)	2 (0.3)	1 (0.3)	0	2 (0.3)	2 (0.6)	0
Deaths[c], n (%)	2 (0.3)	1 (0.3)	0	2 (0.3)	2 (0.6)	0

Abbreviations: AE: Adverse event; PBO: Placebo; ADA: Adalimumab; SAE: Serious adverse event; UPA: Upadacitinib
a: Severe AEs were defined as events with Grade 3 or above based on the Rheumatology CTC for AEs
b: As assessed by investigator
c: Any death including non-treatment-emergent deaths

The most frequently reported AEs (≥5% of patients) in week 26, the upadacitinib group were upper respiratory tract infection (5.7%) and nasopharyngitis (5.5%). There were no individual categories of SAEs reported by ≥0.5% of upadacitinib group. The most commonly reported SAEs in the upadacitinib group were appendicitis (0.3%), gastroenteritis (0.3%) and spontaneous abortion (0.3%) (59). (Appendix F).

Serious infections occurred in 1.8%, 1.5%, and 0.8% patients treated with upadacitinib 15 mg QD + MTX, adalimumab 40 mg + MTX, and placebo + MTX, respectively. No adjudicated MACE was reported in the upadacitinib group through week 26. Through Week 14, oral candidiasis was reported in two subjects in the upadacitinib group and one subject in the adalimumab group. There were two

patients with MACE in the adalimumab group (0.6%) and three in the placebo group (0.5%) through week 26. Only one patient had renal dysfunction in the adalimumbab group (0.3%). Gastroenteritis was reported by 3 patients in the placebo group (0.5%) and 2 patients in the updacitinib 15mg group (0.3%) through 26 weeks. For adjudicated venous thromboembolic events (VTE) through week 26, one patient had deep vein thrombosis (DVT) (0.2%) and another had a pulmonary embolism (PE) (0.2%) in the upadacitinib group, three patients had a PE in the adalimumab group (0.9%) and one had a PE in the placebo group (0.2%) (59). (Appendix F)

B.2.10.2 Summary of safety data from SELECT-NEXT

A summary of the safety events reported during the placebo-controlled period (Period 1) for the SELECT-NEXT study is outlined in Table 29.

Upadacitinib, at a dose of 15mg and 30 mg, generally showed a safety profile consistent with previously reported results from Phase II clinical trials, with no new safety signals detected (51). Through week 12, serious AEs were observed in 4.1% patients receiving upadacitinib 15 mg QD + csDMARDs, 2.7% patients receiving upadacitinib 30 mg QD + csDMARDs, and 2.3% patients receiving placebo + csDMARDs. Any category of severe AE (Grade 3 or above) was observed in 3.6% patients receiving upadacitinib 15 mg QD, 3.2% patients receiving upadacitinib 30 mg, and 2.3% patients receiving placebo + MTX. AEs leading to discontinuation were similar in the placebo + csDMARDs (3.2%) and upadacitinib 15 mg QD + csDMARDs groups (3.2%), and higher in the upadacitinib 30 mg QD + csDMARDs group (5.9%). However, no more than one patient in any treatment group discontinued due to a specific AE, with the exception of pneumonia (reported in two patients in upadacitinib 30 mg + csDMARDs). There were no deaths reported in any group through week 12 (60).

Table 29: Summary of key safety events from SELECT-NEXT

	SELECT-NEXT		
	Week 12		
	PBO (N=221)	UPA 15 mg (N=221)	UPA 30 mg (N=219)
Any AE, n (%)	108 (48.9)	125 (56.6)	118 (53.9)

	SELECT-NEXT		
	Week 12		
	PBO (N=221)	UPA 15 mg (N=221)	UPA 30 mg (N=219)
Any SAE, n (%)	5 (2.3)	9 (4.1)	6 (2.7)
Any AE leading to discontinuation of study drug, n (%)	7 (3.2)	7 (3.2)	13 (5.9)
Any severe AE[a], n (%)	5 (2.3)	8 (3.6)	7 (3.2)
Any AE with reasonable possibility of being related to study drug[b], n (%)	45 (20.4)	47 (21.3)	52 (23.7)
Any AE leading to death, n (%)	0	0	0
Deaths[c], n (%)	0	0	0

Abbreviations: AE: Adverse event; PBO: Placebo; ADA: Adalimumab; SAE: Serious adverse event; UPA: Upadacitinib
a: Severe AEs were defined as events with Grade 3 or above based on the Rheumatology CTC for AEs
b: As assessed by investigator
c: Any death including non-treatment-emergent deaths

The most frequently reported AEs (≥5% of patients) in the upadacitinib 15 mg group were nausea (7.2%), nasopharyngitis (5.4%) and upper respiratory tract infection (5.4%), while those reported in the upadacitinib 30 mg group were nasopharyngitis (5.9%) and upper respiratory tract infection (5.5%) (60). There was one category of SAE reported by ≥0.5% of upadacitinib 15 mg group, which was a wrist fracture reported by 2 (0.9%) patients. Other most commonly reported SAEs in the upadacitinib 15 mg group were coronary artery disease (0.5%), enterocolitis infectious (0.5%), spinal compression fracture (0.5%), osteoarthritis (0.5%), ovarian germ cell teratoma benign (0.5%), suicide attempt (0.5%) and nephrolithiasis (0.5%), while those reported in upadacitinib 30 mg group were varicella zoster virus infection (0.5%), viral upper respiratory tract infection (0.5%), wound infection staphylococcal (0.5%), osteoarthritis (0.5%), B-cell small lymphocytic lymphoma (0.5%), chronic lymphocytic leukaemia (0.5%) and ischaemic stroke (0.5%) (60). (Appendix F).

A higher incidence of infection was reported in the upadacitinib 15 mg QD + csDMARDs (64 of 221 [29.0%]) and 30 mg + csDMARDs (69 of 219 [31.5%]) treatment groups compared to placebo + csDMARDs (47 of 221 [21.3%]). Serious infections were reported in the upadacitinib 15 mg QD + csDMARDs and placebo + csDMARDs groups once each, respectively, and three times in the upadacitinib 30 mg + csDMARDs group. Three opportunistic infections were reported in the upadacitinib 30 mg + csDMARDs group, and one was reported in the placebo +

csDMARD group. Oral candidiasis were reported in 2 subjects (0.9%) in upadacitinib 30 mg and 1 subject (0.5%) in placebo. There were three cases of herpes zoster, one in each treatment arm; all were reported to involve a single dermatome. Diarrhoea was reported in 1.5% of patients in the upadacitinib 15mg group and 2.7% of patients in the placebo group through 12 weeks. One MACE event occurred in the upadacitinib 30 mg group. No deaths, gastrointestinal perforation, renal dysfunction or venous thromboembolic events (pulmonary embolism or deep vein thrombosis) were reported (60). (Appendix F).

B.2.10.3 Summary of safety data from SELECT-MONOTHERAPY

A summary of the safety events reported during the controlled period (Period 1) for the SELECT-MONOTHERAPY study is outlined in Table 30.

Through Week 14, TEAEs occurred at similar frequencies in the cMTX (47.2%), upadacitinib 15 mg QD (47.5%) and upadacitinib 30 mg QD (48.8%) groups. SAEs were more frequently observed in upadacitinib 15 mg QD group (5.1%) as compared to cMTX and upadacitinib 30 mg QD groups (2.8% each). The percentage of subjects with TEAEs leading to discontinuation of study drug was low across all treatment groups. One death was reported in the upadacitinib 15 mg group. The cause of the death was reported as haemorrhagic stroke due to a ruptured aneurysm.

Table 30: Summary of key safety events from SELECT-MONOTHERAPY

	Week 14		
	cMTX (N=216)	**UPA 15 mg QD (N=217)**	**UPA 30 mg (N=215)**
Any AE, n (%)	102 (47.2)	103 (47.5)	105 (48.8)
Any SAE, n (%)	6 (2.8)	11 (5.1)	6 (2.8)
Any AE leading to discontinuation of study drug, n (%)	6 (2.8)	8 (3.7)	6 (2.8)
Any severe AE, n (%)	5 (2.3)	7 (3.2)	9 (4.2)
Any AE with reasonable possibility of being related to study drug[a], n (%)	43 (19.9)	49 (22.6)	56 (26.0)
Any AE leading to death, n (%)	0	1 (0.5)	0
Deaths[b], n (%)	0	1 (0.5)	0

Abbreviations: AE: Adverse event; cMTX: continuing methotrexate; SAE: Serious adverse event; UPA: Upadacitinib
a: As assessed by investigator
b: Any death including non-treatment-emergent deaths

None of the treatment groups reported AEs in ≥5% of patients. The most frequently reported AEs (>2% of patients) in the upadacitinib 15 mg QD treatment group were urinary tract infection (4.1%), upper respiratory tract infection (4.1%), Blood creatine phosphokinase increased (2.3%) and bronchitis (1.8%) (Appendix F, Table 7). SAEs were reported in no more than one subject in any treatment group, with the exception of cholelithiasis, which was reported in two subjects in the upadacitinib 30 mg group, and acute cholecystitis, which was reported in two subjects in the cMTX group (Appendix F, Table 8).

In Week 14, the most frequently reported serious AEs (≥ 5 subjects in any treatment group) were the following: any hepatic disorder (all but 1 case were due to elevation of transaminases), any herpes zoster, and any creatine phosphokinase (CPK) elevation. The treatment-emergent serious infections reported were limb abscess (one subject in the upadacitinib 15 mg group) and urosepsis (one subject in the cMTX group). Oral candidiasis was reported in two subjects in the upadacitinib 30 mg group. One MACE event occurred in the upadacitinib 15mg group (0.5%) and two events in the 30mg group (0.9%). There were no reports of renal dysnfunction in any group. (Appendix F, Table 9).

B.2.10.4 Summary of safety data from SELECT-BEYOND

A summary of the safety events reported during the placebo-controlled period (Period 1) for the SELECT-BEYOND study is outlined in Table 31.

Through week 12, TEAEs occurred at similar frequencies in the placebo + csDMARDs (56.2%) and upadacitinib 15 mg QD + csDMARDs (55.5%) groups but were numerically higher in the upadacitinib 30 mg QD + csDMARDs group (67.3%). A similar trend was observed in week 24. SAEs were also more frequent in the upadacitinib 30 mg QD + csDMARDs group (7.3%) versus upadacitinib 15 mg QD + csDMARDs (4.9%); none occurred in the placebo + csDMARDs group. Between weeks 12 and 24, AEs and SAEs occurred at similar frequencies in patients who had received upadacitinib 15 mg or 30 mg + csDMARDs from baseline but were reported more frequently among patients who switched from placebo + csDMARDs to

upadacitinib + csDMARDs compared to those who received upadacitinib + csDMARDs from baseline (63).

Through week 12, more AEs leading to discontinuation of study drug occurred in the upadacitinib 30 mg QD + csDMARDs group (9.1%) versus upadacitinib 15 mg QD + csDMARDs (2.4%) and placebo + csDMARDs (5.3%). Between week 12 and 24, AEs leading to discontinuation of study drug were comparable across all groups. In week 12, 5.3% patients in placebo + csDMARDs, 2.4% patients in upadacitinib 15 mg QD + csDMARDs and 9.1% patients in upadacitinib 30 mg QD + csDMARDs group reported AEs (such as worsening of RA, pneumonia, and prostate cancer) leading to discontinuation of study drug. Two deaths were reported, one death in the upadacitinib 30 mg QD + csDMARDs group was reported in the first 12 weeks, due to cardiac failure and pulmonary embolism. The second death, reported between weeks 12 and 24, was an unwitnessed death in the upadacitinib 15 mg QD + csDMARDs group due to cardiac arrest, adjudicated as an undetermined or unknown cause of death (63).

Table 31: Summary of key safety events from SELECT-BEYOND

	Weeks 0–12			Weeks 12–24			
	PBO	UPA 15 mg	UPA 30 mg	PBO to UPA 15 mg	PBO to UPA 30 mg	UPA 15 mg	UPA 30 mg
	n=169	n=164	n=165	n=72	n=75	n=156	n=148
AE	95 (56%)	91 (55%)	111 (67%)	30 (42%)	50 (67%)	82 (53%)	83 (56%)
AE leading to discontinuation	9 (5%)	4 (2%)	15 (9%)	2 (3%)	3 (4%)	5 (3%)	5 (3%)
SAE	0	8 (5%)	12 (7%)	5 (7%)	5 (7%)	5 (3%)	5 (3%)
Infection	51 (30%)	54 (33%)	55 (33%)	16 (22%)	31 (41%)	43 (28%)	47 (32%)
Serious infection	0	1 (1%)	4 (2%)	2 (3%)	1 (1%)	1 (1%)	2 (1%)
Opportunistic infection	0	1 (1%)	2 (1%)	0	0	0	1 (1%)
Herpes zoster	1 (1%)	1 (1%)	4 (2%)	0	1 (1%)	2 (1%)	2 (1%)
Malignancy (excluding non-melanoma skin cancer)	0	1 (1%)	2 (1%)	0	0	1 (1%)	0
Hepatic disorder	2 (1%)	2 (1%)	3 (2%)	0	2 (3%)	4 (3%)	4 (3%)
Gastrointestinal perforation	0	0	0	0	0	0	1 (1%)
Pulmonary embolism events	0	1 (1%)	0	2 (3%)	1 (1%)	0	0
Cardiovascular events	0	1 (1%)	0	0	1 (1%)	2 (1%)	0
Major adverse cardiovascular event	0	1 (1%)	0	0	1 (1%)	0	0
Other cardiovascular events	0	0	0	0	0	1 (1%)	0
Undetermined or unknown cause of death	0	0	0	0	0	1 (1%)	0
Deaths	0	0	1 (1%)	0	0	1 (1%)	0

Abbreviations: AE: Adverse event; PBO: Placebo; SAE: Serious adverse event; UPA: Upadacitinib

The most frequently reported AEs (>5% of patients) by upadacitinib 15 mg group through week 12 were urinary tract infection (9.1%) and upper respiratory tract infection (7.9%), while those reported by the upadacitinib 15 mg group were upper respiratory tract infection (6.1%), nasopharyngitis (5.5%) and urinary tract infection (5.5%) (63). (Appendix F).

In the first 12 weeks, serious infections were more frequently reported in the upadacitinib 30 mg QD + csDMARDs group (2.4%) than the upadacitinib 15 mg QD + csDMARDs (0.6%) group and placebo + csDMARDs group (0%); but were comparable across groups between weeks 12 and 24. Oral candidiasis was the only treatment emergent opportunistic infection reported through Week 12 (one subject in the upadacitinib 15 mg group and two subjects in the upadacitinib 30 mg group). Four opportunistic infections were reported through week 24. Through week 12, herpes zoster was more frequent in the upadacitinib 30 mg QD + csDMARDs group (2.4%) than the upadacitinib 15 mg QD + csDMARDs (0.6%) and placebo + csDMARDs (0.6%). There were two occurrences of MACE, one ischemic stroke (through week 12 in upadacitinib 15 mg group) and one non-fatal myocardial infarction (between week 12 and 24 in the upadacitinib 30 mg group) (63). There was one report of renal dysfunction in the upadacitinib 15mg group (1.1%) and two reports in the 30mg group (2.3%) and none in the placebo group through 24 weeks. (Appendix F).

B.2.11 Ongoing studies

All studies described in this section are ongoing and will provide additional evidence of either the long-term benefit of upadacitinib or comparison of upadacitinib with different comparators:

- SELECT-CHOICE is a planned randomised, active-controlled, double-blind, parallel group Phase III clinical trial that is aiming to assess the efficacy and safety of upadacitinib versus abatacept, in patients who are inadequate responders or intolerant to bDMARDs and are on a stable background of csDMARDs (72). The final completion of the long-term extension period is expected in March 2021.

- SELECT-SUNRISE is a randomised, placebo-controlled, double-blind, parallel group Phase III clinical trial in Japanese subjects with moderate to severe RA who are on a stable dose of csDMARDs and have an inadequate response to csDMARDs (73). The final completion of the long-term extension period is expected in July 2020.

- SELECT-EARLY is a randomised, placebo-controlled, double-blind, parallel group Phase III clinical trial that is aiming to compare upadacitinib monotherapy to methotrexate monotherapy in MTX-naïve subjects with moderately to severely RA (72). The estimated study completion will be March 2021.

B.2.12 Innovation

Upadacitinib is the only JAK inhibitor to date to meet the two independent primary endpoints (ACR20) responses and achievement of clinical remission (DAS28(CRP)<2.6/LDA)) and all the ranked secondary endpoints across all the pivotal phase 3 studies evaluating its safety and efficacy. Upadacitinib plus MTX showed significantly better rates of clinical remission relative to adalimumab (59). The achievement of remission is widely accepted as the gold standard in terms of clinical outcomes in RA with no other licensed JAK inhibitor demonstrating superior rates of clinical remission compared to adalimumab in clinical trials to date (SELECT-COMPARE) (74). Substantial improvements in disease activity measures such as clinical remission and patient reported outcomes (PROs) including pain, fatigue and duration and severity of morning joint stiffness (which are important factors for patients with RA) were observed across all the phase 3 trials including without methotrexate. The results of the pivotal trials highlight the effectiveness of upadacitinib as a monotherapy as well as a combination therapy and considering the once daily oral formulation, this would represent a significant step change in the management of moderate and severe RA in clinical practice.

B.2.13 Interpretation of clinical effectiveness and safety evidence

Upadacitinib targets the JAK-STAT pathway to reduce inflammation and modify the clinical course of RA. Upadacitinib has increased selectivity for JAK1 over JAK2,

JAK3 and TYK2, with the ability to inhibit signalling of key cytokines involved in the pathogenesis of RA. JAK1 selectivity of upadacitinib allows the dose of 15 mg to achieve the highest possible efficacy outcomes, while minimizing the impact to JAK2-mediated haematopoiesis. This is supported by extensive and robust phase 3 clinical programme as well as with indirect evidence in the form of an NMA.

The evidence base provides data across patients who are biologic-naïve, and patients who have previously been exposed to csDMARD treatment and biologic treatments. In UK practice, it is likely that adult patients with moderate to severe RA will go through a sequence of treatments and will switch to advanced therapies, of a different mode of action, after failing their current therapy. Some patients will benefit from switching to a JAK inhibitor and upadacitinib offers superior efficacy across all levels of ACR response (ACR 20/50/70) and clinical remission in comparison to placebo and adalimumab. Importantly, subgroup analyses confirm a consistent benefit in favour of upadacitinib regardless of baseline characteristics including BMI, disease severity and treatment history, suggesting a broad range of patients could benefit from treatment with upadacitinib.

Upadacitinib demonstrated superior efficacy across all levels of ACR response in SELECT-NEXT, SELECT-MONOTHERAPHY, and SELECT-BEYOND when compared to placebo. Across all the three studies, upadacitinib demonstrated higher ACR 20/50/70 and clinical remission across 12 weeks (51, 56). The SELECT-COMPARE trial (through week 26), a head-to-head comparison with adalimumab, demonstrated that upadacitinib was superior in all primary and secondary endpoints (51). A clinically meaningful and statistically significant improvement in quality of life was reported by those treated with upadacitinib. A higher proportion of patients who continued treatment with upadacitinib maintained their response through week 24 compared with those who withdrew treatment.

With regards to safety and tolerability, upadacitinib demonstrated a comparable AE profile to active treatment (adalimumab), as observed in SELECT-COMPARE, which is an established treatment for RA in clinical practice (51). There were no new safety signals of concern.

Conclusions from the evidence of the upadacitinib phase III clinical trial programme are supplemented by integrated analyses of efficacy and a series of indirect comparisons designed to compare upadacitinib to alternative csDMARDs and advanced therapies which were not included in the trial programme, but which are relevant to National Health Service (NHS) clinical practice.

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

B.3.1.1. Identification of studies

A systematic literature review was undertaken to identify published economic evaluations and Health technology assessment (HTA) appraisals to address the decision problem and inform the economic model structure. This review was conducted to identify cost-effectiveness studies from the published literature assessing the cost-effectiveness of interventions for patients with moderate to severe RA. Full details of the search are provided in Appendix G, as well as detailed inclusion/exclusion criteria for the review.

B.3.2 Economic analysis

A de novo economic model was developed to compare upadacitinib versus relevant comparators from the UK National Health Service (NHS) and Personal Social Services (PSS) perspective for the treatment of RA in moderate and severe patients. The model was developed consistent with the assessment group (AG) model/approach in TA375 (28) and the recent submissions of baricitinib (TA466) (24), tofacitinib (TA480) (25) and sarilumab (TA485) (30) for the treatment of RA; with necessary adaptations or additions in order to incorporate the modelling of upadacitinib therapy and additional patient populations. The details about patient populations and comparators considered in the economic analysis are presented in Table 1.

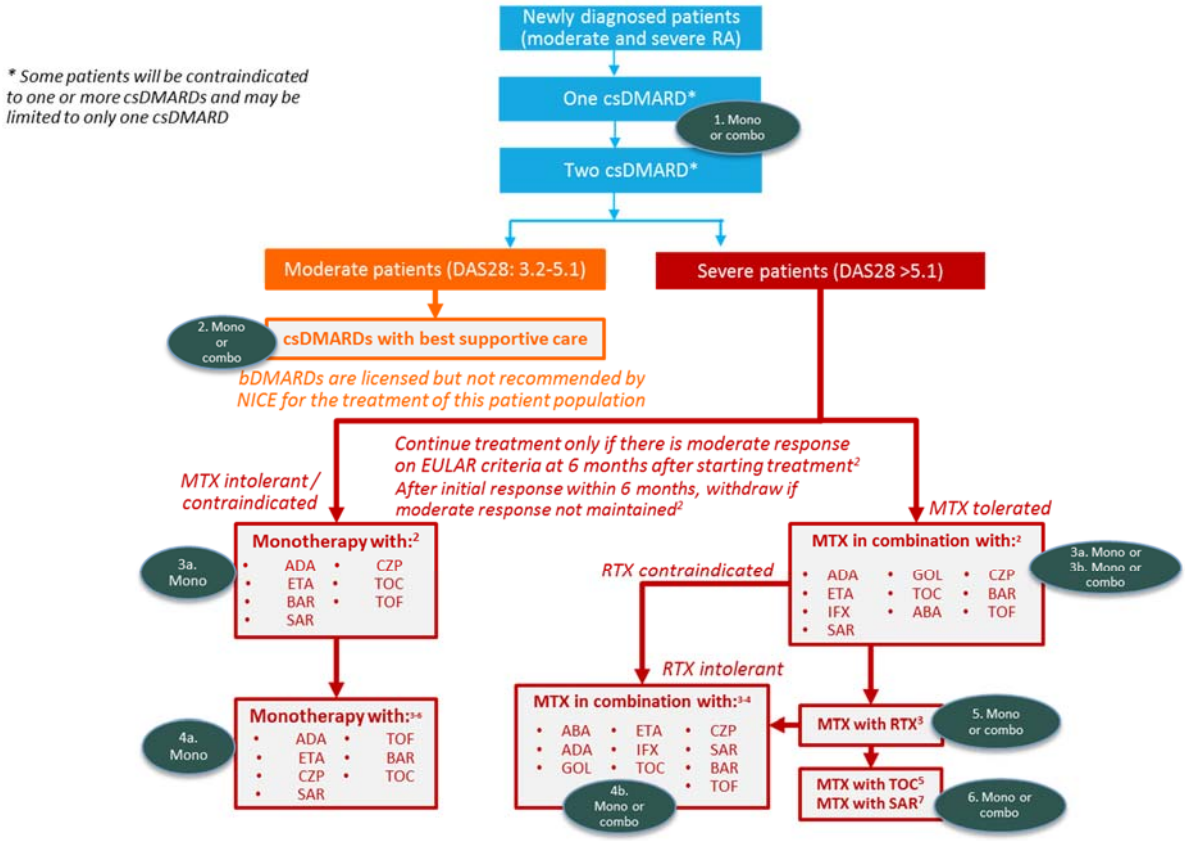
B.3.2.1 Patient population

Patient populations were stratified by severity as defined by Disease Activity Score 28 (DAS28) C-Reactive Protein (CRP) score. Patients with a DAS28 score ≤ 3.2, > 3.2 to 5.1, and > 5.1 are classified into low, moderate, and severe RA, respectively. Only moderate and severe RA populations are considered in this submission, in line with the expected marketing authorisation population for upadacitinib.

Baseline characteristics for each population were derived from the respective upadacitinib clinical trials where data was available and consistent with the NMA selection criteria: SELECT-COMPARE(51), SELECT-NEXT(51), SELECT-MONO(62), SELECT-BEYOND(56), and SELECT-SUNRISE (73) .

The cost-effectiveness evaluation reflects the use of upadacitinib in line with its anticipated marketing authorisation, populations outlined in the final NICE scope, and treatment practice in the UK for patients with RA. The use of upadacitinib in line with its expected marketing authorisation in relation to the existing NICE recommended clinical pathway is detailed in the figure below:

Figure 19: Position of upadacitinib within the existing NICE recommended pathway**



Abbreviations: RA = rheumatoid arthritis, DMARD = disease-modifying antirheumatic drug, csDMARD = conventional DMARD, MTX = methotrexate, DAS28 = Disease Activity Score, bDMARD = biologic DMARD, ADA = adalimumab, CTZ = certolizumab pegol, ETN = etanercept, TCZ = tocilizumab, GOL = golimumab, IFX = infliximab, ABA = abatacept, RTX = rituximab.

Sources: 1. NICE CG79, 2. NICE TA375, 3. NICE TA195, 4. NICE TA225, 5. NICE TA247, 6. NICE TA415, 7, NICE TA485

**Details of the exact NICE recommended comparators within the pathwayare detailed in Table 4 below.*

Two base case cost effectiveness analyses are presented to support the use of upadacitinib monotherapy and combination therapy in moderate RA:

1. After one csDMARD failure

2. After two or more csDMARD failures

Four base case cost effectiveness analyses are presented to support the use of upadacitinib monotherapy and combination therapy in severe RA in those who are methotrexate eligible:

3. Versus first line advanced therapies in combination with methotrexate

4. After first line advanced therapy failure in those who are rituximab ineligible versus advanced therapies

5. After first line advanced therapy failure versus rituximab in combination with methorexate (in rituximab eligible patients)

6. After rituximab in combination with methotrexate failure versus methotrexate in combination with tocilizumab or sarilumab

An additional two cost effectiveness analyses are presented to support the use of upadacitinib monotherapy in severe RA amongst those who are methotrexate ineligible:

3a. Versus first line advanced therapies used as monotherapies (in methotrexate ineligible patients)

4a. After first line advanced therapy failure in those who are methotrexate ineligible

B.3.2.2 Model structure

Model choice and rationale

The de novo cost-effectiveness analysis (CEA) model was developed in Microsoft Excel® 2016 using Visual Basic for Applications (VBA) functionality. The analysis used a discrete-event simulation (DES) structure. To the extent feasible, the model was developed to be consistent with the assessment group (AG) model/approach in TA375 (28) and the recent submissions of baricitinib (TA466)(24) , tofacitinib (TA480) (25) and sarilumab (TA485) (26) for the treatment of RA.

DES models simulate the experience of individual patients. These models do not employ model cycles, as in traditional Markov models. Rather, patients can experience several health events. The time to the next modelling event is simulated for each patient. Patients then jump from event to event, reducing run time and unnecessary model complexity. Patient characteristics are simulated for each patient. Events, costs, and utility are modelled based on each individual patient's characteristics. As simulations are performed at the patient level, DES models offer much more flexibility than traditional Markov models, which do not track patients' 'history' (i.e., prior events and health states), and allow for a more nuanced depiction of patients' experience with RA.

Model structure and flow

Characteristics of patients in each population entering the model were estimated using the relevant Phase III upadacitinib clinical trials (please refer to chapter B2 for more details on the clinical trials). The model assessed the first-line comparators and designated subsequent treatment sequences following first-line therapy, with up to six treatments considered in a treatment sequence. Efficacy of upadacitinib and its comparators were informed by a network meta-analysis (NMA). The model evaluated European League Against Rheumatism (EULAR) response in the base case; with American College of Rheumatology (ACR) responses used in sensitivity analyses (described in section

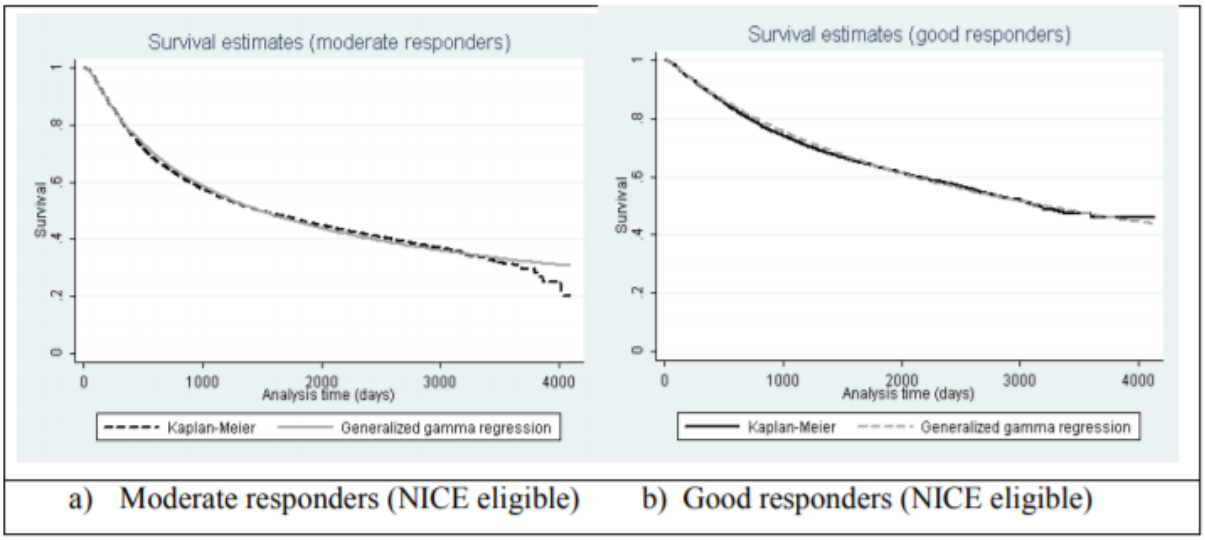
B.3.3 Clinical parameters and variables).

The model schematic is presented in Figure 21. **Model schematic**Patients enter the model upon receipt of the first-line treatment in a treatment sequence. All patients are assumed to remain on a given active treatment for at least 6 months unless death occurs. At the end of 6 months, patients with a good or moderate EULAR response will remain on treatment until they discontinue due to any reason (e.g., loss of response or SAE).

The discontinuation rate after 6 months was estimated based on the Kaplan-Meier curves of discontinuation among RA patients with moderate and good EULAR responses (Figure 20), as reported in the TA375 (28) (see estimation details in

B.3.3 Clinical parameters and variables). At the end of 6 months, patients without a good or moderate EULAR response are assumed to discontinue treatment immediately. Upon treatment discontinuation, patients move on to the next treatment in the sequence and revert to their baseline HAQ (i.e., losing the treatment benefit from the prior treatment).

Figure 20. Kaplan-Meier estimates of the duration on treatment in BSRBR

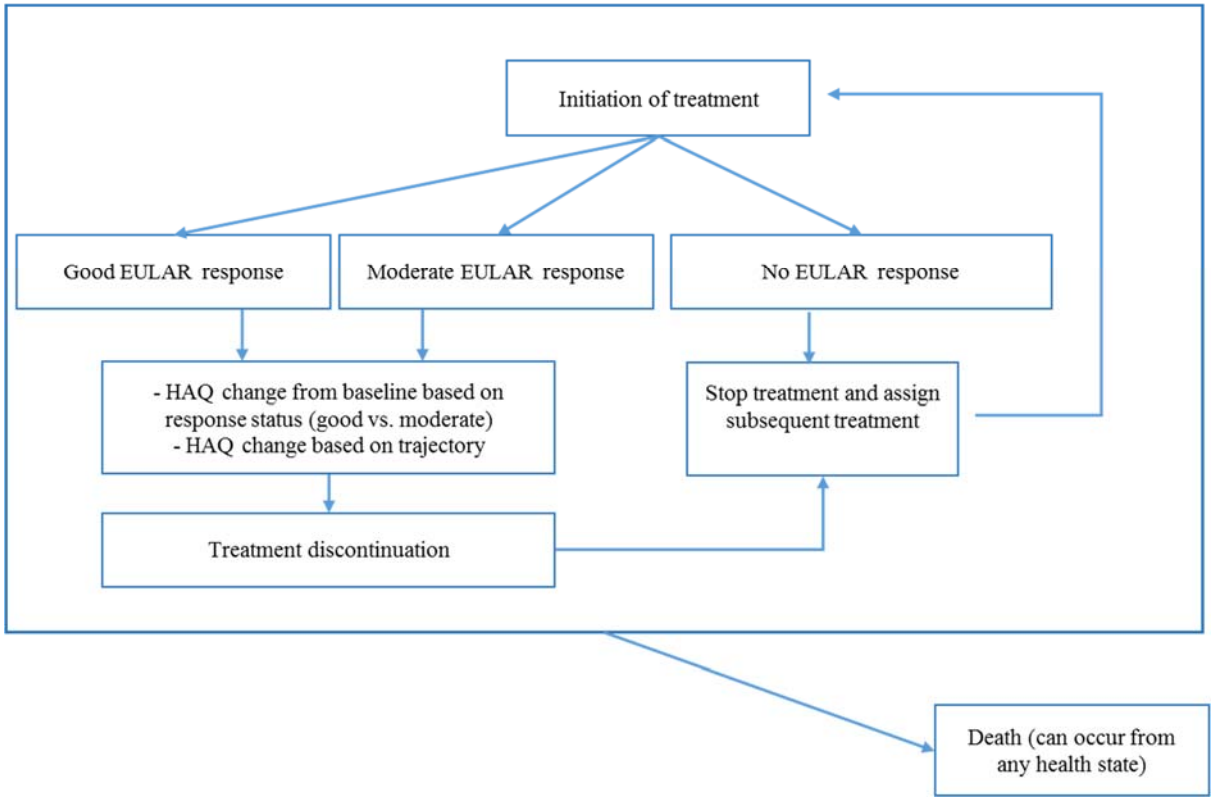


Source: TA375, Figure 112

Patients with severely active RA who transit to best supportive care (BSC) are assumed to remain on BSC until death, and do not achieve treatment response. This is in line with the assumptions made in TA375. Patients with moderately active RA who transit to BSC or MTX could progress into severely active RA and receive a sequence of active treatments for severe disease severity. After progression, upon treatment discontinuation, these patients move on to the next treatment for severely active RA and revert back to the HAQ score when they progressed from moderately to severely active RA. After these progressed patients transition to BSC, they are assumed to remain on BSC until death, similarly to patients who entered the model with severely active RA.

Patients can die at any time during the modelled time horizon and will exit the model upon death. The current model assumes that the risk of mortality is based on age, sex, and baseline HAQ score. This approach is consistent with the assessment group (AG) model/approach in TA375 (28) and Michaud et al. (2012) (75).

Figure 21. Model schematic



Abbreviations: EULAR=European League Against Rheumatism; HAQ=Health Assessment Questionnaire Disability Index.

Table 32. Features of the economic analysis

	Previous appraisals	Current appraisal	
Factor	**TA375 (28)**	**Chosen values**	**Justification**
Model type	Patient-level CEA model using DES structure	Patient-level CEA model using DES structure	Consistent with the assessment group (AG) model/approach in TA375 (28) Provides more flexibility than Markov models, as events are determined based on individual patient characteristics
Were health effects measured in QALYs; if not, what was used?	Yes	Yes	Consistent with the NICE reference case (30)
Discount rate	3.5% annual discount rate for both cost and utility	3.5% annual discount rate for	Consistent with the NICE reference case (30)

		both cost and utility	
Perspective	UK NHS and PSS perspective	UK NHS and PSS perspective	Consistent with the NICE reference case (30)
Abbreviations: QALYs: Quality adjusted Life Years; PSS: Personal Social services; NICE: Nano Institute For Health and Care Excellence; CEA: Cost Effective Analysis; NHS: National Health Service			

B.3.2.3 Intervention technology and comparators

Across both moderate and severe RA patients, two different dose regimens of upadacitinib are considered:

- 15mg QD upadacitinib monotherapy
- 15mg QD upadacitinib combination therapy

The primary set of comparators in each population were selected to reflect UK clinical practice and were largely consistent with the comparators evaluated in TA375 (28) and subsequent appraisals of baricitinib, tofacitinib, and sarilumab (25, 30).

Table 33. Comparator treatments included in the model

Population of interest	Subgroup	Treatment
csDMARD-IR moderate	NA	• Combination therapy with conventional DMARDs (including methotrexate and at least one other DMARD, such as sulfasalazine and leflunomide) • Conventional DMARD monotherapy with dose escalation • Best supportive care (only where conventional DMARDs are not appropriate due to intolerance)
csDMARD-IR severe	Who tolerate methotrexate and it is not contraindicated	• Biological DMARDs in combination with methotrexate (adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab, abatacept, baricitinib, tofacitinib or sarilumab
	Who do not tolerate methotrexate, or it is contraindicated	• Adalimumab, etanercept, certolizumab pegol, tocilizumab, baricitinib, tofacitinib or sarilumab (each as monotherapy)

Population of interest	Subgroup	Treatment
bDMARD-IR severe and who tolerate methotrexate and it is not contraindicated	NA	• Rituximab in combination with methotrexate
	Rituximab is contraindicated or withdrawn due to adverse events and who tolerate methotrexate and it is not contraindicated	• Adalimumab, etanercept, infliximab, abatacept tocilizumab, certolizumab pegol, golimumab, baricitinib, tofacitinib, or sarilumab, each in combination with methotrexate
	Rituximab is contraindicated or withdrawn due to adverse events and who do not tolerate methotrexate, or it is contraindicated	• Adalimumab, etanercept, certolizumab pegol, tofacitinib, tocilizumab, baricitinib, tocilizumab or sarilumab (each as monotherapy)
Severe RA that has not responded adequately to therapy with rituximab and methotrexate	NA	• Tocilizumab, sarilumab in combination with methotrexate
Abbreviations: bDMARD: biologic disease-modifying anti-rheumatic drug; csDMARD: conventional disease-modifying anti-rheumatic drug; IR=inadequate response		

Treatment sequences in the model

The model considered treatment sequences of up to six treatments. The specific treatment sequences modelled in each target population are described in Table 34 to Table 47. These are consistent with those used in TA375 and validated with clinicians through an advisory board.

1b. After one csDMARD failure (moderate RA patients) (MTX eligible)

Table 34. Treatment sequences considered in moderately active csDMARD-IR population after one csDMARD-IR before transition to severely active RA (MTX eligible patients)

Sequence	First-line treatment	Second-line treatment	Third-line treatment	Fourth-line treatment
1	UPA + MTX	Int. csDMARD	MTX	BSC
2	UPA	Int. csDMARD	MTX	BSC
3	Int csDMARD	MTX	BSC	BSC

Sequence	First-line treatment	Second-line treatment	Third-line treatment	Fourth-line treatment
Abbreviations: BSC=best supportive care; csDMARD=conventional disease-modifying anti-rheumatic drug; IR=inadequate response; MTX=methotrexate; N/A=not applicable; RA=rheumatoid arthritis; UPA=upadacitinib				

Table 35. Treatment sequences considered in moderately active csDMARD-IR population following transition to severely active RA (MTX eligible)

Sequence	First-line treatment	Second-line treatment	Third-line treatment	Fourth-line treatment	Fifth-line treatment	Sixth-line treatment
1	ADA + MTX	RTX + MTX	TCZ IV + MTX	MTX	BSC	N/A
2	BRC + MTX	ADA + MTX	RTX + MTX	TCZ IV + MTX	MTX	BSC
Abbreviations: ADA=adalimumab; BRC=baricitinib; BSC=best supportive care; csDMARD=conventional disease-modifying anti-rheumatic drug; IR=inadequate response; MTX=methotrexate; N/A=not applicable; RA=rheumatoid arthritis; RTX=rituximab; SC=subcutaneous injection; TCZ=tocilizumab; UPA=upadacitinib.						

1a. After one csDMARD failure (moderate RA patients) (MTX ineligible)

Table 36. Treatment sequences considered in moderately active csDMARD-IR population after one csDMARD-IR before transition to severely active RA (MTX ineligible patients)

Sequence	First-line treatment	Second-line treatment	Third-line treatment
1	UPA	Int. csDMARD	BSC
2	Int. csDMARD	BSC	N/A

Table 37. Treatment sequences considered in moderately active csDMARD-IR population following transition to severely active RA (methotrexate ineligible)

Sequence	First-line treatment	Second-line treatment	Third-line treatment	Fourth-line treatment	Fifth-line treatment	Sixth-line treatment

1	ADA	SRL	BSC	BSC	BSC	N/A
2	BRC	ADA	SRL	BSC	BSC	BSC

Abbreviations: ADA=adalimumab; BRC=baricitinib; BSC=best supportive care; csDMARD=conventional disease-modifying anti-rheumatic drug; IR=inadequate response; MTX=methotrexate; N/A=not applicable; RA=rheumatoid arthritis; RTX=rituximab; SC=subcutaneous injection; TCZ=tocilizumab; UPA=upadacitinib

2b. After two or more csDMARD failures (moderate RA) (MTX eligible)

Table 38. Treatment sequences considered in moderately active csDMARD-IR population after two or more csDMARD-IR before transition to severely active RA (MTX eligible patients)

Sequence	First-line treatment	Second-line treatment	Third-line treatment
1	UPA + MTX	MTX	BSC
2	UPA	MTX	BSC
3	MTX	BSC	N/A

Abbreviations: BSC=best supportive care; csDMARD=conventional disease-modifying anti-rheumatic drug; IR=inadequate response; MTX=methotrexate; N/A=not applicable; RA=rheumatoid arthritis; UPA=upadacitinib.

Table 39. Treatment sequences considered in moderately active csDMARD-IR population following transition to severely active RA (methotrexate eligible)

Sequence	First-line treatment	Second-line treatment	Third-line treatment	Fourth-line treatment	Fifth-line treatment	Sixth-line treatment
1	ADA + MTX	RTX + MTX	TCZ IV + MTX	MTX	BSC	N/A
2	BRC + MTX	ADA + MTX	RTX + MTX	TCZ IV + MTX	MTX	BSC

Abbreviations: ADA=adalimumab; BRC=baricitinib; BSC=best supportive care; csDMARD=conventional disease-modifying anti-rheumatic drug; IR=inadequate response; MTX=methotrexate; N/A=not applicable; RA=rheumatoid arthritis; RTX=rituximab; SC=subcutaneous injection; TCZ=tocilizumab; UPA=upadacitinib.

2a. After two or more csDMARD failures (moderate RA) (MTX ineligible)

Table 40. Treatment sequences considered in moderately active csDMARD-IR population after two or more csDMARD-IR before transition to severely active RA (MTX ineligible patients)

Sequence	First-line treatment	Second-line treatment	Third-line treatment
1	UPA	BSC	BSC
2	BSC	BSC	N/A

Abbreviations: BSC=best supportive care; csDMARD=conventional disease-modifying anti-rheumatic drug; N/A=not applicable; UPA=upadacitinib.

Table 41. Treatment sequences considered in moderately active csDMARD-IR population following transition to severely active RA (methotrexate *in*eligible)

Sequence	First-line treatment	Second-line treatment	Third-line treatment	Fourth-line treatment	Fifth-line treatment	Sixth-line treatment
1	ADA	SRL	BSC	BSC	BSC	N/A
2	BRC*	ADA	SRL	BSC	BSC	BSC

Abbreviations: ADA=adalimumab; BRC=baricitinib; BSC=best supportive care; csDMARD=conventional disease-modifying anti-rheumatic drug; IR=inadequate response; MTX=methotrexate; N/A=not applicable; RA=rheumatoid arthritis; RTX=rituximab; SC=subcutaneous injection; TCZ=tocilizumab; UPA=upadacitinib.

*Assume same efficacy as BRC+MTX (from csDMARD-IR NMA)

3b. First line advanced therapy treatment of severe RA (MTX eligible)

Table 42. Treatment sequences considered in first line advanced therapy treatment of severe RA (MTX eligible)

Sequence	First-line treatment	Second-line treatment	Third-line treatment	Fourth-line treatment	Fifth-line treatment
1	UPA + MTX	RTX + MTX	TCZ IV + MTX	MTX	BSC
2	UPA	RTX + MTX	TCZ IV + MTX	MTX	BSC
3	ABT IV + MTX	RTX + MTX	TCZ IV + MTX	MTX	BSC
4	ABT SC + MTX	RTX + MTX	TCZ IV + MTX	MTX	BSC

Sequence	First-line treatment	Second-line treatment	Third-line treatment	Fourth-line treatment	Fifth-line treatment
5	ADA + MTX	RTX + MTX	TCZ IV + MTX	MTX	BSC
6	BRC + MTX	RTX + MTX	TCZ IV + MTX	MTX	BSC
7	CTZ + MTX	RTX + MTX	TCZ IV + MTX	MTX	BSC
8	ETN + MTX	RTX + MTX	TCZ IV + MTX	MTX	BSC
9	GOL + MTX	RTX + MTX	TCZ IV + MTX	MTX	BSC
10	IFX + MTX	RTX + MTX	TCZ IV + MTX	MTX	BSC
11	SRL + MTX	RTX + MTX	TCZ IV + MTX	MTX	BSC
12	TCZ IV + MTX	RTX + MTX	SRL + MTX	MTX	BSC
13	TCZ SC + MTX	RTX + MTX	SRL + MTX	MTX	BSC
14	TFC + MTX	RTX + MTX	TCZ IV + MTX	MTX	BSC

Abbreviations: ABT=abatacept; ADA=adalimumab; BRC=baricitinib; BSC=best supportive care; csDMARD=conventional disease-modifying anti-rheumatic drug; CTZ=certolizumab pegol; ETN=etanercept; GOL=golimumab; INF=infliximab: IR=inadequate response; IV=intravenous infusion; MTX=methotrexate; N/A=not applicable; RA=rheumatoid arthritis; RTX=rituximab; SC=subcutaneous injection; SRL=sarilumab; TCZ=tocilizumab; TFC=tofacitinib; UPA=upadacitinib.

5. After failure of first line advanced therapy (MTX eligible)

Table 43. Treatment sequences considered after failure of first line advanced therapy in MTX eligible patients (RTX eligible)

Sequence	First-line treatment	Second-line treatment	Third-line treatment	Fourth-line treatment
1	UPA + MTX	TCZ IV + MTX	MTX	BSC
2	UPA*	TCZ IV + MTX	MTX	BSC
3	RTX + MTX	TCZ IV + MTX	MTX	BSC

Abbreviations: bDMARD=biologic disease-modifying anti-rheumatic drug; BSC=best supportive care; IR=inadequate response; IV=intravenous infusion; MTX=methotrexate; N/A=not applicable; RTX=rituximab; TCZ=tocilizumab; UPA=upadacitinib.

*Assume same efficacy as BRC+MTX (from bDMARD-IR NMA)

4b. After failure of first line advanced therapy (MTX eligible, RTX ineligible)

Table 44. Treatment sequences considered after failure of first line advanced therapy in MTX eligible patients (RTX ineligible)

Sequence	First-line treatment	Second-line treatment	Third-line treatment	Fourth-line treatment
1	UPA + MTX	TCZ IV + MTX	MTX	BSC
2	UPA	TCZ IV + MTX	MTX	BSC
3	ABT IV + MTX	TCZ IV + MTX	MTX	BSC
4	ABT SC + MTX*	TCZ IV + MTX	MTX	BSC
5	ADA + MTX**	TCZ IV + MTX	MTX	BSC
6	BRC + MTX	TCZ IV + MTX	MTX	BSC
7	CTZ + MTX	TCZ IV + MTX	MTX	BSC
8	GOL + MTX	TCZ IV + MTX	MTX	BSC
9	ETN + MTX	TCZ IV + MTX	MTX	BSC
10	IFX + MTX	TCZ IV + MTX	MTX	BSC
11	SRL + MTX	TCZ IV + MTX	MTX	BSC
12	TCZ IV + MTX	SRL + MTX	MTX	BSC
13	TCZ SC + MTX	SRL + MTX	MTX	BSC
14	TFC + MTX	TCZ IV + MTX	MTX	BSC

Abbreviations: ABT=abatacept; ADA=adalimumab; BRC=baricitinib; BSC=best supportive care; csDMARD=conventional disease-modifying anti-rheumatic drug; CTZ=certolizumab pegol; ETN=etanercept; GOL=golimumab; INF=infliximab: IR=inadequate response; IV=intravenous infusion; MTX=methotrexate; N/A=not applicable; RA=rheumatoid arthritis; RTX=rituximab; SC=subcutaneous injection; SRL=sarilumab; TCZ=tocilizumab; TFC=tofacitinib; UPA=upadacitinib.

*Assume same efficacy as ABT IV+MTX (from bDMARD-IR NMA)

**Assume same efficacy as BRC+MTX (from bDMARD-IR NMA)

6. After failure of rituximab in combination with methotrexate

Table 45: Treatment sequences considered in severely active RA, RTX- IR population

Sequence	First-line treatment	Second-line treatment	Third-line treatment
1	UPA + MTX	MTX	BSC
2	UPA*	MTX	BSC
3	SRL + MTX	MTX	BSC
4	TCZ + MTX	MTX	BSC

Abbreviations: BSC=best supportive care; IR=inadequate response; IV=intravenous infusion; MTX=methotrexate; N/A=not applicable; RTX=rituximab; SC=subcutaneous injection; SRL=sarilumab; TCZ=tocilizumab; UPA=upadacitinib.

*Assume same efficacy as BRC+MTX (from bDMARD-IR NMA)

3a. First line advanced therapy treatment of severe RA (MTX ineligible)

Table 46. Treatment sequences considered in first line advanced therapy treatment of severe RA (MTX ineligible)

Sequence	First-line treatment	Second-line treatment	Third-line treatment
1	UPA	SRL*	BSC
2	ADA	SRL*	BSC
3	BRC*	SRL*	BSC
4	CTZ*	SRL*	BSC
5	ETN	SRL*	BSC
6	SRL*	BRC*	BSC
7	TCZ IV	SRL*	BSC
8	TCZ SC	SRL*	BSC
9	TFC*	SRL*	BSC

Abbreviations: ABT=abatacept; ADA=adalimumab; BRC=baricitinib; BSC=best supportive care; csDMARD=conventional disease-modifying anti-rheumatic drug; CTZ=certolizumab pegol; ETN=etanercept; GOL=golimumab; INF=infliximab: IR=inadequate response; IV=intravenous infusion; MTX=methotrexate; N/A=not applicable; RA=rheumatoid arthritis; RTX=rituximab; SC=subcutaneous injection; SRL=sarilumab; TCZ=tocilizumab; TFC=tofacitinib; UPA=upadacitinib.

*Assume same efficacy as ADA monotherapy (from csDMARD-IR NMA)

4a. After failure of first line advanced therapy treatment of severe RA (MTX ineligible)

Table 47*:* Treatment sequences considered after failure of first line advanced therapy treatment of severe RA (MTX ineligible)

Sequence	First-line treatment	Second-line treatment
1	UPA*	BSC
2	ADA*	BSC
3	BRC*	BSC
4	CTZ*	BSC

Sequence	First-line treatment	Second-line treatment
5	ETN*	BSC
6	SRL*	BSC
7	TCZ IV	SRL*
8	TCZ SC	SRL*
9	TFC*	BSC

Abbreviations: ABT=abatacept; ADA=adalimumab; BRC=baricitinib; BSC=best supportive care; csDMARD=conventional disease-modifying anti-rheumatic drug; CTZ=certolizumab pegol; ETN=etanercept; GOL=golimumab; INF=infliximab: IR=inadequate response; IV=intravenous infusion; MTX=methotrexate; N/A=not applicable; RA=rheumatoid arthritis; RTX=rituximab; SC=subcutaneous injection; SRL=sarilumab; TCZ=tocilizumab; TFC=tofacitinib; UPA=upadacitinib.

*Assume same efficacy as BRC+MTX (from bDMARD-IR NMA)

B.3.3 Clinical parameters and variables

Baseline characteristics

Patient characteristics were modelled based on data from the relevant upadacitinib clinical trials. IPD were not available for all comparators considered in the model, and therefore the patient characteristics derived from the upadacitinib clinical trials were used for all treatment sequences, regardless of treatment arm. The following baseline characteristics were considered in the model:

- Age
- Sex
- HAQ
- DAS28 CRP
- Disease duration
- Weight

Summary statistics for patient characteristics for both the moderate and severe csDMARD-IR populations were derived from the SELECT-COMPARE(51), SELECT-NEXT(51), SELECT-MONO(62), and SELECT-SUNRISE (73) phase III clinical trials based on an analysis of IPD. Summary statistics for both the RTX-eligible and RTX-ineligible bDMARD-IR populations were informed using IPD from the Phase III

SELECT-BEYOND (56) clinical trial. Only severely active RA patients (i.e., DAS28 CRP >5.1) were included in the analysis for the bDMARD-IR population.

To create patient cohorts (e.g. 10,000 in the base case cost effectiveness analysis) for the DES model, baseline characteristics were sampled to preserve correlations between all normally distributed, continuous variables (i.e., age, HAQ, weight, DAS28, duration of disease). Correlations were preserved using variance-covariance matrices (estimated based on IPD) and Cholesky decomposition (76). Patients' sex was simulated independently of the continuous baseline characteristics based on a binomial distribution. Sampling of continuous baseline characteristics were bounded by the minimum and maximum values observed in the relevant upadacitinib Phase III trials. HAQ scores were restricted to the 25 valid values ranging from 0 to 3 by an increment of 0.125, consistent with the assessment group (AG) model/approach in TA375 (28). To assign HAQ scores to each individual patient at baseline, initially, HAQ scores were sampled based on a continuous normal distribution. HAQ scores were then adjusted based on the probabilities of the nearest legitimate HAQ scores. For example, if a HAQ score of 1.8 was drawn, the value would be randomly adjusted to either 1.750 or 1.875 based on the inverse of their respective distances from 1.8. Therefore, there would be a 60% probability the HAQ value being 1.750 (60% = 1 - |1.8 - 1.750| / 0.125) and a 40% probability of being 1.875 (40% = 1 - |1.8 - 1.875| / 0.125)

The inputs used to sample patient characteristics are presented in Table 48 to Table 50**.**

Table 48. Baseline characteristics for csDMARD-IR, moderately active RA

Baseline characteristics described as continuous inputs					
	Mean	**SD**	**Minimum**	**Maximum**	**Source**
Age (years)	54.3	12.6	19	83	SELECT-COMPARE(51), SELECT-NEXT(51), SELECT-MONO (62), SELECT-SUNRISE(73) IPD
HAQ	1.1	0.6	0	3	
DAS28 CRP	4.5	0.4	3.2	5.1	
Disease duration (years)	6.9	7.3	0	42	

Baseline characteristics described as continuous inputs					
Weight (kg)	74.4	19.7	40	167	
Baseline characteristics described as categorical inputs					
	Proportion	**Source**			
Female	78.4%	SELECT-COMPARE(51), SELECT-NEXT(51), SELECT-MONO (62), SELECT-SUNRISE(73) IPD			

Table 49. Baseline characteristics for csDMARD-IR, severely active RA

Baseline characteristics described as continuous inputs					
	Mean	**SD**	**Minimum**	**Maximum**	**Source**
Age (years)	54.5	11.8	19	86	SELECT-COMPARE(51), SELECT-NEXT(51), SELECT-MONO (62), SELECT-SUNRISE(73) IPD
HAQ	1.7	0.6	0	3	
DAS28 CRP	6.1	0.7	5.1	8.5	
Disease duration (years)	7.7	8.0	0	54	
Weight (kg)	77.1	20.3	35	173	
Baseline characteristics described as categorical inputs					
	Proportion	**Source**			
Female	79.8%	SELECT-COMPARE(51), SELECT-NEXT(51), SELECT-MONO (62), SELECT-SUNRISE(73) IPD			

Table 50. Baseline characteristics for bDMARD-IR, severely active RTX-eligible and RTX-ineligible RA

Baseline characteristics described as continuous inputs					
	Mean	**SD**	**Minimum**	**Maximum**	**Source**
Age (years)	57.0	11.0	23	84	SELECT-BEYOND (56) IPD
HAQ	1.7	0.6	0	3	
DAS28 CRP	6.2	0.7	5.1	8.4	
Disease duration (years)	13.0	9.3	1	47	
Weight (kg)	82.2	20.0	38	148	
Baseline characteristics described as categorical inputs					

Baseline characteristics described as continuous inputs		
	Proportion	**Source**
Female	84.1%	SELECT-BEYOND(56) IPD

Clinical response

Clinical response in the base-case model is based on the EULAR response as explained in Table 24 . This approach is consistent with the assessment group (AG) model/approach in TA375 (28) and prior NICE submissions in RA (25, 30, 31, 34, 77, 78). The probability of achieving a good or moderate EULAR response was derived from NMAs that evaluated treatment response for RA treatments in both the csDMARD-IR and bDMARD-IR populations. As few clinical trials identified in the SLR reported EULAR results, the NMA network for EULAR was not complete for all relevant treatments for RA. Therefore, the EULAR results were informed by an NMA using data from the more commonly reported ACR response. EULAR response was estimated based on a mapping algorithm from ACR to EULAR. The mapping algorithm was established based on the Veterans Affairs Rheumatoid Arthritis (VARA) registry, a multi-centre United States (US) database of veterans with RA. This algorithm converts ACR response to EULAR response based on data from the US VARA database shown in Table 51. The mapping algorithm was described and used in TA375 (28).

Table 51. The relationship between EULAR responses and ACR responses in the VARA database

Patient category	Less	ACR20	ACR50	ACR70	Total
EULAR ESR response, all patients					
None	755	4	2	0	759
Moderate	136	27	2	2	163
Good	57	26	10	2	83

Abbreviations: ACR=American College of Rheumatology; ESR=Erythrocyte sedimentation rate; EULAR=European League Against Rheumatism.

A single NMA was conducted among the moderately to severely active csDMARD-IR population, due to the availability of comparator data which is derived from trials

including moderate to severe RA patients. Therefore, the same efficacy inputs were used for both the moderately active csDMARD-IR population and severely active csDMARD-IR populations in the CEA model, consistent with the approach used in TA375. Subgroup moderate RA EULAR response data from the relevant clinical trials was run in the model as a sensitivity scenario analysis. The bDMARD-IR NMA was not stratified based on eligibility for RTX. As such, the same efficacy inputs were used for both the RTX-eligible and RTX-ineligible bDMARD-IR populations in the CEA model.

It should also be noted that for moderate RA patients the same efficacy for upadacitinib was assumed for patients after one csDMARD failure and after two or more. Data presented in Table 16 showing ACR20 response for all trials segregated between those with one or more than one csDMARD failure supports the assumption of efficacy equivalence. Also, as noted in Section B.1.3 Health condition and position of the technology in the treatment pathway, in the "positioning of upadacitinib" section, use after one csDMARD by UK clinicians would follow the recommendations of EULAR guidelines that advanced therapies should be used earlier in the pathway (ie. After one rather than two or more csDMARD failures) in those with poor prognostic factors. Such unfavourable prognostic factors are defined as high acute phase reactant levels, high swollen joint counts, the presence of RF and/or ACPA, especially at high levels and the presence of early erosions. The data in Table 16 shows the assumption of at least equivalent efficacy those with poor prognostic factors for upadacitinib is supported by the clinical data.

Response rates for the base-case model were based on NMAs with random effects to include both three month and six month efficacy data. The details of the NMA are described in Section B.2.9 Indirect and mixed treatment comparisons. The base-case probabilities of achieving a good and moderate EULAR response are provided in Table 52 and Table 53. The base-case model assumed that response rates for a specific treatment only depends on the modelled population (i.e., csDMARD-IR, bDMARD-IR); response rates do not change by line of therapy.

Table 52. EULAR response rates at weeks 24 for csDMARD-IR RA populations

Treatment	EULAR response	
	Good	Moderate
ABT IV + MTX	[redacted]	[redacted]
ABT SC + MTX	[redacted]	[redacted]
ADA	[redacted]	[redacted]
ADA + MTX	[redacted]	[redacted]
BRC + MTX	[redacted]	[redacted]
cDMARD	[redacted]	[redacted]
Intensive cDMARD	[redacted]	[redacted]
CTZ + MTX	[redacted]	[redacted]
ETN	[redacted]	[redacted]
ETN + MTX	[redacted]	[redacted]
GOL + MTX	[redacted]	[redacted]
IFX + MTX	[redacted]	[redacted]
RTX + MTX	[redacted]	[redacted]
SRL	[redacted]	[redacted]
SRL + MTX	[redacted]	[redacted]
TCZ IV	[redacted]	[redacted]
TCZ IV + MTX	[redacted]	[redacted]
TCZ SC + MTX	[redacted]	[redacted]
TFC	[redacted]	[redacted]
TFC + MTX	[redacted]	[redacted]
UPA	[redacted]	[redacted]
UPA + MTX	[redacted]	[redacted]

Abbreviations: ABT=abatacept; ADA=adalimumab; BRC=baricitinib; csDMARD=conventional disease-modifying anti-rheumatic drug; CTZ=certolizumab pegol; ETN=etanercept; EULAR=European League Against Rheumatism; GOL=golimumab; IFX=infliximab; IV= intravenous injection; MTX=methotrexate; RA=rheumatoid arthritis; RTX=rituximab; SC=subcutaneous injection; SRL=sarilumab; TCZ=tocilizumab; TFC=tofacitinib; UPA=upadacitinib

Table 53. EULAR response rates at week 24 for bDMARD-IR RA populations

Treatment	EULAR response	
	Good	Moderate
ABT IV + MTX	[redacted]	[redacted]
BRC + MTX	[redacted]	[redacted]
cDMARD	[redacted]	[redacted]
CTZ + MTX	[redacted]	[redacted]
GOL + MTX	[redacted]	[redacted]
RTX + MTX	[redacted]	[redacted]
SRL + MTX	[redacted]	[redacted]
TCZ IV + MTX	[redacted]	[redacted]
TCZ SC + MTX	[redacted]	[redacted]

Patient population	Treatments	Assumptions
csDMARD-IR	ABT IV / SC	Same efficacy as ADA monotherapy (in csDMARD-IR NMA)
	CTZ	Same efficacy as ADA monotherapy (in csDMARD-IR NMA)
	BRC	Same efficacy as ADA monotherapy (in csDMARD-IR NMA)
	TCZ SC	Same efficacy as TCZ IV monotherapy (in csDMARD-IR NMA)
bDMARD-IR	ADA+MTX	Same efficacy as BRC +MTX (in bDMARD-IR NMA)
	INF + MTX	Same efficacy as BRC +MTX (in bDMARD-IR NMA)
	ETN+MTX	Same efficacy as BRC +MTX (in bDMARD-IR NMA)
	ABT SC+MTX	Same efficacy as ABT IV+MTX (in bDMARD-IR NMA)
	UPA	Same efficacy as BRC +MTX (in bDMARD-IR NMA). Rationale: Upa mono efficacy equivalent to BRC+MTX efficacy in csDMARD-IR NMA
	ADA	Same efficacy as BRC +MTX (in bDMARD-IR NMA)
	ETN	Same efficacy as BRC +MTX (in bDMARD-IR NMA)
	CTZ	Same efficacy as BRC +MTX (in bDMARD-IR NMA)
	TFC	Same efficacy as BRC +MTX (in bDMARD-IR NMA)
	BRC	Same efficacy as BRC +MTX (in bDMARD-IR NMA)
	SRL	Same efficacy as BRC +MTX (in bDMARD-IR NMA)
	TCZ IV	Same efficacy as BRC +MTX (in bDMARD-IR NMA)
	TCZ SC	Same efficacy as BRC +MTX (in bDMARD-IR NMA)

Treatment	EULAR response	
	Good	Moderate
TFC + MTX	[redacted]	[redacted]
UPA + MTX	[redacted]	[redacted]

Abbreviations: ABT=abatacept; BRC=baricitinib; bDMARD=biologic disease-modifying anti-rheumatic drug; CTZ=certolizumab pegol; GOL=golimumab; EULAR=European League Against Rheumatism; INF=infliximab; MTX=methotrexate; RA=rheumatoid arthritis; RTX=rituximab; SRL=sarilumab; TCZ=tocilizumab; TFC=tofacitinib; UPA=upadacitinib.

Assumptions have been made on the treatments for which no efficacy data is available, as shown in Table 54.

Table 54: Assumptions on EULAR response rates

The probabilities of ACR 20-49 and ACR >50 response is also presented in section B.2.9.9.

Initial change in HAQ

Quality-adjusted life years (QALYs) in the CEA model are estimated via HAQ score, which has shown good correlation with the generic EQ-5D instrument (79). In the model, patients who experience a good or moderate EULAR response at 6 months

after initial treatment experience an initial reduction in HAQ from baseline. The initial HAQ value reduction depends on the EULAR response level, but is independent of treatments received, as detailed in Table 55. The mean reduction in HAQ from baseline was derived by the authors of TA375 (28) using the British Society of Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR-RA) database (80). The Assessment Group reported their approach to analyse BSRBR-RA to derive mean reduction in HAQ in the TA375 report. (28) Specifically, the mean reductions in HAQ at 6 months for a patient with mean characteristics of the overall sample from the BSRBR-RA database were estimated based on autoregressive latent trajectory models (81). This resulted in estimates of 0.317 for moderate responders and 0.673 for good responders. However, due to limited data availability, the same reduction in HAQ is applied for all classes of treatment. This assumption was used in TA375 and recent submissions to NICE in RA including for baricitinib and tofacitinib which belong to the same JAK inhibitor class of drugs as upadacitinib. (25, 28, 30). In the base-case, the reduction in HAQ is assumed to occur linearly from the initiation of treatment to 6 months. This assumption is probably conservative given the outcome data from SELECT-COMPARE (Table 8) and SELECT-BEYOND (Table 11) where both 3- and 6-month data is available which suggests that substantially more than half of the clinical response achieved at 6 months has been achieved by 3 months.

Table 55. Initial reduction in HAQ by EULAR response based on BSRBR-RA database

EULAR response	Mean reduction in HAQ	SE
Good	0.673	0.112
Moderate	0.317	0.048

Abbreviations: BSRBR-RA=British Society of Rheumatology Biologics Register for Rheumatoid Arthritis; EULAR: European League Against Rheumatism; HAQ=Health Assessment Questionnaire Disability Index; SE=standard errors

In the base-case, the reduction in HAQ is assumed to occur at 6 months. Two scenario analyses were conducted assuming that patients experience the entire reduction in HAQ at either treatment initiation or at 6 months, respectively.

In addition, a scenario analysis was conducted using the initial reduction in HAQ by EULAR response estimated with the Phase III trial data (Table 56). Month 3 EULAR response and the respective HAQ reduction was used as it allows for the use of all

relevant clinical trials for the analysis. Included patients had non-missing HAQ and DAS28 CRP scores at baseline and month 3.

Table 56. Initial reduction in HAQ by EULAR response based on Phase III trials of upadacitinib

EULAR response	Mean reduction in HAQ	SE
Good	0.755	0.019
Moderate	0.481	0.016
Abbreviations: EULAR: European League Against Rheumatism; HAQ=Health Assessment Questionnaire Disability Index; SE=standard error.		

Long-term HAQ progression

Patients with a good or moderate EULAR response at month 6 are assumed to continue receiving treatment until treatment discontinuation. While on treatment after month 6, patients experience long-term HAQ progression as described below:

- Consistent with the assessment group (AG) model/approach in TA375 and prior submissions' models in RA (25, 28, 30), HAQ progression for patients receiving csDMARDs and BSC is based on a latent class growth model (LCGM), described in Norton et al. (2014). (82) It was assumed that following the initial 6-month response period, HAQ scores remained constant until a patient experienced a HAQ progression event (i.e., HAQ changed in a step-wise manner, based on patients' baseline characteristics, and response). At each progression event, utility and costs were estimated assuming linear change in HAQ costs and utility. No HAQ progression has been assumed after year 15 for patients remaining on csDMARD, which is consistent with the approach used in TA375. (28)

- Patients receiving bDMARDs and JAK inhibitors were assumed to experience no long-term HAQ progression. HAQ values remained flat while on treatment after month 6. This assumption is consistent with the assessment group (AG) model/approach in TA375 (28), as well as the submissions for JAK inhibitors baricitinib and tofacitinib (25).

In a scenario analysis, patients receiving csDMARDs and BSC were assumed to experience a linear HAQ progression based on Malottki et al. (2011) (83),

(csDMARDs: 0.045/year; BSC: 0.06/year). This increase amounted to an increase in HAQ by 0.125 every 2.7 years and 2.0 years for csDMARDs and BSC, respectively.

Another scenario analysis assuming non-flat HAQ progression for bDMARDs and JAK inhibitors were conducted. Patients on bDMARDs and JAK inhibitors were assumed to experience a 0.125 increase in HAQ every 5 years.

Long-term treatment discontinuation

Treatment discontinuation was estimated by EULAR response (good versus moderate), based on the analysis presented in TA375 (28) of the treatment durations observed in the BSRBR-RA database. Discontinuation rate was contingent on the EULAR response and was independent of treatments used, consistent with the assessment group (AG) model/approach in TA375 (28). The discontinuation curves were digitized to create pseudo-IPD, and a series of parametric survival models were used to fit to the pseudo-IPD: exponential, Weibull, log-normal, log-logistic, generalized gamma and Gompertz. Model fit was evaluated based on AIC and BIC statistics. The following covariates were included in these models: age; gender; disease duration at baseline; DAS28 score, number of previous DMARDs; and HAQ at baseline.

The treatment discontinuation curve with a generalized gamma distribution achieved the best fit for EULAR moderate responders and was the second-best fitting curve for discontinuation of EULAR good responders. It was also selected as the best-fit distribution for treatment discontinuation in the TA375. (28) As a result, it was used in the base-case model. Alternative parametric distributions were tested in scenario analyses. The parameters and fit statistics used to estimate treatment discontinuation are presented in Appendix J.

Mortality

Patients were at risk of death throughout the modelled time horizon. All-cause mortality rates for the UK population were obtained from UK life tables based on patient age and sex (Appendix J) (84). Consistent with the assessment group (AG) model/approach in TA375 and recent RA submissions to NICE, a HR was applied to

the general population mortality rates based on baseline HAQ (25, 28) to estimate mortality for patients with RA in the model. HRs applied by TA375 were originally reported in Michaud et al. (2012) (75), and are presented in Table 57. Only baseline HAQ was considered when predicting mortality in TA375 as well as in the present model. Additionally, HRs were assumed to be constant over time, and patients were assumed not to live beyond 100 years.

Table 57. Hazard ratios for mortality by HAQ category

HAQ category	HR	SE
0	1.0	0.0
0.125-0.375	1.4	0.18
0.5-0.875	1.5	0.18
1.0-1.375	1.8	0.20
1.5-1.875	2.7	0.33
2.0-2.375	4.0	0.54
2.5-3.0	5.5	0.97
Abbreviations: HAQ=Health Assessment Questionnaire Disability Index; HR=hazard ratio; SE=standard error		

B.3.4 Measurement and valuation of health effects

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

The EQ-5D-5L questionnaire was used to collect HRQOL data in the upadacitinib phase III trials, however, to align modelling of Health-related quality of life (HRQOL) with previous submissions (TA375 and others (25, 28) by linking to HAQ scores, data from alternative sources were used in the base case, as outlined below. EQ-5D data from the trials was used to validate the output from the model.

B.3.4.2 Mapping

In the base-case, utility values were estimated by mapping HAQ scores to EQ-5D over the entire model horizon. This approach fits with the DES model framework in which HAQ progression is simulated over continuous time and in which there are not defined “health states” to which specific EQ-5D utility values can be directly attributed. Therefore, for the cost-effectiveness evaluation of upadacitinib HRQOL was modelled using the standard approach of mapping to EQ-5D from HAQ.

An SLR of quality of life inputs did not find cause to deviate from this approach. HAQ is a widely used measure in RA clinical trials and has been shown to correlate well with EQ-5D. EQ-5D was estimated based on the four-class mixture model detailed in Hernandez et al. (2014) (85).

The mapping algorithm was applied in the CEA model using a 3-step process:

1. Estimation of pain VAS

In the base-case, pain was estimated based on HAQ using IPD from the Phase III upadacitinib trials for the csDMARD-IR (SELECT-NEXT, SELECT-MONOTHERAPY, SELECT-SUNRISE, SELECT COMPARE trials) and bDMARD-IR (SELECT-BEYOND) populations (Table 58) (51, 56, 62, 72, 73). Analysis of best fit between predicted and observed utility values indicated that mapping using upadacitinib phase 3 trial data provided a better fit than using the mapping method used in TA375. This analysis is presented in Appendix J.

In a scenario analysis, pain scores were estimated based on the pain by HAQ mapping detailed in TA3757. The pain scores in TA375 were estimated using data from the US National Data Bank for Rheumatic Diseases (NDB), with mean pain score (and standard error) estimated for each valid HAQ score (Table 58).

2. Assignment to latent classes

The probability of belonging to each of the four latent classes was estimated for patients in the CEA based on the simulated HAQ score and pain VAS using the coefficients outlined in the Hernandez et al. (2014) study (85).

3. Estimation of utility based on class assignment and covariates

Weighted by the probabilities of the class assignment in Step 2, utility was estimated based on patient simulated HAQ, pain, and age using the coefficients outlined in Hernandez et al. (2014) (85).

To prevent impossible EQ-5D values, the estimated utility values were rescaled based on the bounds described in Dolan et al. (1995) (86). Patients with a utility value of 0.883 (i.e., the highest possibly utility for EQ-5D) or greater were assumed to have perfect utility (i.e., EQ-5D=1). Alternatively, values that were less than -0.594

(i.e., the lowest possibly utility for EQ-5D) were assumed to equal the worst utility (i.e., EQ-5D = -0.594). Values in between the upper and lower bounds were rescaled based on a truncated normal distribution. This rescaling approach is consistent with the approach used in TA375.

The base-case analysis assumed that HAQ change (initial reduction and progression) occurred linearly over time. The utility of a valid HAQ progression event (ΔHAQ=0.125) equals the average of the utility based on the prior HAQ and the new HAQ value.

Table 58. Mapping of HAQ to pain VAS score

HAQ score	Base-case (Phase III upadacitinib trials)		Sensitivity (TA375)	
	Pain score (VAS)	SE	Pain score (VAS)	SE
0	[redacted]	[redacted]	11.83	0.60
0.125	[redacted]	[redacted]	18.32	0.93
0.25	[redacted]	[redacted]	19.38	0.99
0.375	[redacted]	[redacted]	22.57	1.15
0.5	[redacted]	[redacted]	24.95	1.27
0.625	[redacted]	[redacted]	27.64	1.41
0.75	[redacted]	[redacted]	30.46	1.55
0.875	[redacted]	[redacted]	32.40	1.65
1	[redacted]	[redacted]	35.20	1.80
1.125	[redacted]	[redacted]	37.55	1.92
1.25	[redacted]	[redacted]	41.38	2.11
1.375	[redacted]	[redacted]	44.07	2.25
1.5	[redacted]	[redacted]	46.83	2.39
1.625	[redacted]	[redacted]	50.07	2.55
1.75	[redacted]	[redacted]	53.29	2.72
1.875	[redacted]	[redacted]	55.40	2.83
2	[redacted]	[redacted]	57.41	2.93
2.125	[redacted]	[redacted]	58.93	3.01
2.25	[redacted]	[redacted]	61.82	3.15
2.375	[redacted]	[redacted]	63.94	3.26
2.5	[redacted]	[redacted]	67.75	3.46
2.625	[redacted]	[redacted]	69.33	3.54
2.75	[redacted]	[redacted]	67.73	3.46

HAQ score	Base-case (Phase III upadacitinib trials)		Sensitivity (TA375)	
	Pain score (VAS)	SE	Pain score (VAS)	SE
2.875	[redacted]	[redacted]	61.37	3.13
3	[redacted]	[redacted]	58.02	2.96
Abbreviations: HAQ=Health Assessment Questionnaire Disability Index; SE=standard error; VAS=visual analogue scale				

B.3.4.3 Health-related quality-of-life studies

B.3.4.3.1 Identification of studies

A systematic review was conducted to identify studies from the published literature reporting health state utility values (HSUVs) associated with patients with RA. Full details are available in Appendix H.

B.3.4.4 Adverse reactions

SAEs were considered in the base-case analysis. Any AE meeting the International Conference of Harmonisation E2A criteria (including serious infection) was considered in the model as these are the major AEs associated with treatments that could affect RA patients (25). AEs that are not serious were less likely to be associated with high costs and disutility and were not considered in the model. The rate of SAEs was derived from an analysis of SELECT-COMPARE (51) patient-level data. SELECT-COMPARE was used for this analysis as the trial included long-term safety (52 weeks) data for comparators from each class of therapy represented in the model, csDMARDs, bDMARDs and JAK inhibitors. Rates were dependent on class of therapy, rather than specific drugs. Although the approach represents a simplification of the disease and safety profiles of RA therapies, it is considered a conservative approach, as upadacitinib is considered to have a favourable safety and tolerability profile in patients with moderate to severe active RA compared to other treatments. Rates used in the model are presented in Table 59. This approach is consistent with that used by the baricitinib NICE submission, which analysed similar data from the RA-BEAM trial to produce class-level SAE rates (25).

Table 59. Incidence of SAE

Drug class	Rate of SAE per patient-year
csDMARD	0.096
bDMARD	0.156

JAK inhibitor	0.129
Abbreviation: bDMARD=biologic disease-modifying anti-rheumatic drug; csDMARD=conventional disease-modifying anti-rheumatic drug; JAK=janus kinase; SAE=serious adverse event.	

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

Utility values associated with HAQ scores were used to capture the HRQoL impact of treatments. Mapping was based on a model reported by Hernandez et al. 2012 (85), with full details of the mapping rationales and parameters presented in section B.3.4.2 Mapping.

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

The costs and healthcare resource use included in the model are as follows:

- Drug acquisition costs
- Drug administration costs
- Drug monitoring costs
- SAE costs
- Hospitalisation cost (dependent upon HAQ score)

This aligns with the resource use inputs considered in the AG's model in TA375. Each cost component is described in detail below.

B.3.5.1 Resource identification, measurement and valuation studies

B.3.5.1.1 Identification of studies

A systematic review was conducted to identify cost and resource use data from the published literature associated with patients with rheumatoid arthritis (RA). Full details of the search are provided in Appendix I.

B.3.5.2 Intervention and comparators' costs and resource use

The perspective adopted for the analysis was that of the UK NHS and personal social services. All costs were reported in British Pound Sterling with a 2018 price base. For costs not available for the most recent year but only from previous years,

values were inflated to 2018 prices using the Personal Social Services Research Unit (PSSRU) hospital & community health services (HCHS) inflation rate index.

Drug acquisition costs were calculated in the model as a function of unit drug costs and dosing schedules for each treatment (details are presented in Appendix J). The model included only doses currently approved in the UK. For treatments with multiple approved doses with the same annual cost, the dose with better efficacy was included in the model (i.e., baricitinib 2 mg, sarilumab 150 mg, tofacitinib 10 mg were not included in the current model) to be conservative in the comparison with upadacitinib. Unit drug costs for advanced therapies were retrieved from the Monthly Index of Medical Specialties (MIMS) database (87). For conventional treatments that are available as generics, unit costs were obtained from the electronic Market Information Tool (eMIT) from the Commercial Medicines Unit of the NHS, which provides mean product prices for generic medicines drawn from information from about 95% of NHS Trusts (88). Loading doses were considered in the calculation of drug cost during the first year on treatment, when applicable. Assumptions regarding dosing schedules are presented in Appendix J. The dosing schedule for upadacitinib was based on the 15md QD dose as defined in the drug's SmPC (51, 56, 59, 62, 73, 89). This dose is consistent with the expected dosing for upadacitinib in the UK label application. For comparator treatments, doses approved in the UK were considered. For drugs with weight-based dosing (e.g., infliximab and golimumab), doses for patients were computed based on the simulated baseline weight of each patient.

IV and oral formulations for MTX are available in the UK setting. For simplicity, the model only considered oral MTX, which is the most common formulation used in UK clinical practice (90). As MTX is inexpensive compared to advanced therapies, inclusion of only the oral formulation is expected to have minor impact on model results and represents a more conservative modelling approach. Similarly, the cost of csDMARD was assumed to equal the cost of MTX, which is considered a more conservative approach than including more expensive csDMARDs. The cost of intensive csDMARD was based on the cost of hydroxychloroquine + prednisolone + sulfasalazine + MTX estimated in TA375 and inflated to 2018 costs (28). For simplicity, patient weight was not considered in the cost of intensive csDMARD, as the cost of hydroxychloroquine was considered marginal compared to the cost of

advanced therapies. For treatments used in combination with MTX, the annual cost of MTX was added to the annual cost of the treatments.

Many of the approved drugs in the UK have patient access schemes (PAS). For drugs with a publicly available PAS, the drug cost in the base-case considered the PAS. Abatacept, baricitinib, tocilizumab, tofacitinib, and sarilumab have a confidential PAS; no assumptions were made regarding the PAS for these drugs (i.e., no discount was assumed). Certolizumab pegol and golimumab have a non-confidential PAS, which was considered in the model. For infliximab, the dosing of which is weight-based, vial wastage has been assumed.

The cost of BSC was estimated based on TA375 and inflated to 2018 costs (28). The costs of BSC are reflective of healthcare costs for patients who are managed without targeted therapy. The costs were approximated based on use of post-biologic csDMARD therapy (e.g., leflunomide, gold, cyclosporine).

Drug administration costs depended on the route of administration for a given treatment (Table 60). The unit costs of administration for drugs administered by IV infusion or SC injection were based on the values reported in TA375, based on previous NICE guidance and submissions, including TA247 (32) and the baricitinib appraisal (25). All costs were inflated to 2018 GBP using the HCHS Index (91). As described in TA375, the cost of an administration of a SC injection was based on the assumption that 10% of injections would be performed by district nurses (28).

Table 60. Drug administration costs

Route of administration	Cost (2018 £)	Source
IV	158.68	TA375(28) as based on previous NICE guidance and submissions, including TA247 (32) and assumptions used in the Birmingham Rheumatoid Arthritis Model.
SC	3.14	
Oral	0.00	
Abbreviation: IV=intravenous; SC=subcutaneous.		

A summary of annual drug and administration costs is presented in Table 61.

Table 61. Annual drug and administration cost of intervention and comparators

Treatment	Drug and administration cost (2018 £)	
	During response period (months 0 – 6)	Subsequent annual cost
ABT IV	7,278	11,834

Treatment	Drug and administration cost (2018 £)	
	During response period (months 0 – 6)	Subsequent annual cost
ABT SC	7,889	15,779
ADA	4,019	8,039
BRC	5,254	10,508
BSC	124	742
csDMARD	8	17
Intensive csDMARD	107	215
CTZ	2,518	9,327
ETN	4,279	8,557
GOL	4,976	9,953
IFX	6,233	7,377
MTX	8	17
RTX	2,096	4,191
SRL	5,950	11,900
TCZ IV	5,343	10,686
TCZ SC	5,956	11,911
TFC	4,501	9,001
UPA	[redacted]	[redacted]

Abbreviation: ABT=abatacept; ADA=adalimumab; BRC=baricitinib; BSC=best supportive care; csDMARD=conventional disease-modifying anti-rheumatic drug; CTZ=certolizumab pegol; ETN=etanercept; GOL=golimumab; IFX=infliximab; IV=intravenous; MTX=methotrexate; RTX=rituximab; SC=subcutaneous; SRL=sarilumab; TCZ=tocilizumab; TFC=tofacitinib; UPA=upadacitinib.

B.3.5.3 Health-state unit costs and resource use

Monitoring costs

Monitoring costs were applied during the time on treatment (Table 62). In line with TA375 and the baricitinib model (25, 28), the same monitoring costs were applied to patients receiving csDMARDs, bDMARDs, and JAK inhibitors. Patients on BSC did not receive pre-treatment monitoring costs but were assigned the same monthly monitoring costs as patients on active treatment. The monitoring costs were derived from Malottki et al. (2011), consistent with the assessment group (AG) model/approach in TA375 and prior NICE submissions in RA (25, 28, 30), and inflated to 2018 GBP using the HCHS index (83, 91).

Table 62. Monitoring costs

Time-period	Cost (2018 £)	Source
Pre-treatment	175	NHS Reference Costs (92); Malottki et al. (2011) (83)
First 6 months	1752	
Monthly	138	

Hospitalisation costs per HAQ

In line with TA375, hospitalization costs by HAQ were based on an analysis conducted by a prior submission by Roche using the Norfolk Arthritis Register (NOAR) database on inpatient days and joint replacement multiplied by NHS reference costs (28). Given limited data in the literature, the Assessment Group assumed the lowest hospitalization costs with a relatively slower increase rate by HAQ, based on the NOAR analysis and other data used in other prior submissions (Table 63). In the model, each possible HAQ score was associated with an annual hospitalization cost, allowing for changes in hospitalization costs as HAQ increased. Patients incurred hospitalization costs based on current HAQ throughout the modelled time horizon. During the initial 6-month response period, HAQ costs were calculated as the average of costs based on baseline HAQ and costs based on reduced HAQ following response. After the initial response period, HAQ changes were assumed to occur in a step-wise manner. HAQ costs during this period were estimated assuming linear change from the prior HAQ cost to the new HAQ cost when HAQ change occurred.

Table 63. Annual hospitalization costs based on HAQ

HAQ	Cost (2018 £)
0	280.65
0.125	187.30
0.25	151.95
0.375	147.39
0.5	131.89
0.625	121.77
0.75	88.58
0.875	157.99
1	227.08
1.125	302.89
1.25	388.08
1.375	430.36
1.5	458.69
1.625	487.66
1.75	508.14
1.875	707.05
2	1,003.91
2.125	1,068.34
2.25	1,290.95

HAQ	Cost (2018 £)
2.375	1,737.64
2.5	2,041.66
2.625	2,313.81
2.75	2,684.70
2.875	3,432.35
3	4,379.18
Abbreviation: HAQ=Health Assessment Questionnaire Disability Index.	

Adverse reaction unit costs and resource use

The base-case model included costs of SAE, which was estimated based on the costs of treatment for serious infections (Table 64). Incidence of SAEs for the intervention and comparators were derived from an analysis of SELECT-COMPARE (51) patient-level data, as detailed in B.3.4.4 Adverse reactions. SAEs were assigned a disutility of -0.012 per event consistent with Oppong et al. (2013) (93) and the TA375 submission, as referenced in TA375 directly from the manufacturer submission. The disutility was assumed to occur upon the initiation of the first treatment within a treatment sequence. Only first-line treatments were assigned AE disutility (e.g., patients who moved on later lines of treatment did not experience additional disutility due to AEs). Although this is a simplification of the treatment pathway, it is consistent with the approaches used in TA375 and prior NICE submissions in RA (25, 28, 30).

Cost and disutility of AEs were derived from Oppong et al. (2013) (93), as used and referenced in TA375 (28).

Table 64. Adverse event costs

Cost per event (2018 £)	Value	Source
csDMARD	1,524	Pfizer submission for TA375 as referenced in TA375; HCHS index (91)
bDMARD	1,538	
JAK inhibitor	1,538	
Abbreviation: bDMARD= biologic disease-modifying anti-rheumatic drug; csDMARD= conventional synthetic disease-modifying anti-rheumatic drug(s); HCHS= hospital & community health services; JAK= Janus kinase		

Miscellaneous unit costs and resource use

No additional costs or resource use items were included in the model that which have not already been listed above.

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

B.3.6.1 Summary of base-case analysis inputs

The summary of base-case analysis inputs is presented in Appendix J.

B.3.6.2 Assumptions

The model assumptions and justifications are summarized in Table 65-Table 63c**: Upadacitinib Model outcomes utility and long-term outcome assumptions compared to TA375**.

Table 65a. Upadacitinib Model Structure and resource use / cost and adverse event assumptions compared to TA 375

Section of submission	Base case modelling approach / assumption	Detail if appropriate	Same as TA375 (ScHARR model)	Rationale if diverges from TA 375 / additional clarification
B.3.2.2.	**HE Model structure**	Based on the ScHARR patient-level model using a discrete event simulation structure with a 6-month cycle length	Yes	
B.3.2.3.	**Positioning of advanced therapy**	The same as in TA375 for severe RA and subsequent RA drug appraisals. The same as TA375 for moderate RA except Abbvie provide an additional position for the use of upadacitinib after one csDMARD failure (moderate RA)	Yes	The Abbvie NICE Clinical advisory board held July 2018 indicated UK clinicians would want to use upadacitinib after one csDMARD failure in line with EULAR guidelines (as well as after two or more)(1)
B.3.2.3.	**Treatment sequencing**	Except 1) Abbvie provide an additional position after one csDMARD failure (moderate RA) as described above and 2) treatment sequence for moderate RA patients once they transition from moderate RA to severe included	Yes	Except 1) Abbvie NICE Clinical advisory board held July 2018 indicated UK clinicians would want to use upadacitinib after one csDMARD failure in line with EULAR guidelines - see above. 2) Most recent NICE RA appraisal (sarilumab) ScHARR ERG requested and the NICE Committee agreed the addition of a treatment sequence for patients who transition from moderate RA to severe to the base case model.
B.3.3.	**Baseline characteristics**	Derived from upadacitinib clinical trial IPD	No	TA375 baseline characteristics from BSRBR IPD data (not available to AbbVie)
B.3.5.2.	**Drug acquisition costs**	Upadacitinib PAS price and list prices for comparators except those with non- confidential PAS discounts. Confidential PAS prices not known.	No	Confidential comparator PAS prices not known by AbbVie but known to the ERG conducting TA375
B.3.5.2.	**Best supportive care cost**		Yes	

Section of submission	Base case modelling approach / assumption	Detail if appropriate	Same as TA375 (ScHARR model)	Rationale if diverges from TA 375 / additional clarification
B.3.5.2.	**Drug administration costs**		Yes	
B.3.5.3.	**Monitoring costs**		Yes	
B.3.5.3.	**Non drug associated health care costs**	Hospitalisation costs per HAQ score based on NOAR analysis (70)	Yes	
B.3.5.3.	**Adverse event costs**	Oppong et al 2013 (102)	Yes	
B.3.4.4.	**Adverse event rates**	Based on upadacitinib SELECT-COMPARE study	No	SELECT -COMPARE has head to head AE data for upadacitinib, a bDMARD (adalimumab) and csDMARD. Used to populate the model. TA375 based on a review of bDMARDs. Same approach as AbbVie model in TA375 that only serious adverse events included.
B.3.5.3.	**Adverse event disutilities**	Oppong et al 2013 (102)	Yes	

Table 63b. Upadacitinib Model treatment effectiveness assumptions compared to TA375

Section of submission	Base case modelling approach / assumption	Detail if appropriate	Same as TA375 (ScHARR model)	Rationale if diverges from TA 375 / additional clarification
B.3.3.	**Clinical response measure**	EULAR response mapped from ACR20 NMAs	Yes	
B.3.3.	**Relative effectiveness source**	csDMARD failure NMA and bDMARD failure NMA	Yes	Whilst a csDMARD-IR NMA was carried out for TA375 a bDMARD-IR NMA was not carried out because this was not a population covered by the decision problem
B.3.3.	**Type of NMA carried out**	Combined 12 week and 26-week NMA	No	TA375 used a 26week NMA to populate a HE model with a 6-month cycle length (6 months is the NICE recommended follow up for review of RA drugs). All four of upadacitinib registration studies break randomization at 12-14 weeks. An approach was needed to estimate upadacitinib efficacy at 6 months (tofacitinib in its NICE appraisal faced a similar challenge)
B.3.3.	**Source of efficacy data for appraised drug**	For upadacitinib + MTX: SELECT-NEXT, SELECT COMPARE and SELECT-SUNRISE (csDMARD-IR population) and SELECT-BEYOND (bDMARD-IR population) For upadacitinib monotherapy: SELECT-MONOTHERAPY (csDMARD-IR population)	Yes	TA375 appraised studies with advanced therapies used in combination or as monotherapies. Based on the SLR of clinical effectiveness carried out by AbbVie neither upadacitinib nor any of its advanced therapy competitors have monotherapy clinical trial data in the bDMARD-IR population For illustrative purposes, an assumption of comparable efficacy between upadacitinib monotherapy and baricitinib + MTX in the bDMARD-IR population has been made to estimate the cost effectiveness of upadacitinib monotherapy in this population. This assumption was supported by the comparable efficacy between upadacitinib monotherapy and baricitinib in combination with MTX estimated by the csDMARD-IR NMA.

Table 63c: Upadacitinib Model outcomes utility and long-term outcome assumptions compared to TA375

Section of submission	Base case modelling approach / assumption	Detail if appropriate	Same as TA375 (ScHARR model)	Rationale if diverges from TA 375 / additional clarification
B.3.3.	**Initial change in HAQ**	Based on UK BSRBR-RA database analysis (87)	Yes	
B.3.3.	**Initial HAQ change occurs at the end of six months**		Yes	
B.3.3.	**No treatment discontinuation in initial 6 months**		Yes	
B.3.3.	**Long term HAQ progression**	csDMARD and BSC HAQ progression based on Norton et al 2014 (89). Advanced therapy (bDMARD, JAKs including upadacitinib) no HAQ progression	Yes	No JAKs were appraised in TA375 but the assumption that no HAQ progression in advanced therapies (bDMARDs) was extended to JAKs and accepted in NICE appraisals of the JAKs baricitinib and tofacitinib
B.3.3.	**Upon treatment discontinuation reversion to baseline HAQ**		Yes	
B.3.3.	**Mortality rate**	RA mortality rates based on Michaud et al 2012 (75)	Yes	
B.3.4.2.	**Mapping HAQ to utilities: Stage 1 HAQ mapped to pain VAS score**	Derived from upadacitinib clinical trials	No	TA375 used a map based on the US National Database (NDB) and UK ERAS data (the approach followed in the baricitinib and sarilumab appraisals). The approach used by AbbVie is in line with that accepted by the ERG and the NICE Committee for the tofacitinib NICE appraisal which showed the best fit to actual observed trial EQ-5D data using a HAQ to pain VAS score map based on clinical trial data (better than the one based on the US NDB and ERAS dataset). Similar findings were found using upadacitinib trial data which is presented in Appendix J.
B.3.4.2.	**Mapping HAQ to utilities: Stage 2 & 3 utility assigned based on HAQ / pain VAS score / age / sex**	Mapping based on Hernandez et al 2014 (92)	Yes	

B.3.7 Base-case results

B.3.7.1 Base-case incremental cost-effectiveness analysis results

Whilst the NICE reference case specifies probabilistic analysis (PSA), deterministic base case analyses have been carried out due to the time constraints associated with running PSAs. As seen in the PSA section, the difference between deterministic and probabilistic results is relatively minimal. The base case deterministic cost-effectiveness results for the following populations are presented below:

- Use of upadacitinib monotherapy and combination therapy in moderate RA:
    1. After one csDMARD failure
    2. After two or more csDMARD failure
- Use of upadacitinib monotherapy and combination therapy in severe RA in those who are methotrexate eligible:
    3. Versus first line advanced therapies in combination with methotrexate
    4. After first line advanced therapy failure in those who are rituximab ineligible versus advanced therapies
    5. After first line advanced therapy failure versus rituximab in combination with methotrexate (in rituximab eligible patients)
    6. After rituximab in combination with methotrexate failure versus methotrexate in combination with tocilizumab or sarilumab
- Use of upadacitinib monotherapy in severe RA amongst those who are methotrexate ineligible:

    3a. Versus first line advanced therapies used as monotherapies (in methotrexate ineligible patients)

    4a. After first line advanced therapy failure in those who are methotrexate ineligible

1b. One csDMARD failure, MTX eligible, moderate RA

The results of the base case analysis for the moderate, MTX eligible patient population after one csDMARD failure are presented in Table 66 and Table 67, for upadacitinib combination therapy and upadacitinib monotherapy, respectively. Compared to intensive csDMARD, upadacitinib combination therapy and upadacitinib monotherapy were associated with QALY gains, and increased costs, generating incremental cost-effectiveness ratio (ICER) of £62,907 per QALY, and £65,914 per QALY, respectively.

Table 66. One csDMARD failure, MTX eligible, moderate RA – versus UPA 15mg + MTX (deterministic results)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus UPA 15mg + MTX (£/QALY)
Intensive csDMARD	[redacted]	15.255	[redacted]	-	-	62,907
UPA 15mg + MTX	[redacted]	15.255	[redacted]	[redacted]	[redacted]	Reference

Abbreviations: csDMARD=conventional disease-modifying anti-rheumatic drug, LYG = Life Year Gained, MTX= Methotrexate, QALY = Quality Adjusted Life Year, RA = Rheumatoid Arthritis, UPA= Upadacitinib

Table 67. One csDMARD failure, MTX eligible, moderate RA – versus UPA 15mg (deterministic results)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus UPA 15mg + MTX (£/QALY)
Intensive csDMARD	[redacted]	15.255	[redacted]	-	-	65,914
UPA 15mg + MTX	[redacted]	15.255	[redacted]	[redacted]	[redacted]	Reference

Abbreviations: csDMARD=conventional disease-modifying anti-rheumatic drug, LYG = Life Year Gained, MTX= Methotrexate, QALY = Quality Adjusted Life Year, RA = Rheumatoid Arthritis, UPA= Upadacitinib

1a. One csDMARD failure, MTX ineligible, moderate RA

The results of the base case analysis for the moderate, MTX ineligible patient population after one csDMARD failure are presented in Table 68. Compared to intensive csDMARDs, upadacitinib monotherapy generated QALY gains, and was associated with higher costs, generating an ICER of £48,877 per QALY.

Table 68. One csDMARD failure, MTX ineligible, moderate RA – versus UPA 15mg (deterministic results)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus UPA 15mg (£/QALY)
Intensive csDMARD	[redacted]	15.255	[redacted]	-	-	48,877
UPA 15mg	[redacted]	15.255	[redacted]	[redacted]	[redacted]	Reference

Abbreviations: csDMARD=conventional disease-modifying anti-rheumatic drug, LYG = Life Year Gained, MTX= Methotrexate, QALY = Quality Adjusted Life Year, RA = Rheumatoid Arthritis, UPA= Upadacitinib

2b. Two csDMARD failure, MTX eligible, moderate RA

The results of the base case analysis for the moderate, MTX eligible patient population after two csDMARD failure are presented in Table 69 and Table 70, for upadacitinib combination therapy and upadacitinib monotherapy, respectively. Compared to MTX, upadacitinib combination therapy and upadacitinib monotherapy were associated with substantial QALY gains and increased costs, generating ICERs of £47,486 per QALY and £47,576 per QALY, respectively.

Table 69. Two csDMARD failure, MTX eligible, moderate RA – versus UPA 15mg + MTX (deterministic results)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus UPA 15mg + MTX (£/QALY)
MTX	[redacted]	15.255	[redacted]	-	-	47,486
UPA 15mg + MTX	[redacted]	15.255	[redacted]	[redacted]	[redacted]	Reference

Abbreviations: csDMARD=conventional disease-modifying anti-rheumatic drug, LYG = Life Year Gained, MTX= Methotrexate, QALY = Quality Adjusted Life Year, RA = Rheumatoid Arthritis, UPA= Upadacitinib

Table 70. Two csDMARD failure, MTX eligible, moderate RA – versus UPA 15mg (deterministic results)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus UPA 15mg (£/QALY)
MTX	[redacted]	15.255	[redacted]	-	-	47,576
UPA 15mg	[redacted]	15.255	[redacted]	[redacted]	[redacted]	Reference

Abbreviations: csDMARD=conventional disease-modifying anti-rheumatic drug, LYG = Life Year Gained, MTX= Methotrexate, QALY = Quality Adjusted Life Year, RA = Rheumatoid Arthritis, UPA= Upadacitinib

2a. Two csDMARD failures, MTX ineligible, moderate RA

The results of the base case analysis for the moderate, MTX ineligible patient population after two csDMARD failures are presented in Table 71. Compared to BSC, upadacitinib monotherapy was associated with a substantial QALY gain (0.795) and increased costs, generating an ICER of £34,537 per QALY.

Table 71. Two csDMARD failure, MTX ineligible, moderate RA – versus UPA 15mg (deterministic results)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus UPA 15mg (£/QALY)
BSC	[redacted]	15.255	[redacted]	-	-	34,537
UPA 15mg	[redacted]	15.255	[redacted]	[redacted]	[redacted]	Reference

Abbreviations: BSC=best supportive care, csDMARD=conventional disease-modifying anti-rheumatic drug, LYG = Life Year Gained, MTX=methotrexate; QALY = quality-adjusted life year, RA=rheumatoid arthritis; UPA=upadacitinib.

3b. csDMARD-IR, MTX eligible, severe RA

The results of the base case analysis for the csDMARD-IR, MTX eligible severe patient population for upadacitinib combination therapy are presented in Table 72. When compared to infliximab + MTX, upadacitinib combination therapy generated an ICER of

£49,418 per QALY. Upadacitinib combination therapy demonstrated higher total QALYs compared to all alternative treatments, apart from certolizumab + MTX. When compared with certolizumab + MTX, upadacitinib combination therapy was less costly and less effective and was cost effective against CTZ + MTX at a cost effectiveness threshold of £30,000 since CTZ + MTX was associated with an ICER of £4,520,624 versus upadacitinib combination therapy. All other comparators were dominated by upadacitinib combination therapy.

Table 72. csDMARD-IR, MTX eligible, severe RA – versus UPA 15mg + MTX (deterministic results)

Technologies	Total costs (£)	Total QALYs	Total LYG	Full incremental costs (£)	Full incremental QALYs	ICER incremental (£/QALY)
IFX + MTX	[redacted]	[redacted]	14.2	-	-	Reference
UPA 15mg + MTX	[redacted]	[redacted]	14.2	[redacted]	[redacted]	49,418
ADA + MTX	[redacted]	[redacted]	14.2	[redacted]	[redacted]	Dominated
ETN + MTX	[redacted]	[redacted]	14.2	[redacted]	[redacted]	Dominated
GOL + MTX	[redacted]	[redacted]	14.2	[redacted]	[redacted]	Dominated
TFC + MTX	[redacted]	[redacted]	14.2	[redacted]	[redacted]	Dominated
CTZ + MTX	[redacted]	[redacted]	14.2	[redacted]	[redacted]	4,520,624
BRC + MTX	[redacted]	[redacted]	14.2	[redacted]	[redacted]	Dominated
TCZ IV + MTX	[redacted]	[redacted]	14.2	[redacted]	[redacted]	Dominated
TCZ SC + MTX	[redacted]	[redacted]	14.2	[redacted]	[redacted]	Dominated
ABT IV + MTX	[redacted]	[redacted]	14.2	[redacted]	[redacted]	Dominated
SRL + MTX	[redacted]	[redacted]	14.2	[redacted]	[redacted]	Dominated
ABT SC + MTX	[redacted]	[redacted]	14.2	[redacted]	[redacted]	Dominated

Abbreviations: ABT=abatacept; ADA=adalimumab; BRC=baricitinib; BSC=best supportive care; csDMARD=conventional disease-modifying anti-rheumatic drug; CTZ=certolizumab pegol; ETN=etanercept; GOL=golimumab; INF=infliximab: IR=inadequate response; IV=intravenous infusion; LYG = Life Year Gained , MTX=methotrexate; N/A=not applicable; QALY = quality-adjusted life year RA=rheumatoid arthritis; RTX=rituximab; SC=subcutaneous injection; SRL=sarilumab; TCZ=tocilizumab; TFC=tofacitinib; UPA=upadacitinib.

The results of the base case analysis for the csDMARD-IR, MTX eligible severe patient population for upadacitinib monotherapy are presented in Table 73. In the incremental analysis, upadacitinib monotherapy generated ICERs of £117,383 per QALY. When compared with certolizumab + MTX, upadacitinib monotherapy was less costly and less effective and was cost effective against CTZ + MTX at a cost effectiveness threshold of £30,000 since CTZ + MTX was associated with an ICER of £150,997. The other treatments were dominated or extendedly dominated.

Table 73. csDMARD-IR, MTX eligible, severe RA - versus UPA 15 mg (deterministic results)

Technologies	Total costs (£)	Total QALYs	Total LYG	Full incremental costs (£)	Full incremental QALYs	ICER incremental (£/QALY)
IFX + MTX	[redacted]	[redacted]	14.2	-	-	Reference
UPA 15mg	[redacted]	[redacted]	14.2	[redacted]	[redacted]	117,383
ADA + MTX	[redacted]	[redacted]	14.2	[redacted]	[redacted]	Dominated
ETN + MTX	[redacted]	[redacted]	14.2	[redacted]	[redacted]	Dominated
GOL + MTX	[redacted]	[redacted]	14.2	[redacted]	[redacted]	Ext. dominated
TFC + MTX	[redacted]	[redacted]	14.2	[redacted]	[redacted]	Ext. dominated
CTZ + MTX	[redacted]	[redacted]	14.2	[redacted]	[redacted]	150,997
BRC + MTX	[redacted]	[redacted]	14.2	[redacted]	[redacted]	Dominated
TCZ IV + MTX	[redacted]	[redacted]	14.2	[redacted]	[redacted]	Dominated
TCZ SC + MTX	[redacted]	[redacted]	14.2	[redacted]	[redacted]	Dominated
ABT IV + MTX	[redacted]	[redacted]	14.2	[redacted]	[redacted]	Dominated
SRL + MTX	[redacted]	[redacted]	14.2	[redacted]	[redacted]	Dominated
ABT SC + MTX	[redacted]	[redacted]	14.2	[redacted]	[redacted]	Dominated

Abbreviations: ABT=abatacept; ADA=adalimumab; BRC=baricitinib; BSC=best supportive care; csDMARD=conventional disease-modifying anti-rheumatic drug; CTZ=certolizumab pegol; ETN=etanercept; GOL=golimumab; INF=infliximab: IR=inadequate response; IV=intravenous infusion; LYG = Life Year Gained , MTX=methotrexate; N/A=not applicable; QALY = quality-adjusted life year RA=rheumatoid arthritis; RTX=rituximab; SC=subcutaneous injection; SRL=sarilumab; TCZ=tocilizumab; TFC=tofacitinib; UPA=upadacitinib.

5. bDMARD-IR, MTX eligible, RTX eligible, severe RA

The results of the base case analysis for the bDMARD-IR, MTX eligible, RTX eligible severe patient population are presented in Table 74 and Table 75. Upadacitinib combination therapy and upadacitinib monotherapy were dominated by rituximab + MTX.

Table 74. bDMARD-IR, MTX eligible, RTX eligible, severe RA – versus UPA 15mg + MTX (deterministic results)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus UPA 15mg + MTX (£/QALY)
RTX + MTX	[redacted]	13.424	[redacted]	-	-	Dominant
UPA 15mg + MTX	[redacted]	13.424	[redacted]	[redacted]	[redacted]	Reference

Abbreviations: bDMARD = Biologic Disease-modifying Antirheumatic Drug, LYG = Life Year Gained, MTX=methotrexate; QALY = quality-adjusted life year, RA=rheumatoid arthritis; RTX=rituximab; UPA=upadacitinib.

Table 75. bDMARD-IR, MTX eligible, RTX eligible, severe RA – versus UPA 15mg (deterministic results)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus UPA 15mg (£/QALY)
RTX + MTX	[redacted]	13.424	[redacted]	-	-	Dominant
*UPA 15mg	[redacted]	13.424	[redacted]	[redacted]	[redacted]	Reference

Abbreviations: bDMARD = Biologic Disease-modifying Antirheumatic Drug, LYG = Life Year Gained, MTX=methotrexate; QALY = quality-adjusted life year, RA=rheumatoid arthritis; RTX=rituximab; UPA=upadacitinib.

*Assume same efficacy as BRC + MTX since no efficacy estimate available UPA 15mg MONO in bDMARD-IR NMA (UPA 15mg estimated as having the same efficacy as BRC+MTX in the csDMARD-IR NMA)

4b. bDMARD-IR, MTX eligible, RTX ineligible, severe RA

The results of the base case analysis for the bDMARD-IR, MTX eligible, RTX ineligible severe patient population for upadacitinib combination therapy are presented in Table 76. In the incremental analysis, all treatments were dominated or extendedly

dominated by upadacitinib combination therapy, except tocilizumab IV + MTX which was associated with higher costs and more benefits, generating an incremental ICER at £767,043 per QALY.

Table 76. bDMARD-IR, MTX eligible, RTX ineligible, severe RA – versus UPA 15mg + MTX (deterministic results)

Technologies	Total costs (£)	Total LYG	Total QALYs	Full incremental costs (£)	Full incremental QALYs	ICER incremental (£/QALY)
UPA 15mg + MTX	[redacted]	13.424	[redacted]	-	-	Reference
ADA + MTX	[redacted]	13.424	[redacted]	[redacted]	[redacted]	Dominated
IFX + MTX	[redacted]	13.424	[redacted]	[redacted]	[redacted]	Dominated
ETN + MTX	[redacted]	13.424	[redacted]	[redacted]	[redacted]	Dominated
CTZ + MTX	[redacted]	13.424	[redacted]	[redacted]	[redacted]	Dominated
GOL + MTX	[redacted]	13.424	[redacted]	[redacted]	[redacted]	Dominated
TFC + MTX	[redacted]	13.424	[redacted]	[redacted]	[redacted]	Dominated
BRC + MTX	[redacted]	13.424	[redacted]	[redacted]	[redacted]	Dominated
TCZ SC + MTX	[redacted]	13.424	[redacted]	[redacted]	[redacted]	Dominated
SRL + MTX	[redacted]	13.424	[redacted]	[redacted]	[redacted]	Ext. dominated
TCZ IV + MTX	[redacted]	13.424	[redacted]	[redacted]	[redacted]	767,043
ABT IV + MTX	[redacted]	13.424	[redacted]	[redacted]	[redacted]	Dominated
ABT SC + MTX	[redacted]	13.424	[redacted]	[redacted]	[redacted]	Dominated

Abbreviations: ABT=abatacept; ADA=adalimumab; bDMARD = Biologic Disease-modifying Antirheumatic Drug; BRC=baricitinib; BSC=best supportive care; csDMARD=conventional disease-modifying anti-rheumatic drug; CTZ=certolizumab pegol; ETN=etanercept; GOL=golimumab; INF=infliximab: IR=inadequate response; IV=intravenous infusion; , LYG = Life Year Gained, MTX=methotrexate; N/A=not applicable; QALY = quality-adjusted life year RA=rheumatoid arthritis; RTX=rituximab; SC=subcutaneous injection; SRL=sarilumab; TCZ=tocilizumab; TFC=tofacitinib; UPA=upadacitinib.

*Assume same efficacy as BRC +MTX (from bDMARD-IR NMA) since no efficacy estimate available for these comparators in bDMARD-IR
**Assume same efficacy as ABT IV+MTX (from bDMARD-IR NMA)

The results of the base case analysis for the bDMARD-IR, MTX eligible, RTX ineligible severe patient population for upadacitinib monotherapy are presented in Table 77. In the incremental analysis, all treatments were dominated or extendedly dominated by upadacitinib monotherapy, except tocilizumab IV + MTX which was associated with higher costs and more benefits, generating an incremental ICER at £348,956 per QALY.

Table 77. bDMARD-IR, MTX eligible, RTX ineligible, severe RA – versus UPA 15mg (deterministic results)

Technologies	Total costs (£)	Total LYG	Total QALYs	Full incremental costs (£)	Full incremental QALYs	ICER incremental (£/QALY)
UPA 15mg	[redacted]	13.424	[redacted]	-	-	Reference
ADA + MTX	[redacted]	13.424	[redacted]	[redacted]	[redacted]	Dominated
IFX + MTX	[redacted]	13.424	[redacted]	[redacted]	[redacted]	Dominated
ETN + MTX	[redacted]	13.424	[redacted]	[redacted]	[redacted]	Dominated
CTZ + MTX	[redacted]	13.424	[redacted]	[redacted]	[redacted]	Dominated
GOL + MTX	[redacted]	13.424	[redacted]	[redacted]	[redacted]	Dominated
TFC + MTX	[redacted]	13.424	[redacted]	[redacted]	[redacted]	Dominated
BRC + MTX	[redacted]	13.424	[redacted]	[redacted]	[redacted]	Ext. dominated
TCZ SC + MTX	[redacted]	13.424	[redacted]	[redacted]	[redacted]	Dominated
SRL + MTX	[redacted]	13.424	[redacted]	[redacted]	[redacted]	Ext. dominated
TCZ IV + MTX	[redacted]	13.424	[redacted]	[redacted]	[redacted]	348,956
ABT IV + MTX	[redacted]	13.424	[redacted]	[redacted]	[redacted]	Dominated
ABT SC + MTX	[redacted]	13.424	[redacted]	[redacted]	[redacted]	Dominated

Abbreviations: ABT=abatacept; ADA=adalimumab; bDMARD = Biologic Disease-modifying Antirheumatic Drug; BRC=baricitinib; BSC=best supportive care; csDMARD=conventional disease-modifying anti-rheumatic drug; CTZ=certolizumab pegol; ETN=etanercept; GOL=golimumab; INF=infliximab: IR=inadequate response; IV=intravenous infusion; , LYG = Life Year Gained , MTX=methotrexate; N/A=not applicable; QALY = quality-adjusted life year RA=rheumatoid arthritis; RTX=rituximab; SC=subcutaneous injection; SRL=sarilumab; TCZ=tocilizumab; TFC=tofacitinib; UPA=upadacitinib.

*Assume same efficacy as BRC +MTX (from bDMARD-IR NMA) since no efficacy estimate available for these comparators in bDMARD-IR NMA (UPA 15mg estimated as having the same efficacy as BRC+MTX in the csDMARD-IR NMA)
**Assume same efficacy as ABT IV+MTX (from bDMARD-IR NMA)

6. *bDMARD-IR, MTX eligible, RTX-IR, severe RA*

The results of the base case analysis for the bDMARD-IR, MTX eligible, RTX-IR severe patient population are presented in Table 78 and Table 79. Upadacitinib combination therapy dominates sarilumab + MTX. Compared to tocilizumab IV + MTX, upadacitinib combination therapy was less costly and less effective and the ICER associated with TCZ IV + MTX compared to upadacitinib combination therapy was £200,420. Similar to upadacitinib combination therapy, upadacitinib monotherapy dominated sarilumab + MTX, and was less costly and less effective compared to tocilizumab IV + MTX and the ICER associated with TCZ IV + MTX compared to upadacitinib combination therapy was £194,375 .

Table 78. bDMARD-IR, MTX eligible, RTX IR, severe RA – versus UPA 15mg + MTX (deterministic results)

Technologies	Total costs (£)	Total LYG	Total QALYs	Full incremental costs (£)	Full incremental QALYs	ICER incremental (£/QALY)
UPA 15mg + MTX	[redacted]	13.424	[redacted]	-	-	Reference
SRL + MTX	[redacted]	13.424	[redacted]	[redacted]	[redacted]	Dominated
TCZ IV + MTX	[redacted]	13.424	[redacted]	[redacted]	[redacted]	200,420

Abbreviations: bDMARD = Biologic Disease-modifying Antirheumatic Drug; IV= Intravenous; , LYG = Life Year Gained , MTX = methotrexate, QALY = quality-adjusted life year , RA = rheumatoid arthritis, RTX = rituximab; SRL = sarilumab; TCZ = tocilizumab; UPA = Upadacitinib

Table 79. bDMARD-IR, MTX eligible, RTX IR, severe RA – versus UPA 15mg (deterministic results)

Technologies	Total costs (£)	Total LYG	Total QALYs	Full incremental costs (£)	Full incremental QALYs	ICER incremental (£/QALY)
UPA 15mg*	[redacted]	13.424	[redacted]	-	-	Reference
SRL + MTX	[redacted]	13.424	[redacted]	[redacted]	[redacted]	Dominated
TCZ IV + MTX	[redacted]	13.424	[redacted]	[redacted]	[redacted]	194,375

Abbreviations: bDMARD = Biologic Disease-modifying Antirheumatic Drug; IV= Intravenous; LYG = Life Year Gained, MTX = methotrexate, QALY = quality-adjusted life year; RA = rheumatoid arthritis, RTX = rituximab; SRL = sarilumab; TCZ = tocilizumab; UPA = Upadacitinib

*Assume same efficacy as BRC+MTX (from bDMARD-IR NMA) since no efficacy estimate available UPA 15mg MONO in bDMARD-IR NMA (UPA 15mg estimated as having the same efficacy as BRC+MTX in the csDMARD-IR NMA)

3a. csDMARD-IR, MTX ineligible, severe RA

The results of the base case analysis for the csDMARD-IR, MTX ineligible severe patient population for upadacitinib monotherapy are presented in Table 80. Upadacitinib monotherapy dominates or extendedly dominates most of the comparators except tocilizumab IV. Tocilizumab IV is associated with higher costs and more benefits, generating an ICER of £324,600 versus upadacitinib monotherapy. Tocilizumab SC is extendedly dominated by TCZ IV. Upadacitinib monotherapy provides more benefits and more costs than adalimumab and is associated with an ICER of £12,792.

Table 80. csDMARD-IR, MTX ineligible, severe RA – versus UPA 15mg (deterministic results)

Technologies	Total costs (£)	Total LYG	Total QALYs	Full incremental costs (£)	Full incremental QALYs	ICER incremental (£/QALY)
ADA	[redacted]	14.197	[redacted]	-	-	Reference
ETN	[redacted]	14.197	[redacted]	[redacted]	[redacted]	Ext.dominated
UPA 15mg	[redacted]	14.197	[redacted]	[redacted]	[redacted]	12,792
TFC	[redacted]	14.197	[redacted]	[redacted]	[redacted]	Dominated
CTZ*	[redacted]	14.197	[redacted]	[redacted]	[redacted]	Dominated
BRC*	[redacted]	14.197	[redacted]	[redacted]	[redacted]	Dominated
SRL	[redacted]	14.197	[redacted]	[redacted]	[redacted]	Dominated
TCZ IV	[redacted]	14.197	[redacted]	[redacted]	[redacted]	324,600
TCZ SC**	[redacted]	14.197	[redacted]	[redacted]	[redacted]	Ext. dominated

Abbreviations: ADA = adalimumab, BRC = Baricitinib; csDMARD=conventional disease-modifying anti-rheumatic drug , CTZ = certolizumab pegol, ETN = etanercept, GOL = golimumab, IFX = infliximab, IV= Intravenous; LYG = Life Year Gained, MTX = methotrexate, QALY = quality-adjusted life year , RA = rheumatoid arthritis, RTX = rituximab; SC= Subcutaneous; SRL = sarilumab; TCZ = tocilizumab

*Assume same efficacy as ADA monotherapy (ADA efficacy from csDMARD-IR NMA) since no efficacy estimated for this comparator in the csDMARD-IR NMA
**Assume same efficacy as TCZ IV monotherapy (TCZ IV efficacy from csDMARD-IR NMA) since no efficacy estimated for this comparator in the csDMARD-IR NMA

4a. bDMARD-IR, MTX ineligible, severe RA

The results of the base case analysis for the bDMARD-IR, MTX ineligible severe patient population for upadacitinib monotherapy are presented in Table 81. In the incremental analysis, all treatments are dominated or extendedly dominated by upadacitinib monotherapy.

Table 81. bDMARD-IR, MTX ineligible, severe RA – versus UPA 15mg (deterministic results)

Technologies	Total costs (£)	Total LYG	Total QALYs	Full incremental costs (£)	Full incremental QALYs	ICER incremental (£/QALY)
UPA 15mg*	[redacted]	13.424	[redacted]	-	-	Reference
ADA*	[redacted]	13.424	[redacted]	[redacted]	[redacted]	Dominated
ETN*	[redacted]	13.424	[redacted]	[redacted]	[redacted]	Dominated
CTZ*	[redacted]	13.424	[redacted]	[redacted]	[redacted]	Dominated
TFC*	[redacted]	13.424	[redacted]	[redacted]	[redacted]	Ext. dominated
BRC*	[redacted]	13.424	[redacted]	[redacted]	[redacted]	Ext. dominated
SRL*	[redacted]	13.424	[redacted]	[redacted]	[redacted]	Dominated
TCZ SC*	[redacted]	13.424	[redacted]	[redacted]	[redacted]	Dominated
TCZ IV*	[redacted]	13.424	[redacted]	[redacted]	[redacted]	Dominated

Abbreviations: ADA = adalimumab, bDMARD = Biologic Disease-modifying Antirheumatic Drug, BRC = Baricitinib; CTZ = certolizumab pegol, ETN = etanercept, GOL = golimumab, IFX = infliximab, IV= Intravenous; LYG = Life Year Gained; MTX = methotrexate, QALY = quality-adjusted life year, RA = rheumatoid arthritis, RTX = rituximab; SC= Subcutaneous; SRL = sarilumab; TCZ = tocilizumab

*Assume same efficacy as BRC+MTX (BRC efficacy estimated from from bDMARD-IR NMA) since no efficacy estimate available for these comparators in bDMARD-IR NMA (UPA 15mg estimated as having the same efficacy as BRC+MTX in the csDMARD-IR NMA)

B.3.8 Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted to simultaneously vary multiple parameters, based on their distributions, and re-estimate model outputs. Monte Carlo simulation methods were applied in order to make random draws for parameter inputs. The number of patients included in the PSA and the number of iterations per patient were selected in order to maximize model efficiency (Table 82) (94). The methods to sample model inputs are described in Table 83.

Table 82. Model settings for PSA

Population	Cohort size	Number of model iterations
csDMARD-IR, moderately active RA	100	1,000
csDMARD-IR, severely active RA	100	1,000

Abbreviations: csDMARD=conventional disease-modifying anti-rheumatic drug; IR=inadequate response; RA=rheumatoid arthritis; PSA = Probabilistic Analysis

Table 83. Inputs for probabilistic sensitivity analysis

Parameters	Distribution	Base-case Mean	Base-case SE	Alpha	Beta	Descriptions
Efficacy inputs						
Proportion of good/moderate responders by treatment	NMA CODA	N/A				The proportion of patients with moderate and good response for upadacitinib and its comparators were varied using 1,000 draws from the joint posterior distribution (i.e., CODA) of the 24-week NMA for probabilities of EULAR good and moderate response. Please note that the observed input data was study-level and limited, distributions are assumed.
Initial HAQ reduction, good response	Normal	0.673	0.112	N/A	N/A	The initial reduction in HAQ inputs are modelled using normal distributions where estimates of mean and SE were obtained from the baricitinib submission.
Initial HAQ reduction, moderate response	Normal	0.317	0.048	N/A	N/A	
Treatment discontinuation						
Good EULAR response						Parameters of the distribution used to estimate treatment discontinuation by EULAR response were varied using a multivariate normal distribution. Correlations between the parameters were preserved using the variance-covariance matrix and Cholesky decomposition.
Gamma location parameter	Multivariate normal	2.897	0.0234	N/A	N/A	
Gamma scale parameter	Multivariate normal	1.045	0.0432	N/A	N/A	
Gamma shape parameter	Multivariate normal	0.551	0.0723	N/A	N/A	
Moderate EULAR response						
Gamma location parameter	Multivariate normal	2.796	0.0419	N/A	N/A	
Gamma scale parameter	Multivariate normal	0.293	0.0606	N/A	N/A	
Gamma shape parameter	Multivariate normal	4.470	0.9242	N/A	N/A	
Administration costs						

Administration cost - IV	Gamma	158.8	7.9	400	0.4	Administration costs were varied using the gamma distribution with the mean value as specified in the base-case. SEs were assumed to be 5% of the mean.
Administration cost - SC	Gamma	3.1	0.2	400	0.01	
Monitoring costs						
Pre-treatment	Gamma	175.3	8.8	400	0.4	Monitoring costs were varied using the gamma distribution with the mean value as specified in the base-case. SEs were assumed to be 5% of the mean.
First 6 months	Gamma	1753.4	87.7	400	4.4	
Monthly	Gamma	138.2	6.9	400	0.3	
SAE costs and disutility						
SAE cost / event - csDMARD	Gamma	1525.4	76.3	400	3.8	SAE costs and disutility were varied using the gamma distribution and beta distribution, respectively, with the mean value as specified in the base-case. SEs were assumed to be 5% of the mean.
SAE cost / event - JAK	Gamma	1539.2	77.0	400	3.8	
SAE cost / event - bDMARD	Gamma	1539.2	77.0	400	3.8	
SAE disutility / event	Beta	-0.012	0.0006	395.2	32537.2	
Annual cost of hospitalization based on HAQ						
HAQ score 0	Gamma	262	13	384	0.7	Hospitalization costs were varied using the gamma distribution with the mean value as specified in the base-case. SEs were obtained from the baricitinib submission.
0.125		193	10	384	0.5	
0.25		166	9	384	0.4	
0.375		149	8	384	0.4	
0.5		130	7	384	0.3	
0.625		112	6	384	0.3	
0.75		96	5	384	0.2	
0.875		162	8	384	0.4	
1		231	12	384	0.6	
1.125		301	15	384	0.8	

1.25		370	19	384	1.0	
1.375		410	21	384	1.1	
1.5		451	23	384	1.2	
1.625		489	25	384	1.3	
1.75		529	27	384	1.4	
1.875		715	37	384	1.9	
2		901	46	384	2.3	
2.125		1,082	55	384	2.8	
2.25		1,269	65	384	3.3	
2.375		1,636	84	384	4.3	
2.5		1,997	102	384	5.2	
2.625		2,370	121	384	6.2	
2.75		2,736	140	384	7.1	
2.875		3,442	176	384	9.0	
3		4,138	211	384	10.8	
HR for HAQ adjusted mortality						
HAQ score 0	Lognormal	1.0	0.0	N/A	N/A	HR for mortality for each HAQ score was varied using the lognormal distribution with the mean value as specified in the base-case. SEs were obtained from the NICE TA375 submission.
0.125		1.4	0.2	N/A	N/A	
0.25		1.4	0.2	N/A	N/A	
0.375		1.4	0.2	N/A	N/A	
0.5		1.5	0.2	N/A	N/A	
0.625		1.5	0.2	N/A	N/A	

0.75		1.5	0.2	N/A	N/A	
0.875		1.5	0.2	N/A	N/A	
1		1.8	0.2	N/A	N/A	
1.125		1.8	0.2	N/A	N/A	
1.25		1.8	0.2	N/A	N/A	
1.375		1.8	0.2	N/A	N/A	
1.5		2.7	0.3	N/A	N/A	
1.625		2.7	0.3	N/A	N/A	
1.75		2.7	0.3	N/A	N/A	
1.875		2.7	0.3	N/A	N/A	
2		4.0	0.5	N/A	N/A	
2.125		4.0	0.5	N/A	N/A	
2.25		4.0	0.5	N/A	N/A	
2.375		4.0	0.5	N/A	N/A	
2.5		5.5	1.0	N/A	N/A	
2.625		5.5	1.0	N/A	N/A	
2.75		5.5	1.0	N/A	N/A	
2.875		5.5	1.0	N/A	N/A	
3		5.5	1.0	N/A	N/A	
Utility						
Coefficients for Hernandez utility mapping	Multivariate normal	See Appendix J for parameter estimates		N/A	N/A	Coefficients to estimate membership to the four latent classes and coefficients to estimate EQ-5D utility values based on simulated HAQ, pain, and age (from

					Hernandez et al. 2014(85)) were varied using a multivariate normal distribution. Correlations between inputs were preserved using the variance-covariance matrix and Cholesky decomposition.

Abbreviations: ABA = abatacept, ACR = American College of Rheumatology; ADA = adalimumab, bDMARD = biologic DMARD, csDMARD = conventional DMARD, CTZ = certolizumab pegol, DAS28 = Disease Activity Score, DMARD = disease-modifying antirheumatic drug, DSA = Deterministic Sensitivity Analysis; ETN = etanercept, EULAR = European League Against Rheumatism; GOL = golimumab, HAQ = Health Assessment Questionnaires; IFX = infliximab, IV= Intravenous; MTX = methotrexate, RA = rheumatoid arthritis, RTX = rituximab; SAEs = Severe adverse events; SC= Subcutaneous; SE= Standard Error; TCZ = tocilizumab, VAS = Visual Analogue Sco

The results of probabilistic sensitivity analysis are presented in Table 84.

Table 84. Probabilistic analysis results

Patient population	Population position	Comparator (multiple comparators – most cost-effective chosen)	Upadacitinib: Upa + MTX or upa mono	Base case ICER (upa - comparator) (probabilistic)	Probability upadacitinib cost effective at £20k threshold	Probability upadacitinib cost effective at £30k threshold
After one csDMARD failure (MTX eligible population)	1b	Int csDMARD	Upa + MTX	£68,406	0%	0%
		Int csDMARD	Upa mono	£68,958	0%	0%
After one csDMARD failure (MTX ineligible population)	1a	Int csDMARD	Upa mono	£52,781	0%	0%
After two csDMARD failure (MTX eligible population)	2b	MTX	Upa + MTX	£50,612	0%	0%
		MTX	Upa mono	£50,641	0%	0%
After two csDMARD failure (MTX ineligible population)	2a	BSC	Upa mono	£36,296	0%	8%
Severe RA (first line advanced therapies MTX eligible population)	3b	IFX + MTX	Upa + MTX	£62,451	27%	33%
		IFX + MTX	Upa mono	£113,326	30%	33%
Severe RA (first line advanced therapies MTX ineligible population)	3a	ADA	Upa mono	£8,173	76%	85%

Patient population	Population position	Comparator (multiple comparators – most cost-effective chosen)	Upadacitinib: Upa + MTX or upa mono	Base case ICER (upa - comparator) (probabilistic)	Probability upadacitinib cost effective at £20k threshold	Probability upadacitinib cost effective at £30k threshold
After first line advanced therapy failure (in rituximab eligible patients)	5	RTX + MTX	Upa + MTX	Dominated	0%	0%
		RTX + MTX	Upa mono	Dominated	0%	0%
After first line advanced therapy failure (in rituximab ineligible patients) (MTX eligible)	4b	TCZ IV + MTX	Upa + MTX	Dominant	100%	100%
		TCZ IV + MTX	Upa mono	1,344,943*	100%	100%
After first line advanced therapy failure (MTX ineligible)	4a	ADA	Upa mono	Dominant	100%	100%
After RTX + MTX failure	6	TCZ IV + MTX	Upa + MTX	236,672*	100%	100%
		TCZ IV + MTX	Upa mono	178,466*	100%	100%

Abbreviations: BSC = Best supportive care; csDMARD = conventional DMARD, CTZ = certolizumab pegol, DAS28 = Disease Activity Score, DMARD = disease-modifying antirheumatic drug, IFX = infliximab, IV= Intravenous; MTX = methotrexate, RA = rheumatoid arthritis, RTX = rituximab; SAEs = Severe adverse events; SC= Subcutaneous; TCZ = tocilizumab

*upadacitinib is less costly and less effective.

B.3.8.2 Deterministic sensitivity analysis

The robustness of the CEA model was tested by a set of deterministic sensitivity analysis (DSAs) and scenario analyses. One parameter or model assumption was varied at a time while holding the other parameters at base-case values. Results were presented in a tornado diagram. The detailed list of parameters and assumptions tested in the DSA and scenario analyses is presented in Table 85.

Table 85: DSA model setting parameters

Parameters of Model Setting	Base-case Input	DSA Inputs	
		Low Input (Mean - SE)	High Input (Mean + SE)
Efficacy			
Efficacy based on ACR response	Details in NMA results section		
Change in HAQ occurs at treatment initiation	Linear change in HAQ during the initial treatment period (6 months)	HAQ during the initial treatment period = baseline HAQ - initial HAQ reduction by response	
Change in HAQ occurs at 6 months		HAQ during the initial treatment period = baseline HAQ	
Upadacitinib - proportion of patients with good EULAR response[a]			
csDMARD-IR population			
UPA	[redacted]	[redacted]	[redacted]
UPA + MTX	[redacted]	[redacted]	[redacted]
bDMARD-IR population			
UPA + MTX	[redacted]	[redacted]	[redacted]
Upadacitinib - proportion of patients with moderate EULAR response[a]			
csDMARD-IR population			
UPA	[redacted]	[redacted]	[redacted]
UPA+ MTX	[redacted]	[redacted]	[redacted]
bDMARD-IR population			
UPA+ MTX	[redacted]	[redacted]	[redacted]
Comparators - proportion of patients with good EULAR response[a]			
csDMARD-IR population			
ABT IV + MTX	[redacted]	[redacted]	[redacted]
ABT SC + MTX	[redacted]	[redacted]	[redacted]
ADA	[redacted]	[redacted]	[redacted]

ADA + MTX	[redacted]	[redacted]	[redacted]
BRC + MTX	[redacted]	[redacted]	[redacted]
csDMARD	[redacted]	[redacted]	[redacted]
Intensive csDMARD	[redacted]	[redacted]	[redacted]
CTZ + MTX	[redacted]	[redacted]	[redacted]
ETN	[redacted]	[redacted]	[redacted]
ETN + MTX	[redacted]	[redacted]	[redacted]
GOL + MTX	[redacted]	[redacted]	[redacted]
IFX + MTX	[redacted]	[redacted]	[redacted]
RTX + MTX	[redacted]	[redacted]	[redacted]
SRL	[redacted]	[redacted]	[redacted]
SRL + MTX	[redacted]	[redacted]	[redacted]
TCZ IV	[redacted]	[redacted]	[redacted]
TCZ SC	[redacted]	[redacted]	[redacted]
TCZ IV + MTX	[redacted]	[redacted]	[redacted]
TCZ SC + MTX	[redacted]	[redacted]	[redacted]
TFC	[redacted]	[redacted]	[redacted]
TFC + MTX	[redacted]	[redacted]	[redacted]
bDMARD-IR population			
ABT IV + MTX	[redacted]	[redacted]	[redacted]
BRC + MTX	[redacted]	[redacted]	[redacted]
CTZ + MTX	[redacted]	[redacted]	[redacted]
GOL + MTX	[redacted]	[redacted]	[redacted]
RTX + MTX	[redacted]	[redacted]	[redacted]
SRL + MTX	[redacted]	[redacted]	[redacted]
TCZ IV + MTX	[redacted]	[redacted]	[redacted]
TCZ SC + MTX	[redacted]	[redacted]	[redacted]
TFC + MTX	[redacted]	[redacted]	[redacted]
Comparators - proportion of patients with moderate EULAR response[a]			
csDMARD-IR population			
ABT IV + MTX	[redacted]	[redacted]	[redacted]
ABT SC + MTX	[redacted]	[redacted]	[redacted]
ADA	[redacted]	[redacted]	[redacted]
ADA + MTX	[redacted]	[redacted]	[redacted]
BRC + MTX	[redacted]	[redacted]	[redacted]
csDMARD	[redacted]	[redacted]	[redacted]
Intensive csDMARD	[redacted]	[redacted]	[redacted]
CTZ + MTX	[redacted]	[redacted]	[redacted]

ETN	[redacted]	[redacted]	[redacted]
ETN + MTX	[redacted]	[redacted]	[redacted]
GOL + MTX	[redacted]	[redacted]	[redacted]
IFX + MTX	[redacted]	[redacted]	[redacted]
RTX + MTX	[redacted]	[redacted]	[redacted]
SRL	[redacted]	[redacted]	[redacted]
SRL + MTX	[redacted]	[redacted]	[redacted]
TCZ IV	[redacted]	[redacted]	[redacted]
TCZ SC	[redacted]	[redacted]	[redacted]
TCZ IV + MTX	[redacted]	[redacted]	[redacted]
TCZ SC + MTX	[redacted]	[redacted]	[redacted]
TFC	[redacted]	[redacted]	[redacted]
TFC + MTX	[redacted]	[redacted]	[redacted]
bDMARD-IR population			
ABT IV + MTX	[redacted]	[redacted]	[redacted]
BRC + MTX	[redacted]	[redacted]	[redacted]
CTZ + MTX	[redacted]	[redacted]	[redacted]
GOL + MTX	[redacted]	[redacted]	[redacted]
RTX + MTX	[redacted]	[redacted]	[redacted]
SRL + MTX	[redacted]	[redacted]	[redacted]
TCZ IV + MTX	[redacted]	[redacted]	[redacted]
TCZ SC + MTX	[redacted]	[redacted]	[redacted]
TFC + MTX	[redacted]	[redacted]	[redacted]
Initial reduction in HAQ for responders			
Moderate response	0.317	0.269	0.365
Good response	0.673	0.561	0.785
Treatment discontinuation parametric distribution			
Weibull	See summary of analysis inputs presented in Appendix J for parameter estimates of base-case (Generalized gamma) and scenario analyses (Other distributions)		
Log-normal			
Log-logistic			
Gompertz			
Exponential			
Weibull - based on baricitinib submission			
Utility related measures (in line with the TA375 (28))			
Pain score (VAS), by HAQ			
HAQ score 0	16.09	11.83	N/A
0.125	23.37	18.32	N/A
0.25	26.19	19.38	N/A

0.375	28.33	22.57	N/A
0.5	30.24	24.95	N/A
0.625	34.76	27.64	N/A
0.75	35.54	30.46	N/A
0.875	39.27	32.40	N/A
1	42.93	35.20	N/A
1.125	46.51	37.55	N/A
1.25	50.95	41.38	N/A
1.375	51.16	44.07	N/A
1.5	56.25	46.83	N/A
1.625	58.59	50.07	N/A
1.75	61.80	53.29	N/A
1.875	64.97	55.40	N/A
2	71.93	57.41	N/A
2.125	73.04	58.93	N/A
2.25	74.43	61.82	N/A
2.375	73.37	63.94	N/A
2.5	77.86	67.75	N/A
2.625	75.16	69.33	N/A
2.75	83.83	67.73	N/A
2.875	83.74	61.37	N/A
3	88.00	58.02	N/A
Costs			
Drug and administration costs			
Upadacitinib drug cost/mg			
UPA	[redacted]	[redacted]	[redacted]
Comparators drug cost/mg			
ABT IV	1.2	0.9	1.5
ABT SC	2.4	1.8	3.0
ADA	8.8	6.6	11.0
BRC	7.2	5.4	9.0
csDMARD	0.0	0.0	0.0
CTZ	1.8	1.3	2.2
ETN	3.3	2.5	4.1
GOL	15.3	11.4	19.1
IFX	3.8	2.8	4.7
MTX	0.0	0.0	0.0
RTX	1.6	1.2	2.0

SRL	2.3	1.7	2.9
TCZ IV	1.3	1.0	1.6
TCZ SC	1.4	1.1	1.8
TFC	2.5	1.8	3.1
Annual cost of BSC	742.6	556.9	928.2
Administration costs			
IV	158.8	119.1	198.5
SC	3.1	2.4	3.9
Oral	0.0	0.0	0.0
Hospitalisation costs			
Annual hospitalisation costs, by HAQ			
HAQ score 0	262	196	327
0.125	193	145	242
0.25	166	125	208
0.375	149	112	186
0.5	130	98	163
0.625	112	84	140
0.75	96	72	120
0.875	162	122	203
1	231	173	288
1.125	301	226	376
1.25	370	278	463
1.375	410	307	512
1.5	451	338	563
1.625	489	367	611
1.75	529	397	662
1.875	715	536	894
2	901	676	1,126
2.125	1,082	812	1,353
2.25	1,269	952	1,587
2.375	1,636	1,227	2,046
2.5	1,997	1,497	2,496
2.625	2,370	1,778	2,963
2.75	2,736	2,052	3,420
2.875	3,442	2,582	4,303
3	4,138	3,103	5,172
Monitoring costs			
Pre-treatment (1-time cost)	175	132	219

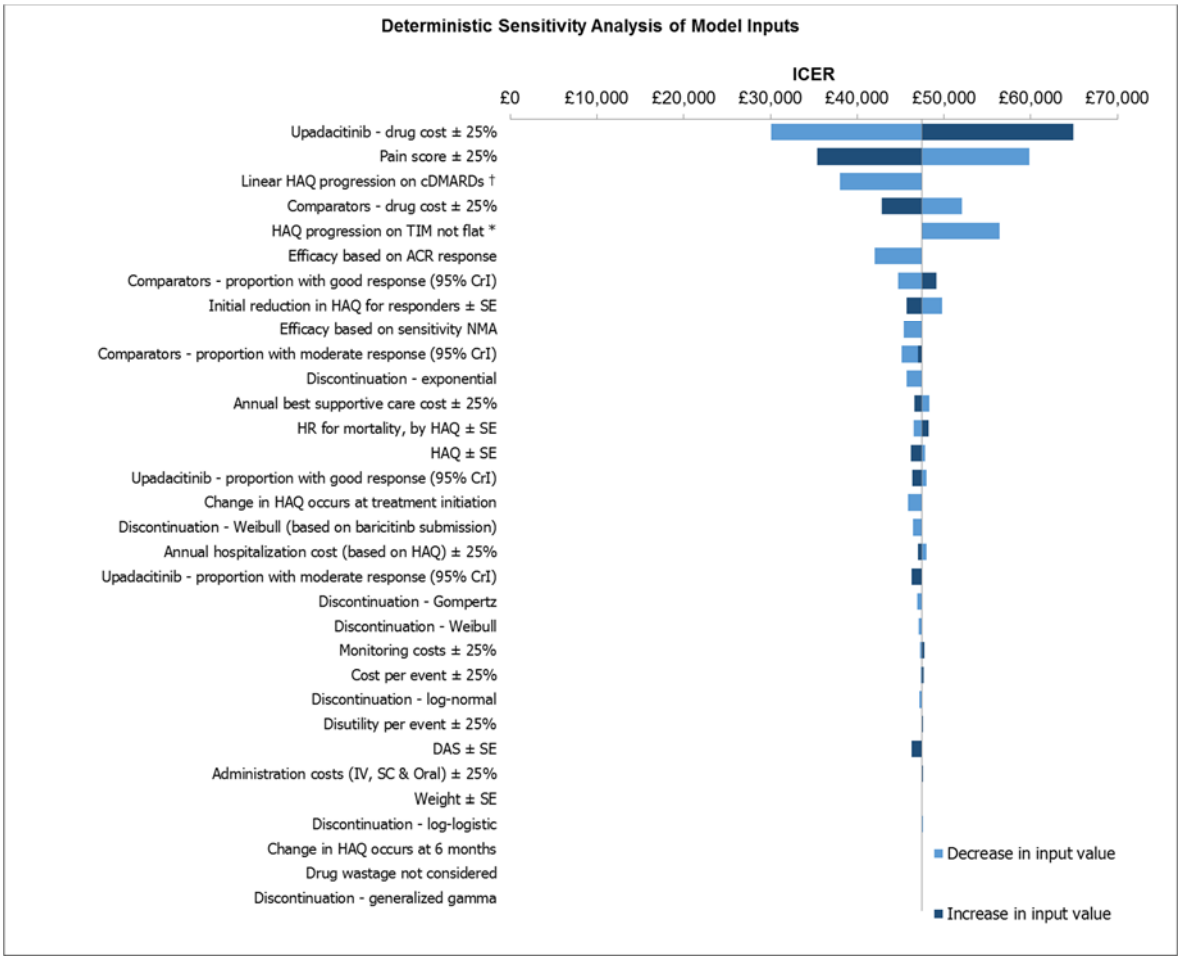
First 6 months	1,753	1,315	2,192
Monthly (after 6 months)	138	104	173
SAEs			
Cost per event	1525.4	1144.1	1906.8
Disutility per event	-0.012	-0.009	-0.015
Mortality			
HR for mortality, by baseline HAQ			
HAQ score 0	1.0	1.0	1.0
0.125	1.4	1.2	1.6
0.25	1.4	1.2	1.6
0.375	1.4	1.2	1.6
0.5	1.5	1.3	1.7
0.625	1.5	1.3	1.7
0.75	1.5	1.3	1.7
0.875	1.5	1.3	1.7
1	1.8	1.6	2.0
1.125	1.8	1.6	2.0
1.25	1.8	1.6	2.0
1.375	1.8	1.6	2.0
1.5	2.7	2.4	3.0
1.625	2.7	2.4	3.0
1.75	2.7	2.4	3.0
1.875	2.7	2.4	3.0
2	4.0	3.5	4.5
2.125	4.0	3.5	4.5
2.25	4.0	3.5	4.5
2.375	4.0	3.5	4.5
2.5	5.5	4.5	6.5
2.625	5.5	4.5	6.5
2.75	5.5	4.5	6.5
2.875	5.5	4.5	6.5
3	5.5	4.5	6.5

Abbreviations: ABA = abatacept, ACR = American College of Rheumatology; ADA = adalimumab, bDMARD = biologic DMARD, csDMARD = conventional DMARD, CTZ = certolizumab pegol, DAS28 = Disease Activity Score, DMARD = disease-modifying antirheumatic drug, DSA = Deterministic Sensitivity Analysis; ETN = etanercept, EULAR = European League Against Rheumatism; GOL = golimumab, HAQ = Health Assessment Questionnaires; IFX = infliximab, IV= Intravenous; MTX = methotrexate, RA = rheumatoid arthritis, RTX = rituximab; SAEs = Severe adverse events; SC= Subcutaneous; SE= Standard Error; TCZ = tocilizumab, VAS = Visual Analogue Score

Two csDMARD failure, MTX eligible, moderate RA

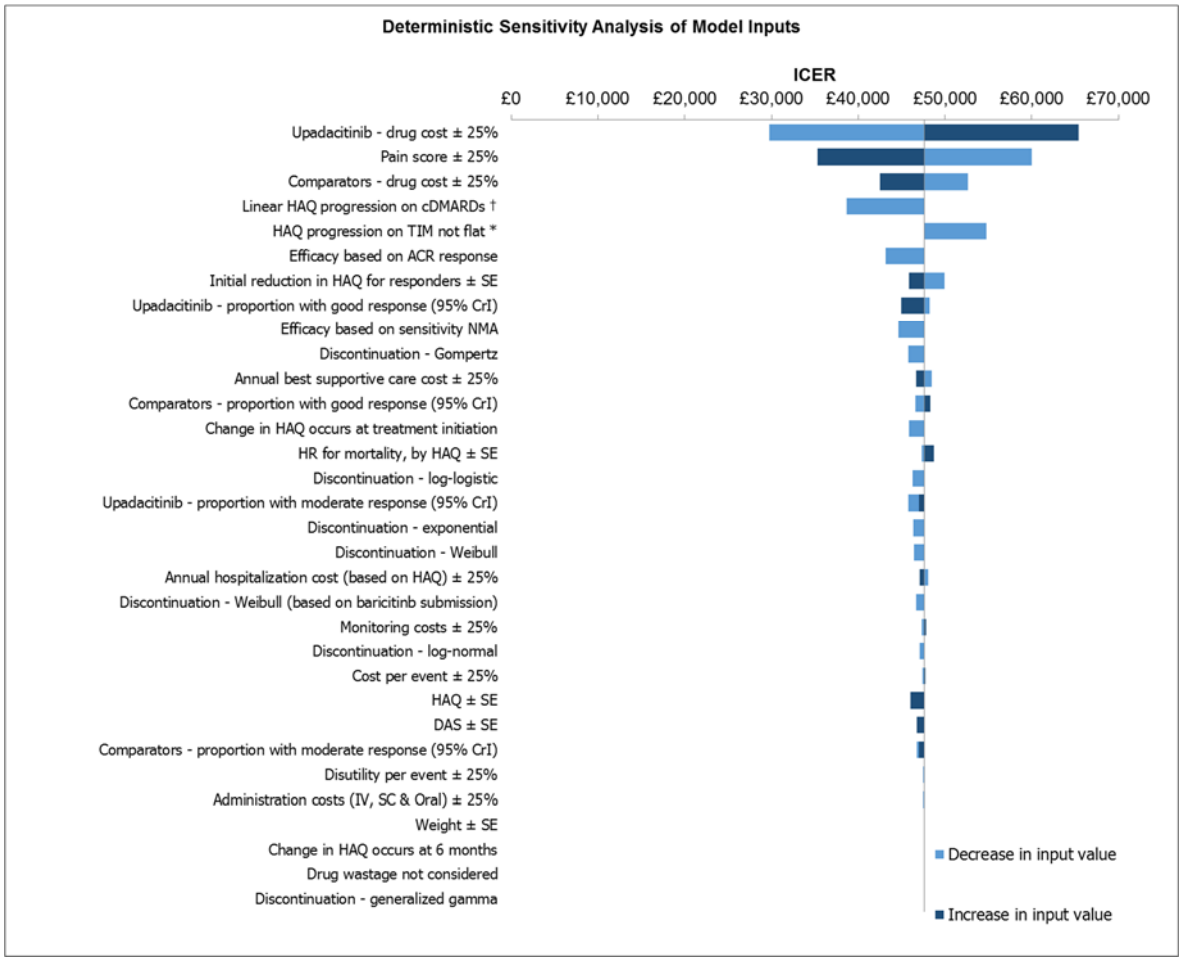
The results of the deterministic sensitivity analysis for the moderate, MTX eligible patient population after two csDMARD failure for upadacitinib monotherapy and upadacitinib combination therapy are presented in Figure 22 and Figure 23. The most influential factors for the model results are presented in the tornado diagrams. The key model drivers are drug costs of upadacitinib, pain score, HAQ progression on advanced therapy, drug costs of comparator and using efficacy based on ACR response.

Figure 22. Tornado diagram in two csDMARD failure, MTX eligible, moderate RA (upadacitinib combination therapy vs. MTX)



Abbreviations: csDMARD = conventional DMARD, ICER= Incremental cost-effectiveness ratio; MTX = methotrexate, RA = rheumatoid arthritis, RTX = rituximab.

Figure 23. Tornado diagram in two csDMARD failure, MTX eligible, moderate RA (upadacitinib monotherapy vs. MTX)

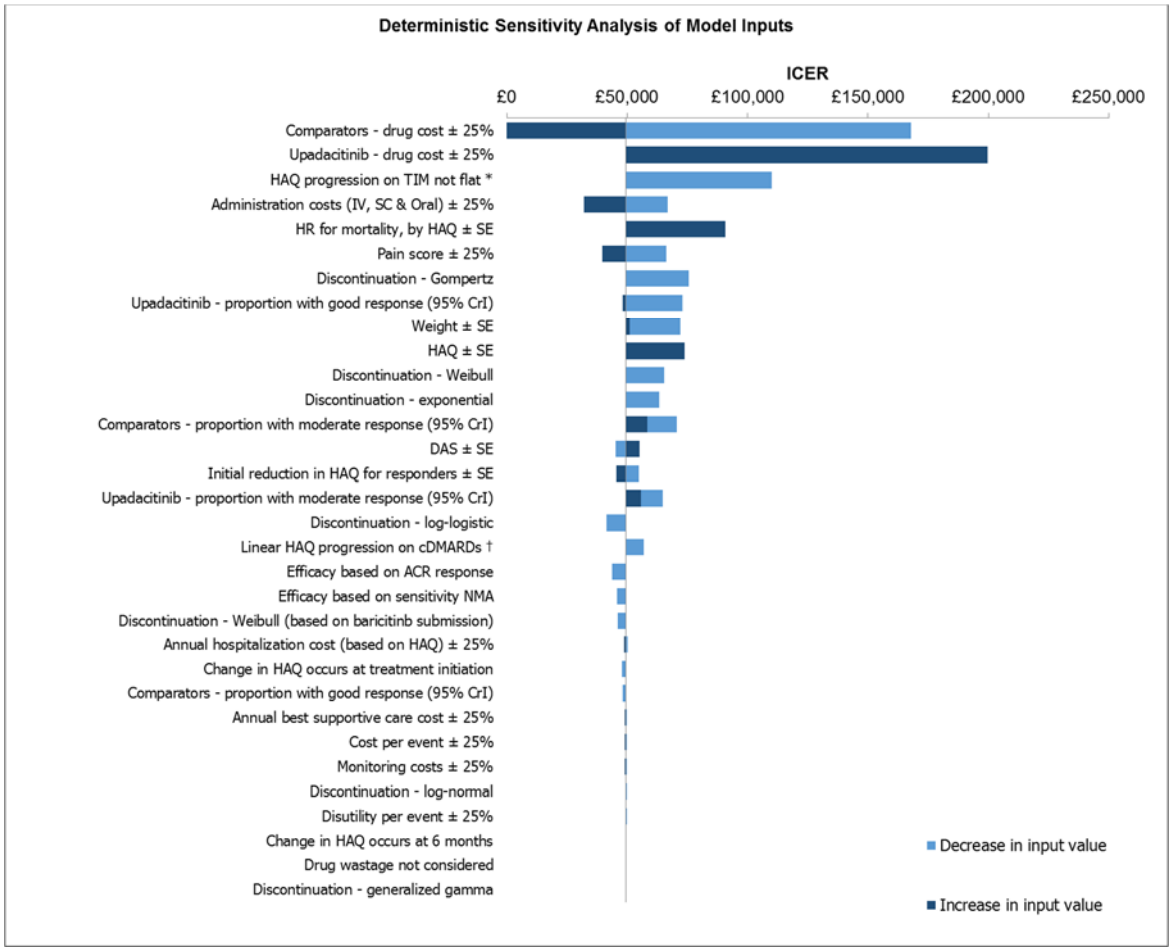


Abbreviations: csDMARD = conventional DMARD, ICER= Incremental cost-effectiveness ratio; MTX = methotrexate, RA = rheumatoid arthritis, RTX = rituximab.

csDMARD-IR, MTX eligible, severe RA

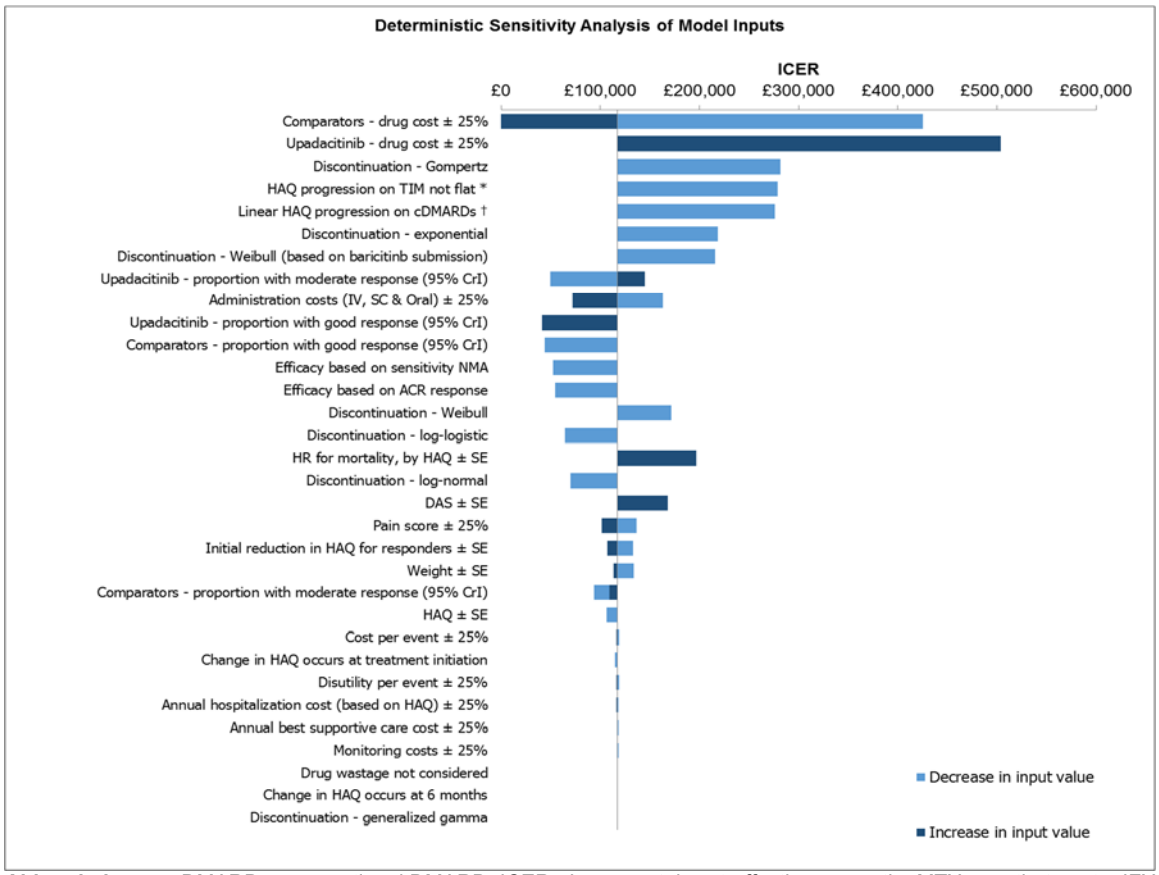
The results of the deterministic sensitivity analysis for the cDMARD-IR, MTX eligible severe patient population for upadacitinib combination therapy and upadacitinib monotherapy are presented in Figure 24 and Figure 25. The most influential factors for the model results are presented in the tornado diagrams. The key model drivers are drug costs of upadacitinib and comparator, HAQ progression on advanced therapy, administration costs and HR for mortality.

Figure 24. Tornado diagram in csDMARD-IR, MTX eligible, severe RA (upadacitinib combination therapy vs. IFX+ MTX)



Abbreviations: csDMARD = conventional DMARD, ICER= Incremental cost-effectiveness ratio; MTX = methotrexate, IFX = infliximab, RA = rheumatoid arthritis, RTX = rituximab.

Figure 25. Tornado diagram in csDMARD-IR, MTX eligible, severe RA (upadacitinib monotherapy vs. IFX + MTX)



Abbreviations: csDMARD = conventional DMARD, ICER= Incremental cost-effectiveness ratio; MTX = methotrexate, IFX = infliximab, RA = rheumatoid arthritis, RTX = rituximab.

B.3.8.3 Scenario analysis

In the scenario analyses, certain model assumption and efficacy inputs were varied while holding the other parameters at base-case values. Results were presented in Table 86.

The key to the scenarios run is:

1. Moderate RA: Same sequence as base case but no transition to severe RA treatments

2. Moderate RA: Use moderate RA subgroup results for efficacy parameter for both csDMARD (int csDMARD and MTX) and upadacitinib. Details of subgroup analysis are presented in Appendix J.

3. Moderate and Severe RA: Use HAQ to VAS pain score mapping algorithm used in TA375 (rationale: model sensitive to this as shown in DSA section in B.3.8.2 Deterministic sensitivity analysis)

4. Moderate and Severe RA: Use conservative NMA as basis of efficacy for all relevant comparators in the treatment sequence

Table 86. Scenario analysis results

Population	Scenario number	Comparator	Base case ICER (vs upadacitinib 15mg + MTX)	Scenario analysis ICER (vs upadacitinib 15mg + MTX)	Base case ICER (vs upadacitinib 15mg)	Scenario analysis ICER (vs upadacitinib 15mg)
Moderate RA (after one csDMARD) (MTX eligible)	1	Int. csDMARD	£62,907	£58,709	£65,914	£59,670
	2	Int. csDMARD	£62,907	£62,163	£65,914	£64,177
	3	Int. csDMARD	£62,907	£72,327	£65,914	£75,769
	4	Int. csDMARD	£62,907	£63,265	£65,914	£64,104
Moderate RA (after two csDMARD) (MTX eligible)	1	MTX	£47,486	£45,331	£47,576	£44,905
	2	MTX	£47,486	£47,049	£47,576	£46,923
	3	MTX	£47,486	£55,305	£47,576	£55,505
	4	MTX	£47,486	£46,735	£47,576	£47,120
Severe RA (versus first line advanced treatments (MTX eligible)	3	IFX + MTX	£49,418	£63,096	£117,383	£140,082
	4	IFX + MTX	£49,418	£43,533	£117,383	£73,462

Abbreviations: csDMARD = conventional DMARD, ICER= Incremental cost-effectiveness ratio; MTX = methotrexate, IFX = infliximab, RA = rheumatoid arthritis, RTX = rituximab.

B.3.8.4 Summary of sensitivity analyses results

In the two csDMARD failure, moderate RA patient populations, the key model drivers are drug costs of upadacitinib, pain score, HAQ progression on advanced therapy, and the drug costs of comparator (Figures 22 and 23). In the csDMARD-IR, severe RA patient population, the key model drivers are similar and in addition include discontinuation rate assumptions and estimations of efficacy and mortality rate hazard rates (Figures 24 and 25). These additional assumptions to which ICERs are sensitive in the severe population may be explained by the relatively small QALY differences between treatments in the base case analysis (as shown in Tables 70 and 71).

In the probabilistic analysis, cost-effectiveness results were seen to be closely aligned to deterministic results in terms of ICERs (as shown by comparing the ICERs in Table 82 to those shown in Tables 68-79).

In the scenario analysis, cost-effectiveness results were seen to be similar to base case results in the moderate RA population when using moderate RA subgroup efficacy data from the trial in place of moderate to severe RA NMA efficacy estimates (Table 84). This was also the case when assuming no transition to severe RA treatments in this population. Both moderate and severe populations were sensitive to the use of the HAQ to VAS pain mapping algorithm used in TA375 in place of that based on one developed using data from the upadacitinib clinical trials. Upadacicinib monotherapy ICERs in severe RA after one cDMARD-IR showed some senisitivity (a reduced ICER) when the conservative NMA results were used in place of the base case.

B.3.9 Subgroup analysis

The base case analysis includes separate analyses by disease severity and line of therapy.

B.3.10 Validation

B.3.10.1 Validation of cost-effectiveness analysis

Face validity

A qualitative evaluation was carried out to assess the accuracy of the decision problem, model structure, evidence/data sources, calculations, and assumptions in replicating the clinical pathway of interest and the plausibility of the analysis results.

The checks were performed early in model conceptualization and frequently throughout model development.

These checks involved comparing the model outputs with the outputs from TA375 (28), while holding the population and treatment regimens constant for both moderately active RA and severely active RA patients. For the moderately and severely active RA population the ICER was comparable between current model and TA375. (28)

Internal validation

The model went through internal certification as a quality assurance measure. A full model-replication audit in VBA was performed and, in any instances, where the replication audit resulted in different outputs underlying issues were scrutinised. Model programming and mathematical calculations have also been checked. The model interface was checked, and it was ensured that all equations and parameters were cross-referenced against their sources and all modules of code were error-free and replicable.

External validation

The model has also been validated by an independent third-party consulting team. The model was checked for errors in model structure, code implementation and model assumptions. The procedures and functions in VBA were visually inspected to identify logical or transitional errors. The third-party team did not find any pressing issues with the model, and any corrections or suggestions were carefully incorporated into the model.

Comparison of model output to TA375

The AbbVie model has been validated against the base case ICERs in TA375 for severe RA to those published in Table 191- TA375 systematic review and economic Evaluation HTA. These TA375 ICERs are in line with the following statement in TAG 375 *"The base case ICERs for the severe active population who can take methotrexate is £41,600"* (TA375).

Table 87: Validation of severe RA ICERs between TA 375 and the AbbVie model

	AbbVie Model (using TA375 base case pain VAS scores)	*TA 375 base case model
MTX	Reference	Reference
ADA + MTX	£39,255	£41,567
ETN + MTX	£40,240	£42,494
IFX + MTX	£37,374	£38,503
CTZ + MTX	£42,055	£39,924
GOL + MTX	£41,026	£41,611

Abbreviations: ADA = adalimumab, CTZ = certolizumab pegol, ETN = etanercept, GOL = golimumab, IFX = infliximab, MTX = methotrexate, TCZ = tocilizumab.

To validate the AbbVie model output against TA375 model output in moderate RA patients the following treatment sequence output has been compared: ADA+MTX then MTX then BSC vs MTX then BSC (after two csDMARD failure, moderate RA). The pain VAS score map used in TA375 was used in the AbbVie model without transition to severe RA and using an annual ADA drug acquisition cost of £9187 to align to the settings and parameters used in TA375:

Table 88: Validation of moderate RA ICERs between TA 375 and the AbbVie model ADA+MTX versus MTX after two csDMARD-IR)

Population	AbbVie model (ICER per QALY gained)	NICE TA375 report, ICER per QALY gained* (2015 £)
csDMARD-IR, moderately active RA	£60,917	£63,513

Abbreviations: csDMARD= conventional disease-modifying anti-rheumatic drug; ICER= Incremental cost-effectiveness ratio; QALY= quality-adjusted life year; RA= Rheumatoid Arthritis; UPA= upadacitinib

* Referenced to Table 246 p415 of TA375 ERG report

A comparison of the incremental QALYs output from the AbbVie model (using a moderate to severe baseline cohort) over a time period of 1 year (the shortest period possible using the model) and the difference between the mean change from baseline of the EQ-5D-5L index between the arms of the upadacitinib trials was carried out and is summarised in the tables below:

Table 89: Incremental QALYs using AbbVie model over one year compared to the difference between the mean change from baseline using the EQ-5D-5L index in the relevant arms of SELECT-COMPARE and SELECT-NEXT

	AbbVie model (1 year) – full initial HAQ change occurs at 6 mths	AbbVie model (1 year) – linear HAQ change first 6 mths	AbbVie model (1 year) – full initial HAQ change occurs at tx initiation	SELECT COMPARE (12 weeks) (EQ-5D-5L)	SELECT COMPARE (26 weeks) (EQ-5D-5L)	SELECT NEXT (12 weeks) (EQ-5D-5L)
csDMARD / intensive csDMARD				0.10	0.11	0.08
ADA + MTX				0.17	0.2	
UPA 15mg + MTX				0.21	0.22	0.19
Difference between UPA 15mg + MTX and cDMARD / int cDMARD	0.019 / 0.014	0.028 / 0.021	0.037/0.028	0.11	0.11	0.11
Difference between ADA + MTX and UPA 15mg + MTX	0.003	0.005	0.006	0.04	0.02	N/A

Abbreviations: csDMARD= conventional disease-modifying anti-rheumatic drug; HAQ= Health Assessment Questionnaire; MTX= methotrexate; UPA= upadacitinib

Table 90: Incremental QALYs using AbbVie model over one year compared to the difference between the mean change from baseline using the EQ-5D-5L index in the relevant arms of SELECT-MONOTHERAPY

	AbbVie model (1 year) – full initial HAQ change occurs at 6 mths	AbbVie model (1 year) – linear HAQ change first 6 mths	AbbVie model (1 year) – full initial HAQ change occurs at tx initiation	SELECT MONOTHERAPY (week 14) (EQ-5D-5L)
MTX				0.08
UPA 15mg mono				0.16
Difference between UPA 15mg mono and MTX	0.015	0.023	0.022	0.08

Abbreviations: csDMARD= conventional disease-modifying anti-rheumatic drug; HAQ= Health Assessment Questionnaire; MTX= methotrexate; UPA= upadacitinib

Table 91: Incremental QALYs using AbbVie model over one year compared to the difference between the mean change from baseline using the EQ-5D-5L index in the relevant arms of SELECT-BEYOND

	AbbVie model (1 year) – full initial HAQ change occurs at 6 mths	AbbVie model (1 year) – linear HAQ change first 6 mths	AbbVie model (1 year) – full initial HAQ change occurs at tx initiation	SELECT BEYOND (week 12) (EQ-5D-5L)
csDMARD				0.08
UPA + MTX				0.15
Difference between UPA + MTX and csDMARD	0.017	0.026	0.035	0.07

Abbreviations: csDMARD= conventional disease-modifying anti-rheumatic drug; HAQ= Health Assessment Questionnaire; MTX= methotrexate; UPA= upadacitinib

The results of the validation process against the EQ-5D-5L index estimates observed in the upadacitinib clinical trials suggests that the model may underestimate the incremental QALY gain associated with the higher efficacy of upadacinitib combination and monotherapy compared to csDMARD and of upadacitinib combination compared to adalimumab combination compared to these observed trial outcomes.

B.3.11 Interpretation and conclusions of economic evidence

Table 92: Summary of deterministic ICERs for upadacitinib versus most cost-effective comparator

Patient population	Population position	Comparator	Upadacitinib : Upa + MTX or upa mono	Base case ICER (upa vs comparator) (deterministic)
After one csDMARD failure (MTX eligible population)	1b	Int csDMARD	Upa + MTX	£62,907
		Int csDMARD	Upa mono	£65,914
After one csDMARD failure (MTX ineligible population)	1a	Int csDMARD	Upa mono	£48,877
After two csDMARD failure (MTX eligible population)	2b	MTX	Upa + MTX	£47,486
		MTX	Upa mono	£47,576
After two csDMARD failure (MTX ineligible population)	2a	BSC	Upa mono	£34,537
Severe RA (first line advanced therapies MTX eligible population)	3b	IFX + MTX	Upa + MTX	£49,418
		IFX + MTX	Upa mono	£117,383
Severe RA (first line advanced therapies MTX ineligible population)	3a	ADA	Upa mono	£12,792
After first line advanced therapy failure (in rituximab eligible patients)	4b	RTX + MTX	Upa + MTX	Dominated
		RTX + MTX	Upa mono	Dominated
After first line advanced therapy failure (in rituximab ineligible patients) (MTX eligible)	5	TCZ IV + MTX	Upa + MTX	*£767,043
		TCZ IV + MTX	Upa mono	*£348,956
After first line advanced therapy failure (MTX ineligible)	4a	ADA	Upa mono	*Dominant
After RTX + MTX failure	6	TCZ IV + MTX	Upa + MTX	*£200,420
		TCZ IV + MTX	Upa mono	*£194,375

Abbreviations: BSC= best supportive care; csDMARD= conventional disease-modifying anti-rheumatic drug; ICER= Incremental cost-effectiveness ratio; IFX= infliximab; IV= intravenous; MTX= methotrexate; RA= Rheumatoid Arthritis; RTX= rituximab; SC= Subcutaneous; TCZ= tocilizumab; UPA= upadacitinib

*Upadacitinib less costly and less benefits

In moderate RA, upadacitinib monotherapy after two or more csDMARD failures in MTX ineligible patients was associated with an ICER of £34,537 per QALY.

In the first line advanced therapy, MTX eligible severe patient population, upadacitinib combination therapy was cost effective against all comparators except infliximab + MTX compared to which it was associated with an ICER of £49,418 per QALY (Table 72). Similarly, in the MTX eligible population, upadacitinib monotherapy was cost effective against all comparators except infliximab + MTX compared to which it was

associated with an ICER of £117,383 per QALY (Table 73). In the MTX ineligible population, upadacitinib monotherapy was cost effective against all comparators (Table 80). In terms of clinical decision making, infliximab cannot be deemed to be the most relevant comparator in this population due its intravenous infusion route of administration which means it is used in a restricted population. Infusion is every 8 weeks and takes on average 1-2 hours in a hospital setting which makes it the relevant option for only a small group of patients. Market share data demonstrates use of infliximab in only 5% of the severe RA population which further supports the limited use of infliximab and limited comparability of updacitinib being used in the same patient population. Current clinical current practice indicates that the majority of patients receive either SC treatments or other JAKs. This indicates that clinicians are more likely to consider other SC options or other JAKs in the same clinical position when deciding the most appropriate option for patients.

In the first line advanced therapy failure, RTX eligible, severe RA population both upadacitinib combination therapy and monotherapy were dominated by rituximab + MTX (Table 74 and Table 75).

In the first line advanced therapy, RTX ineligible, severe RA population, in the MTX eligible population both upadacitinib combination therapy and monotherapy were cost effective against all comparators (as shown in Table 76 and Table 77) . In the MTX ineligible population upadacitinib monotherapy was cost effective against all comparators (as shown in Table 81).

In RTX-IR, severe RA, MTX eligible population both upadacitinib combination therapy and monotherapy were cost effective against all comparators (as shown in Tables Table 78 and Table 79 respectively).

In summary, the results of the cost effectiveness analysis support the use of upadacitinib monotherapy and combination therapy in all severe RA MTX eligible patients in all positions within the patient pathway with the exception of first line advanced therapy failure patients who are eligible for rituximab. Similarly, upadacitinib monotherapy is cost effective against all comparators in the MTX ineligible population in both first line and second line advanced therapy positions.

The comparison to infliximab + MTX of both upadacitinib monotherapy and combination therapy in the first line advanced therapy, MTX eligible population is not appropriate for clinical reasons as outlined above. In addition, as noted by the ERG in TA375, ICERs in this population may be misleading where incremental costs and QALYs may be similar. This is important to note in regard to 1) the relative efficacy of these treatments which as shown in the base case csDMARD-IR NMA are numerically better for upadacitinib monotherapy and combination therapy compared to infliximab + MTX and [redacted] (both efficacy and costs summarised in Table 93 and Table 94). [redacted]

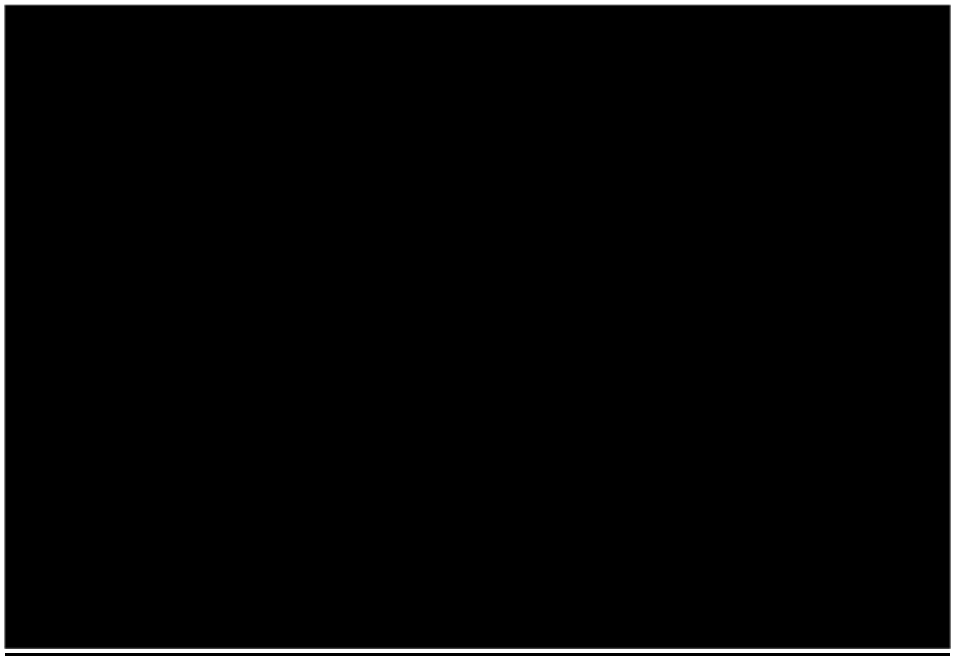
Table 93 EULAR response in the cDMARD-IR population based on the base case NMA

	EULAR Response		
Treatment	**Good**	**Moderate**	**Good plus moderate**
UPA + MTX	[redacted]	[redacted]	[redacted]
UPA	[redacted]	[redacted]	[redacted]
IFX + MTX	[redacted]	[redacted]	[redacted]

Table 94 Summary of drug acquisition and administration costs of upadacitinib compared to infliximab

	Annual drug and administration costs		
Treatment	**Drug**	**Administration**	**Drug plus administratin**
UPA + MTX	[redacted]	0	[redacted]
UPA	[redacted]	0	[redacted]
IFX + MTX	£7393	£1035	£8428

Figure 26 Scatterplot of upadacatinib combination compared to Infliximab + MTX



The model used is aligned to that developed in TA 375 by the ScHARR ERG and used in three subsequent NICE appraisals of RA drugs. This alignment is summarised in Table 65. One differing assumption is the VAS pain mapping approach used by the manufacturer which is shown to be a better fit to observed EQ-5D data replicating an approach supported and accepted in the tofactitinib NICE submission. Similar outputs are provided by the manufacturer's model compared to that used in TA375 as shown by Table 87 and Table 88. On sensitivity analysis, only modelling assumptions differing to TA375 were shown to cause substantive changes in estimated ICERs with the exception of comparator drug costs. Confidential comparator PAS discounts are not known by the manufacturer and consequently they have not been incorporated into the model.

Deterministic results are similar to those estimated using a probabilistic methodology. Key probabilistic ICERs are summarised in Table 84.

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ADDENDUM – revision of sections B.3.7 to B.3.10. in the original 5th July 2019 NICE submission using the updated annual PAS price for upadacitinib of £[redacted] (Addendum sent to NICE on 23rd August 2019)

B.3.7 Base-case results

B.3.7.1 Base-case incremental cost-effectiveness analysis results

Whilst the NICE reference case specifies probabilistic analysis (PSA), deterministic base case analyses have been carried out due to the time constraints associated with running PSAs. As seen in the PSA section, the difference between deterministic and probabilistic results is relatively minimal. The base case deterministic cost-effectiveness results for the following populations are presented below:

- Use of upadacitinib monotherapy and combination therapy in moderate RA:
    1. After one csDMARD failure
    2. After two or more csDMARD failure
- Use of upadacitinib monotherapy and combination therapy in severe RA in those who are methotrexate eligible:
    3. Versus first line advanced therapies in combination with methotrexate
    4. After first line advanced therapy failure in those who are rituximab ineligible versus advanced therapies
    5. After first line advanced therapy failure versus rituximab in combination with methotrexate (in rituximab eligible patients)
    6. After rituximab in combination with methotrexate failure versus methotrexate in combination with tocilizumab or sarilumab

- Use of upadacitinib monotherapy in severe RA amongst those who are methotrexate ineligible:

  3a. Versus first line advanced therapies used as monotherapies (in methotrexate ineligible patients)

  4a. After first line advanced therapy failure in those who are methotrexate ineligible

1b. One csDMARD failure, MTX eligible, moderate RA

The results of the base case analysis for the moderate, MTX eligible patient population after one csDMARD failure are presented in Table A. 1 and Table A. 2, for upadacitinib combination therapy and upadacitinib monotherapy, respectively. Compared to intensive csDMARD, upadacitinib combination therapy and upadacitinib monotherapy were associated with QALY gains, and increased costs, generating incremental cost-effectiveness ratio (ICER) of £21,631 per QALY, and £22,659 per QALY, respectively.

Table A. 1. One csDMARD failure, MTX eligible, moderate RA – versus UPA 15mg + MTX (deterministic results)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus UPA 15mg + MTX (£/QALY)
Intensive csDMARD	[redacted]	15.254	[redacted]	-	-	21,631
UPA 15mg + MTX	[redacted]	15.254	[redacted]	[redacted]	[redacted]	Reference

Abbreviations: csDMARD=conventional disease-modifying anti-rheumatic drug, LYG = Life Year Gained, MTX= Methotrexate, QALY = Quality Adjusted Life Year, RA = Rheumatoid Arthritis, UPA= Upadacitinib

Table A. 2. One csDMARD failure, MTX eligible, moderate RA – versus UPA 15mg (deterministic results)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus UPA 15mg (£/QALY)
Intensive csDMARD	[redacted]	15.254	[redacted]	-	-	22,659
UPA 15mg	[redacted]	15.254	[redacted]	[redacted]	[redacted]	Reference

Abbreviations: csDMARD=conventional disease-modifying anti-rheumatic drug, LYG = Life Year Gained, MTX= Methotrexate, QALY = Quality Adjusted Life Year, RA = Rheumatoid Arthritis, UPA= Upadacitinib

1a. One csDMARD failure, MTX ineligible, moderate RA

The results of the base case analysis for the moderate, MTX ineligible patient population after one csDMARD failure are presented in Table A. 3. Compared to intensive csDMARDs, upadacitinib monotherapy generated QALY gains, and was associated with higher costs, generating an ICER of £16,554 per QALY.

Table A. 3. One csDMARD failure, MTX ineligible, moderate RA – versus UPA 15mg (deterministic results)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus UPA 15mg (£/QALY)
Intensive csDMARD	[redacted]	15.254	[redacted]	-	-	£16,554
UPA 15mg	[redacted]	15.254	[redacted]	[redacted]	[redacted]	Reference

Abbreviations: csDMARD=conventional disease-modifying anti-rheumatic drug, LYG = Life Year Gained, MTX= Methotrexate, QALY = Quality Adjusted Life Year, RA = Rheumatoid Arthritis, UPA= Upadacitinib

2b. Two csDMARD failure, MTX eligible, moderate RA

The results of the base case analysis for the moderate, MTX eligible patient population after two csDMARD failure are presented in Table A. 4 and Table A. 5, for upadacitinib combination therapy and upadacitinib monotherapy, respectively. Compared to MTX, upadacitinib combination therapy and upadacitinib monotherapy were associated with substantial QALY gains and increased costs, generating ICERs of £13,434 per QALY and £13,568 per QALY, respectively.

Table A. 4. Two csDMARD failure, MTX eligible, moderate RA – versus UPA 15mg + MTX (deterministic results)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus UPA 15mg + MTX (£/QALY)
MTX	[redacted]	15.254	[redacted]	-	-	13,434
UPA 15mg + MTX	[redacted]	15.254	[redacted]	[redacted]	[redacted]	Reference

Abbreviations: csDMARD=conventional disease-modifying anti-rheumatic drug, LYG = Life Year Gained, MTX= Methotrexate, QALY = Quality Adjusted Life Year, RA = Rheumatoid Arthritis, UPA= Upadacitinib

Table A. 5. Two csDMARD failure, MTX eligible, moderate RA – versus UPA 15mg (deterministic results)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus UPA 15mg (£/QALY)
MTX	[redacted]	15.254	[redacted]	-	-	£13,568
UPA 15mg	[redacted]	15.254	[redacted]	[redacted]	[redacted]	Reference

Abbreviations: csDMARD=conventional disease-modifying anti-rheumatic drug, LYG = Life Year Gained, MTX= Methotrexate, QALY = Quality Adjusted Life Year, RA = Rheumatoid Arthritis, UPA= Upadacitinib

2a. Two csDMARD failures, MTX ineligible, moderate RA

The results of the base case analysis for the moderate, MTX ineligible patient population after two csDMARD failures are presented in Table A. 6. Compared to BSC, upadacitinib monotherapy was associated with a substantial QALY gain (0.826) and increased costs, generating an ICER of £8,885 per QALY.

Table A. 6. Two csDMARD failure, MTX ineligible, moderate RA – versus UPA 15mg (deterministic results)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus UPA 15mg (£/QALY)
BSC	[redacted]	15.254	[redacted]	-	-	8,885
UPA 15mg	[redacted]	15.254	[redacted]	[redacted]	[redacted]	Reference

Abbreviations: BSC=best supportive care, csDMARD=conventional disease-modifying anti-rheumatic drug, LYG = Life Year Gained, MTX=methotrexate; QALY = quality-adjusted life year, RA=rheumatoid arthritis; UPA=upadacitinib.

3b. csDMARD-IR, MTX eligible, severe RA

The results of the base case analysis for the csDMARD-IR, MTX eligible severe patient population for upadacitinib combination therapy are presented in Table A. 7. In the incremental analysis, most of the treatments were dominated by upadacitinib combination therapy, except certolizumab + MTX. When compared with certolizumab + MTX, upadacitinib combination therapy was less costly and less effective and was cost effective against CTZ + MTX at a cost effectiveness threshold of £30,000 since CTZ + MTX was associated with an ICER of £828,052 versus upadacitinib combination therapy.

Table A. 7. csDMARD-IR, MTX eligible, severe RA – versus UPA 15mg + MTX (deterministic results)

Technologies	Total costs (£)	Total QALYs	Total LYG	Full incremental costs (£)	Full incremental QALYs	ICER incremental (£/QALY)
UPA 15mg + MTX	[redacted]	[redacted]	14.196	-	-	Reference
IFX + MTX	[redacted]	[redacted]	14.196	[redacted]	[redacted]	Dominated
ADA + MTX	[redacted]	[redacted]	14.196	[redacted]	[redacted]	Dominated
ETN + MTX	[redacted]	[redacted]	14.196	[redacted]	[redacted]	Dominated
TFC + MTX	[redacted]	[redacted]	14.196	[redacted]	[redacted]	Dominated
GOL + MTX	[redacted]	[redacted]	14.196	[redacted]	[redacted]	Dominated
CTZ + MTX	[redacted]	[redacted]	14.196	[redacted]	[redacted]	828,052
BRC + MTX	[redacted]	[redacted]	14.196	[redacted]	[redacted]	Dominated
TCZ SC + MTX	[redacted]	[redacted]	14.196	[redacted]	[redacted]	Dominated
SRL + MTX	[redacted]	[redacted]	14.196	[redacted]	[redacted]	Dominated
TCZ IV + MTX	[redacted]	[redacted]	14.196	[redacted]	[redacted]	Dominated
ABT IV + MTX	[redacted]	[redacted]	14.196	[redacted]	[redacted]	Dominated
ABT SC + MTX	[redacted]	[redacted]	14.196	[redacted]	[redacted]	Dominated

The results of the base case analysis for the csDMARD-IR, MTX eligible severe patient population for upadacitinib monotherapy are presented in Table A. 8. In the incremental analysis, most of the treatments were dominated by upadacitinib monotherapy, except certolizumab + MTX. When compared with certolizumab + MTX, upadacitinib monotherapy was less costly and less effective and was cost effective against CTZ + MTX at a cost effectiveness threshold of £30,000 since CTZ + MTX was associated with an ICER of £353,740.

Table A. 8. csDMARD-IR, MTX eligible, severe RA - versus UPA 15 mg (deterministic results)

Technologies	Total costs (£)	Total QALYs	Total LYG	Full incremental costs (£)	Full incremental QALYs	ICER incremental (£/QALY)
UPA 15mg	[redacted]	[redacted]	14.196	-	-	Reference
IFX + MTX	[redacted]	[redacted]	14.196	[redacted]	[redacted]	Dominated
ADA + MTX	[redacted]	[redacted]	14.196	[redacted]	[redacted]	Dominated
ETN + MTX	[redacted]	[redacted]	14.196	[redacted]	[redacted]	Ext. dominated
TFC + MTX	[redacted]	[redacted]	14.196	[redacted]	[redacted]	Dominated
GOL + MTX	[redacted]	[redacted]	14.196	[redacted]	[redacted]	Ext. dominated
CTZ + MTX	[redacted]	[redacted]	14.196	[redacted]	[redacted]	353,740
BRC + MTX	[redacted]	[redacted]	14.196	[redacted]	[redacted]	Dominated
TCZ SC + MTX	[redacted]	[redacted]	14.196	[redacted]	[redacted]	Dominated
SRL + MTX	[redacted]	[redacted]	14.196	[redacted]	[redacted]	Dominated
TCZ IV + MTX	[redacted]	[redacted]	14.196	[redacted]	[redacted]	Dominated
ABT IV + MTX	[redacted]	[redacted]	14.196	[redacted]	[redacted]	Dominated
ABT SC + MTX	[redacted]	[redacted]	14.196	[redacted]	[redacted]	Dominated

Abbreviations: ABT=abatacept; ADA=adalimumab; BRC=baricitinib; BSC=best supportive care; csDMARD=conventional disease-modifying anti-rheumatic drug; CTZ=certolizumab pegol; ETN=etanercept; GOL=golimumab; INF=infliximab: IR=inadequate response; IV=intravenous infusion; LYG = Life Year Gained , MTX=methotrexate; N/A=not applicable; QALY = quality-adjusted life year RA=rheumatoid arthritis; RTX=rituximab; SC=subcutaneous injection; SRL=sarilumab; TCZ=tocilizumab; TFC=tofacitinib; UPA=upadacitinib.

5. bDMARD-IR, MTX eligible, RTX eligible, severe RA

The results of the base case analysis for the bDMARD-IR, MTX eligible, RTX eligible severe patient population are presented in Table 9 and Table 10. Upadacitinib combination therapy and upadacitinib monotherapy were dominated by rituximab + MTX.

Table 9. bDMARD-IR, MTX eligible, RTX eligible, severe RA – versus UPA 15mg + MTX (deterministic results)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus UPA 15mg + MTX (£/QALY)
RTX + MTX	[redacted]	13.423	[redacted]	-	-	Dominant
UPA 15mg + MTX	[redacted]	13.423	[redacted]	[redacted]	[redacted]	Reference

Abbreviations: bDMARD = Biologic Disease-modifying Antirheumatic Drug, LYG = Life Year Gained, MTX=methotrexate; QALY = quality-adjusted life year, RA=rheumatoid arthritis; RTX=rituximab; UPA=upadacitinib.

Table 10. bDMARD-IR, MTX eligible, RTX eligible, severe RA – versus UPA 15mg (deterministic results)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus UPA 15mg (£/QALY)
RTX + MTX	[redacted]	13.423	[redacted]	-	-	Dominant
UPA 15mg*	[redacted]	13.423	[redacted]	[redacted]	[redacted]	Reference

Abbreviations: bDMARD = Biologic Disease-modifying Antirheumatic Drug, LYG = Life Year Gained, MTX=methotrexate; QALY = quality-adjusted life year, RA=rheumatoid arthritis; RTX=rituximab; UPA=upadacitinib.

*Assume same efficacy as BRC + MTX since no efficacy estimate available UPA 15mg MONO in bDMARD-IR NMA (UPA 15mg estimated as having the same efficacy as BRC+MTX in the csDMARD-IR NMA)

4b. bDMARD-IR, MTX eligible, RTX ineligible, severe RA

The results of the base case analysis for the bDMARD-IR, MTX eligible, RTX ineligible severe patient population for upadacitinib combination therapy are presented in Table 11. In the incremental analysis, all treatments were dominated by upadacitinib combination therapy, except tocilizumab IV + MTX which was associated with higher costs and more benefits, generating an incremental ICER at £2,155,336 per QALY.

Table 11. bDMARD-IR, MTX eligible, RTX ineligible, severe RA – versus UPA 15mg + MTX (deterministic results)

Technologies	Total costs (£)	Total LYG	Total QALYs	Full incremental costs (£)	Full incremental QALYs	ICER incremental (£/QALY)
UPA 15mg + MTX	[redacted]	13.423	[redacted]	-	-	Reference
ADA + MTX*	[redacted]	13.423	[redacted]	[redacted]	[redacted]	Dominated
IFX + MTX*	[redacted]	13.423	[redacted]	[redacted]	[redacted]	Dominated
ETN + MTX*	[redacted]	13.423	[redacted]	[redacted]	[redacted]	Dominated
CTZ + MTX	[redacted]	13.423	[redacted]	[redacted]	[redacted]	Dominated
GOL + MTX	[redacted]	13.423	[redacted]	[redacted]	[redacted]	Dominated
TFC + MTX	[redacted]	13.423	[redacted]	[redacted]	[redacted]	Dominated
BRC + MTX	[redacted]	13.423	[redacted]	[redacted]	[redacted]	Dominated
TCZ SC + MTX	[redacted]	13.423	[redacted]	[redacted]	[redacted]	Dominated
SRL + MTX	[redacted]	13.423	[redacted]	[redacted]	[redacted]	Dominated
TCZ IV + MTX	[redacted]	13.423	[redacted]	[redacted]	[redacted]	2,155,336
ABT IV + MTX	[redacted]	13.423	[redacted]	[redacted]	[redacted]	Dominated
ABT SC + MTX**	[redacted]	13.423	[redacted]	[redacted]	[redacted]	Dominated

Abbreviations: ABT=abatacept; ADA=adalimumab; bDMARD = Biologic Disease-modifying Antirheumatic Drug; BRC=baricitinib; BSC=best supportive care; csDMARD=conventional disease-modifying anti-rheumatic drug; CTZ=certolizumab pegol; ETN=etanercept; GOL=golimumab; INF=infliximab: IR=inadequate response; IV=intravenous infusion; , LYG = Life Year Gained, MTX=methotrexate; N/A=not applicable; QALY = quality-adjusted life year RA=rheumatoid arthritis; RTX=rituximab; SC=subcutaneous injection; SRL=sarilumab; TCZ=tocilizumab; TFC=tofacitinib; UPA=upadacitinib.

*Assume same efficacy as BRC +MTX (from bDMARD-IR NMA) since no efficacy estimate available for these comparators in bDMARD-IR
**Assume same efficacy as ABT IV+MTX (from bDMARD-IR NMA)

The results of the base case analysis for the bDMARD-IR, MTX eligible, RTX ineligible severe patient population for upadacitinib monotherapy are presented in Table A. 12. In the incremental analysis, all treatments were dominated or extendedly dominated by upadacitinib monotherapy, except tocilizumab IV + MTX which was associated with higher costs and more benefits, generating an incremental ICER at £693,604 per QALY.

Table A. 12. bDMARD-IR, MTX eligible, RTX ineligible, severe RA – versus UPA 15mg (deterministic results)

Technologies	Total costs (£)	Total LYG	Total QALYs	Full incremental costs (£)	Full incremental QALYs	ICER incremental (£/QALY)
UPA 15mg	[redacted]	13.423	[redacted]	-	-	Reference
ADA + MTX*	[redacted]	13.423	[redacted]	[redacted]	[redacted]	Dominated
IFX + MTX*	[redacted]	13.423	[redacted]	[redacted]	[redacted]	Dominated
ETN + MTX*	[redacted]	13.423	[redacted]	[redacted]	[redacted]	Dominated
CTZ + MTX	[redacted]	13.423	[redacted]	[redacted]	[redacted]	Dominated
GOL + MTX	[redacted]	13.423	[redacted]	[redacted]	[redacted]	Dominated
TFC + MTX	[redacted]	13.423	[redacted]	[redacted]	[redacted]	Dominated
BRC + MTX	[redacted]	13.423	[redacted]	[redacted]	[redacted]	Ext. dominated
TCZ SC + MTX	[redacted]	13.423	[redacted]	[redacted]	[redacted]	Ext. dominated
SRL + MTX	[redacted]	13.423	[redacted]	[redacted]	[redacted]	Ext. dominated
TCZ IV + MTX	[redacted]	13.423	[redacted]	[redacted]	[redacted]	693,604
ABT IV + MTX	[redacted]	13.423	[redacted]	[redacted]	[redacted]	Dominated
ABT SC + MTX**	[redacted]	13.423	[redacted]	[redacted]	[redacted]	Dominated

Abbreviations: ABT=abatacept; ADA=adalimumab; bDMARD = Biologic Disease-modifying Antirheumatic Drug; BRC=baricitinib; BSC=best supportive care; csDMARD=conventional disease-modifying anti-rheumatic drug; CTZ=certolizumab pegol; ETN=etanercept; GOL=golimumab; INF=infliximab: IR=inadequate response; IV=intravenous infusion; , LYG = Life Year Gained , MTX=methotrexate; N/A=not applicable; QALY = quality-adjusted life year RA=rheumatoid arthritis; RTX=rituximab; SC=subcutaneous injection; SRL=sarilumab; TCZ=tocilizumab; TFC=tofacitinib; UPA=upadacitinib.

*Assume same efficacy as BRC +MTX (from bDMARD-IR NMA) since no efficacy estimate available for these comparators in bDMARD-IR NMA (UPA 15mg estimated as having the same efficacy as BRC+MTX in the csDMARD-IR NMA)
**Assume same efficacy as ABT IV+MTX (from bDMARD-IR NMA)

6. *bDMARD-IR, MTX eligible, RTX-IR, severe RA*

The results of the base case analysis for the bDMARD-IR, MTX eligible, RTX-IR severe patient population are presented in Table A. 13 and Table A. 14. Upadacitinib combination therapy dominates sarilumab + MTX. Compared to tocilizumab IV + MTX, upadacitinib combination therapy was less costly and less effective and the ICER associated with TCZ IV + MTX

compared to upadacitinib combination therapy was £419,748. Similar to upadacitinib combination therapy, upadacitinib monotherapy was less costly and less effective compared to tocilizumab IV + MTX and the ICER associated with TCZ IV + MTX compared to upadacitinib 15mg was £297,520.

Table A. 13. bDMARD-IR, MTX eligible, RTX IR, severe RA – versus UPA 15mg + MTX (deterministic results)

Technologies	Total costs (£)	Total LYG	Total QALYs	Full incremental costs (£)	Full incremental QALYs	ICER incremental (£/QALY)
UPA 15mg + MTX	[redacted]	13.423	[redacted]	-	-	Reference
SRL + MTX	[redacted]	13.423	[redacted]	[redacted]	[redacted]	Dominated
TCZ IV + MTX	[redacted]	13.423	[redacted]	[redacted]	[redacted]	419,748

Abbreviations: bDMARD = Biologic Disease-modifying Antirheumatic Drug; IV= Intravenous; , LYG = Life Year Gained , MTX = methotrexate, QALY = quality-adjusted life year , RA = rheumatoid arthritis, RTX = rituximab; SRL = sarilumab; TCZ = tocilizumab; UPA = Upadacitinib

Table A. 14. bDMARD-IR, MTX eligible, RTX IR, severe RA – versus UPA 15mg (deterministic results)

Technologies	Total costs (£)	Total LYG	Total QALYs	Full incremental costs (£)	Full incremental QALYs	ICER incremental (£/QALY)
UPA 15mg*	[redacted]	13.423	[redacted]	-	-	Reference
SRL + MTX	[redacted]	13.423	[redacted]	[redacted]	[redacted]	Ext. dominated
TCZ IV + MTX	[redacted]	13.423	[redacted]	[redacted]	[redacted]	297,520

Abbreviations: bDMARD = Biologic Disease-modifying Antirheumatic Drug; IV= Intravenous; LYG = Life Year Gained, MTX = methotrexate, QALY = quality-adjusted life year; RA = rheumatoid arthritis, RTX = rituximab; SRL = sarilumab; TCZ = tocilizumab; UPA = Upadacitinib

*Assume same efficacy as BRC+MTX (from bDMARD-IR NMA) since no efficacy estimate available UPA 15mg MONO in bDMARD-IR NMA (UPA 15mg estimated as having the same efficacy as BRC+MTX in the csDMARD-IR NMA)

3a. csDMARD-IR, MTX ineligible, severe RA

The results of the base case analysis for the csDMARD-IR, MTX ineligible severe patient population for upadacitinib monotherapy are presented in Table A. 15. Upadacitinib monotherapy dominates or extendedly dominates most of the

comparators except tocilizumab SC. Tocilizumab SC is associated with higher costs and more benefits, generating an ICER of £501,994 versus upadacitinib monotherapy. Tocilizumab IV is extendedly dominated by TCZ SC.

Table A. 15. csDMARD-IR, MTX ineligible, severe RA – versus UPA 15mg (deterministic results)

Technologies	Total costs (£)	Total LYG	Total QALYs	Full incremental costs (£)	Full incremental QALYs	ICER incremental (£/QALY)
UPA 15mg	[redacted]	14.196	[redacted]	-	-	Reference
ADA	[redacted]	14.196	[redacted]	[redacted]	[redacted]	Dominated
ETN	[redacted]	14.196	[redacted]	[redacted]	[redacted]	Dominated
CTZ*	[redacted]	14.196	[redacted]	[redacted]	[redacted]	Dominated
TFC	[redacted]	14.196	[redacted]	[redacted]	[redacted]	Dominated
BRC*	[redacted]	14.196	[redacted]	[redacted]	[redacted]	Dominated
SRL	[redacted]	14.196	[redacted]	[redacted]	[redacted]	Dominated
TCZ SC**	[redacted]	14.196	[redacted]	[redacted]	[redacted]	501,994
TCZ IV	[redacted]	14.196	[redacted]	[redacted]	[redacted]	Ext. dominated

Abbreviations: ADA = adalimumab, BRC = Baricitinib; csDMARD=conventional disease-modifying anti-rheumatic drug , CTZ = certolizumab pegol, ETN = etanercept, GOL = golimumab, IFX = infliximab, IV= Intravenous; LYG = Life Year Gained, MTX = methotrexate, QALY = quality-adjusted life year , RA = rheumatoid arthritis, RTX = rituximab; SC= Subcutaneous; SRL = sarilumab; TCZ = tocilizumab

*Assume same efficacy as ADA monotherapy (ADA efficacy from csDMARD-IR NMA) since no efficacy estimated for this comparator in the csDMARD-IR NMA
**Assume same efficacy as TCZ IV monotherapy (TCZ IV efficacy from csDMARD-IR NMA) since no efficacy estimated for this comparator in the csDMARD-IR NMA

4a. bDMARD-IR, MTX ineligible, severe RA

The results of the base case analysis for the bDMARD-IR, MTX ineligible severe patient population for upadacitinib monotherapy are presented in Table A. 16. In the incremental analysis, all treatments are dominated or extendedly dominated by upadacitinib monotherapy.

Table A. 16. bDMARD-IR, MTX ineligible, severe RA – versus UPA 15mg (deterministic results)

Technologies	Total costs (£)	Total LYG	Total QALYs	Full incremental costs (£)	Full incremental QALYs	ICER incremental (£/QALY)
UPA 15mg*	[redacted]	13.423	[redacted]	-	-	Reference
ADA*	[redacted]	13.423	[redacted]	[redacted]	[redacted]	Dominated
ETN*	[redacted]	13.423	[redacted]	[redacted]	[redacted]	Dominated
CTZ*	[redacted]	13.423	[redacted]	[redacted]	[redacted]	Dominated
TFC*	[redacted]	13.423	[redacted]	[redacted]	[redacted]	Ext. dominated
BRC*	[redacted]	13.423	[redacted]	[redacted]	[redacted]	Ext. dominated
SRL*	[redacted]	13.423	[redacted]	[redacted]	[redacted]	Dominated
TCZ SC*	[redacted]	13.423	[redacted]	[redacted]	[redacted]	Dominated
TCZ IV*	[redacted]	13.423	[redacted]	[redacted]	[redacted]	Dominated

Abbreviations: ADA = adalimumab, bDMARD = Biologic Disease-modifying Antirheumatic Drug, BRC = Baricitinib; CTZ = certolizumab pegol, ETN = etanercept, GOL = golimumab, IFX = infliximab, IV= Intravenous; LYG = Life Year Gained; MTX = methotrexate, QALY = quality-adjusted life year, RA = rheumatoid arthritis, RTX = rituximab; SC= Subcutaneous; SRL = sarilumab; TCZ = tocilizumab

*Assume same efficacy as BRC+MTX (BRC efficacy estimated from from bDMARD-IR NMA) since no efficacy estimate available for these comparators in bDMARD-IR NMA (UPA 15mg estimated as having the same efficacy as BRC+MTX in the csDMARD-IR NMA)

B.3.8 Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

The results of probabilistic sensitivity analysis are presented in Table A. 17.

Table A. 17. Probabilistic analysis results

Patient population	Population position	Comparator (multiple comparators – most cost-effective chosen)	Upadacitinib: Upa + MTX or upa mono	Base case ICER (upa - comparator) (probabilistic)	Probability upadacitinib cost effective at £20k threshold	Probability upadacitinib cost effective at £30k threshold	Probability upadacitinib cost effective at £20k threshold: all comparators	Probability upadacitinib cost effective at £20k threshold: all comparators
After one csDMARD failure (MTX eligible population)	1b	Int csDMARD	Upa + MTX	£23,428	32%	77%	-	-
		Int csDMARD	Upa mono	£23,145	36%	75%	-	-
After one csDMARD failure (MTX ineligible population)	1a	Int csDMARD	Upa mono	£16,248	68%	94%	-	-
After two csDMARD failure (MTX eligible population)	2b	MTX	Upa + MTX	£15,323	75%	75%	-	-
		MTX	Upa mono	£14,867	76%	97%	-	-
After two csDMARD failure (MTX ineligible population)	2a	BSC	Upa mono	£9,560	100%	100%	-	-
Severe RA (first line advanced therapies MTX eligible population)	3b	CTZ+MTX	Upa + MTX	£1,551,735*	100%	100%	100%	100%
		CTZ+MTX	Upa mono	£480,980*	100%	100%	100%	100%
Severe RA (first line advanced therapies MTX ineligible population)	3a	TCZ SC	Upa mono	£511,744*	100%	100%	100%	100%
After first line advanced therapy failure (in rituximab eligible patients)	5	RTX + MTX	Upa + MTX	Dominated	45%	45%	45%	45%
		RTX + MTX	Upa mono	Dominated	43%	40%	43%	40%
After first line advanced therapy failure (in rituximab ineligible patients) (MTX eligible)	4b	TCZ IV + MTX	Upa + MTX	Dominant	100%	100%	100%	100%
		TCZ IV + MTX	Upa mono	£2,006,950*	100%	100%	100%	100%
After first line advanced therapy failure (MTX ineligible)	4a	TCZ SC	Upa mono	£45,253*	100%	100%	100%	100%
After RTX + MTX failure	6	TCZ IV + MTX	Upa + MTX	£444,827*	100%	100%	100%	100%
		TCZ IV + MTX	Upa mono	£304,354*	100%	100%	100%	100%

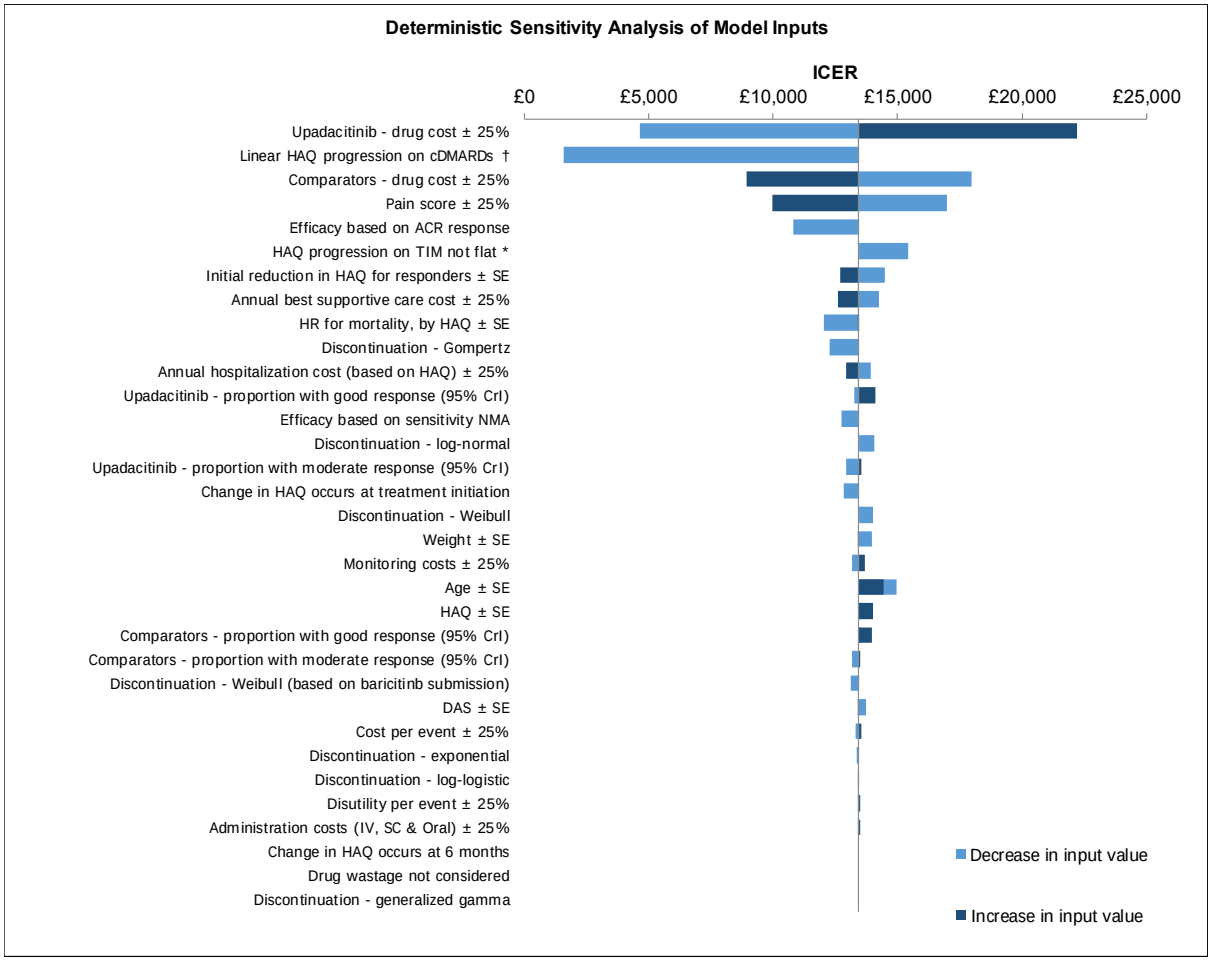
*upadacitinib is less costly and less effective.

B.3.8.2 Deterministic sensitivity analysis

Two csDMARD failure, MTX eligible, moderate RA

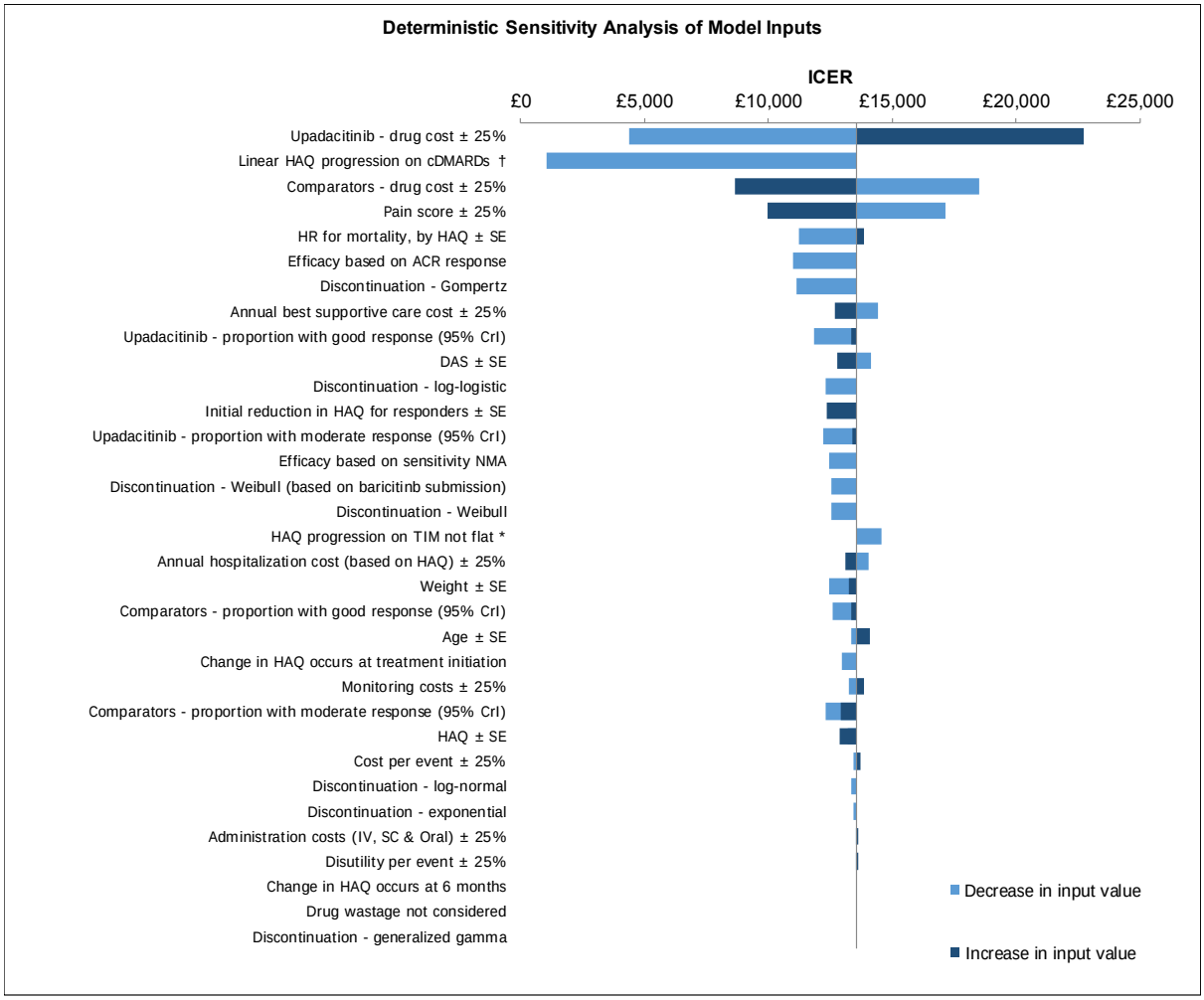
The results of the deterministic sensitivity analysis for the moderate, MTX eligible patient population after two csDMARD failure for upadacitinib monotherapy and upadacitinib combination therapy are presented in Figure A. 1 and Figure A. 2. The most influential factors for the model results are presented in the tornado diagrams. The key model drivers are drug costs of upadacitinib, HAQ progression assumptions, drug costs of comparators and pain score.

Figure A. 1. Tornado diagram in two csDMARD failure, MTX eligible, moderate RA (upadacitinib combination therapy vs. MTX)



Abbreviations: csDMARD = conventional DMARD, ICER= Incremental cost-effectiveness ratio; MTX = methotrexate, RA = rheumatoid arthritis, RTX = rituximab.

Figure A. 2. Tornado diagram in two csDMARD failure, MTX eligible, moderate RA (upadacitinib monotherapy vs. MTX)



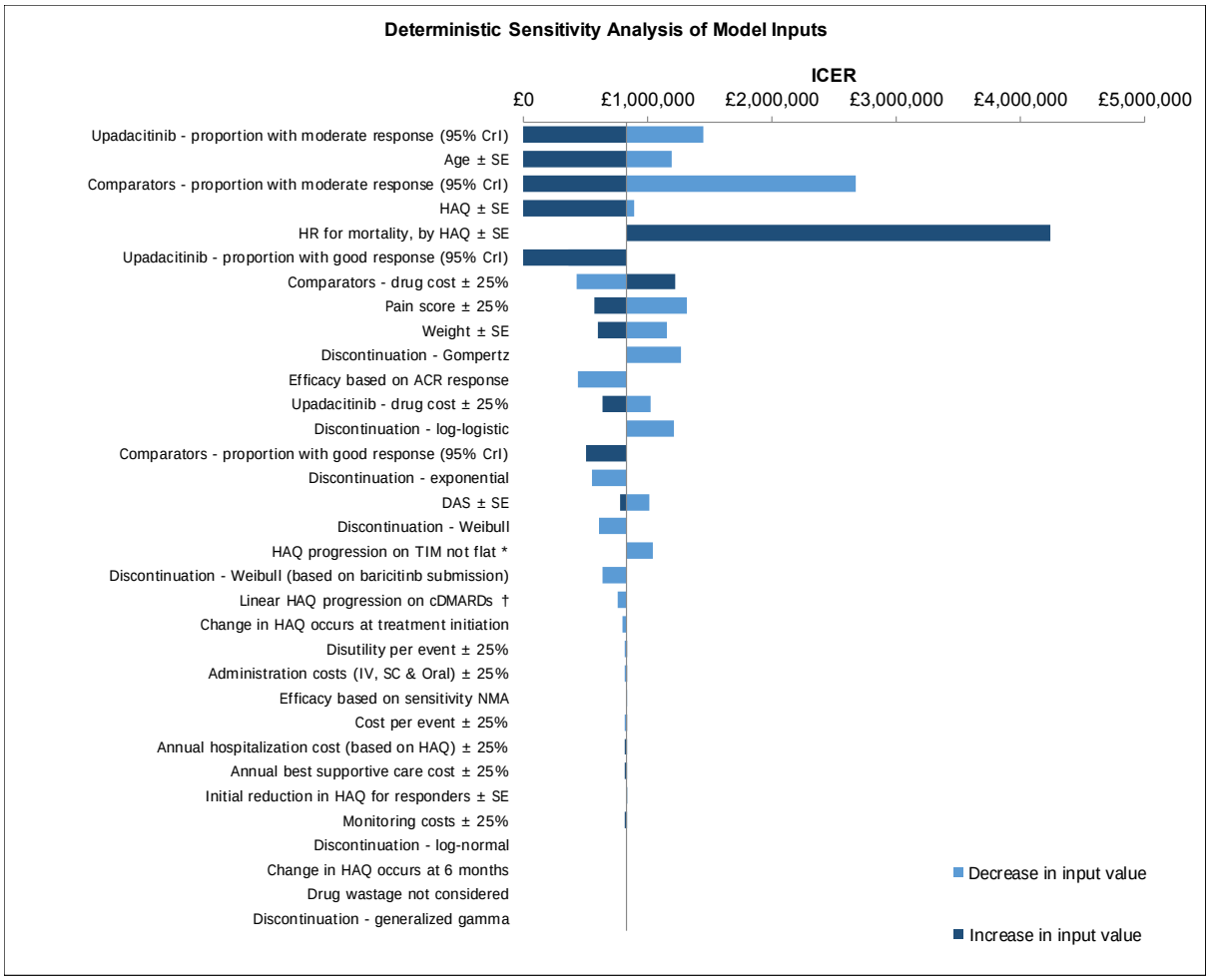
Abbreviations: csDMARD = conventional DMARD, ICER= Incremental cost-effectiveness ratio; MTX = methotrexate, RA = rheumatoid arthritis, RTX = rituximab.

csDMARD-IR, MTX eligible, severe RA

The results of the deterministic sensitivity analysis for the cDMARD-IR, MTX eligible severe patient population for upadacitinib combination therapy and upadacitinib monotherapy are presented in Figure A. 3 and Figure A. 4. The most influential factors for the model results are presented in the tornado diagrams. The key model drivers are the proportion of patients with moderate response rates for upadacitinib and the comparators, drug costs of comparators, age, pain score, HAQ progression and HR for mortality by HAQ. It should be noted that the output in these Figures is deceptive – the zero values in Figures A.3. and A.4. equate to situations where upadacitinib dominates and the most preferential ICERs for certolizumab are the

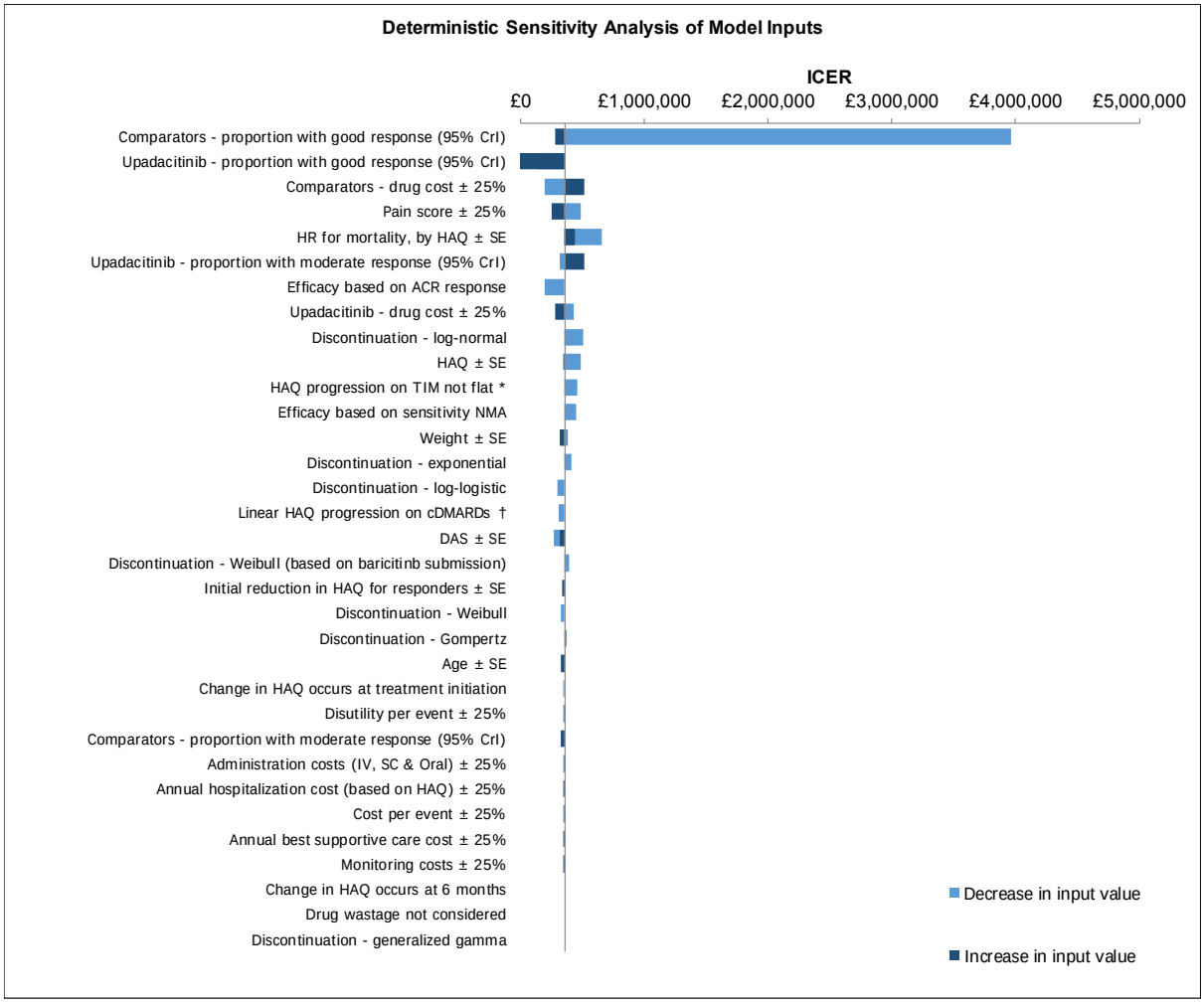
situation where it provides higher benefits at a highly unfavourable ICER (>£300,000 per QALY versus upadacitinib combination therapy and >£140,000 versus upadacitinib monotherapy).

Figure A. 3. Tornado diagram in csDMARD-IR, MTX eligible, severe RA (upadacitinib combination therapy vs. CTZ+ MTX)



Abbreviations: csDMARD = conventional DMARD, ICER= Incremental cost-effectiveness ratio; HR = Hazard ratio; MTX = methotrexate, IFX = infliximab, RA = rheumatoid arthritis, RTX = rituximab.

Figure A. 4. Tornado diagram in csDMARD-IR, MTX eligible, severe RA (upadacitinib monotherapy vs. CTZ + MTX)



Abbreviations: csDMARD = conventional DMARD, ICER= Incremental cost-effectiveness ratio; HR = Hazard ratio; MTX = methotrexate, IFX = infliximab, RA = rheumatoid arthritis, RTX = rituximab.

B.3.8.3 Scenario analysis

In the scenario analyses, certain model assumption and efficacy inputs were varied while holding the other parameters at base-case values. Results were presented in Table A. 18.

The key to the scenarios run is:

1. Moderate RA: Same sequence as base case but no transition to severe RA treatments

2. Moderate RA: Use moderate RA subgroup results for efficacy parameter for both csDMARD (int csDMARD and MTX) and upadacitinib. Details of subgroup analysis are presented in Appendix J.

3. Moderate and Severe RA: Use HAQ to VAS pain score mapping algorithm used in TA375 (rationale: model sensitive to this as shown in DSA section in B.3.8.2 Deterministic sensitivity analysis)

4. Moderate and Severe RA: Use conservative NMA as basis of efficacy for all relevant comparators in the treatment sequence

Table A. 18. Scenario analysis results

Population	Scenario number	Comparator	Base case ICER (vs upadacitinib 15mg + MTX)	Scenario analysis ICER (vs upadacitinib 15mg + MTX)	Base case ICER (vs upadacitinib 15mg)	Scenario analysis ICER (vs upadacitinib 15mg)
Moderate RA (after one csDMARD) (MTX eligible)	1	Int. csDMARD	£21,631	£27,548	£22,659	£28,483
	2	Int. csDMARD	£21,631	£22,661	£22,659	£23,864
	3	Int. csDMARD	£21,631	£24,994	£22,659	£26,109
	4	Int. csDMARD	£21,631	£20,544	£22,659	£19,615
Moderate RA (after two csDMARD) (MTX eligible)	1	MTX	£13,434	£22,220	£13,568	£22,742
	2	MTX	£13,434	£13,599	£13,568	£13,928
	3	MTX	£13,434	£15,645	£13,568	£15,815
	4	MTX	£13,434	£12,446	£13,568	£11,875
Severe RA (versus first line advanced treatments (MTX eligible)	3	CTZ + MTX	£828,052*	£1,139,524*	£353,740*	£456,724*
	4	CTZ + MTX	£828,052*	£363,907*	£353,740*	£250,651*

Abbreviations: csDMARD = conventional DMARD, ICER= Incremental cost-effectiveness ratio; MTX = methotrexate, IFX = infliximab, RA = rheumatoid arthritis, RTX = rituximab.

*upadacitinib is less costly and less effective

B.3.8.4 Summary of sensitivity analyses results

After one and two or more csDMARD failure, moderate RA patient populations, the key model drivers are drug costs of upadacitinib, HAQ progression assumptions, drug costs of comparator and the potential variance in the pain score values used to map utilities (Figures A.1 and A. 2).

In the csDMARD-IR, severe RA patient population, the key model drivers included proportion of patients with moderate response for upadacitinib and comparators, drug costs of comparators, age, pain score, HAQ progression and HR for mortality by HAQ (Figures A.3. and A.4.). It should be noted that the output in these Tornado plots is deceptive – the zero values in Figures A.3. and A.4. equate to situations where upadacitinib dominates and the most preferential ICERs for certolizumab are the situation where it provides higher benefits at a highly unfavourable ICER (>£300,000 per QALY versus upadacitinib combination therapy and >£140,000 versus upadacitinib monotherapy).

In the probabilistic analysis, cost-effectiveness results were seen to be closely aligned to deterministic results in terms of ICERs (as shown by comparing the ICERs in Table A.17. to those shown in Tables A.1. to A.16.).

In the scenario analysis, cost-effectiveness results were seen to be similar to base case results in the moderate RA population when using moderate RA subgroup efficacy data from the trial in place of moderate to severe RA NMA efficacy estimates (Table A.18.). The results demonstrated sensitivity when assuming no transition to severe RA treatments in this population. The severe population was sensitive to HAQ to VAS pain score mapping algorithm and effiacay inputs due to the little incremental QALY gains of CTZ + MTX versus upadacitinib in the base case analysis.

B.3.9 Subgroup analysis

The base case analysis includes separate analyses by disease severity and line of therapy.

B.3.10 Validation

B.3.10.1 Validation of cost-effectiveness analysis

Face validity

A qualitative evaluation was carried out to assess the accuracy of the decision problem, model structure, evidence/data sources, calculations, and assumptions in replicating the clinical pathway of interest and the plausibility of the analysis results. The checks were performed early in model conceptualization and frequently throughout model development.

These checks involved comparing the model outputs with the outputs from TA375, while holding the population and treatment regimens constant for both moderately active RA and severely active RA patients. For the moderately and severely active RA population the ICER was comparable between current model and TA375.

Internal validation

The model went through internal certification as a quality assurance measure. A full model-replication audit in VBA was performed and, in any instances, where the replication audit resulted in different outputs underlying issues were scrutinised. Model programming and mathematical calculations have also been checked. The model interface was checked, and it was ensured that all equations and parameters were cross-referenced against their sources and all modules of code were error-free and replicable.

External validation

The model has also been validated by an independent third-party consulting team. The model was checked for errors in model structure, code implementation and model assumptions. The procedures and functions in VBA were visually inspected to identify logical or transitional errors. The third-party team did not find any pressing issues with the model, and any corrections or suggestions were carefully incorporated into the model.

Comparison of model output to TA375

The AbbVie model has been validated against the base case ICERs in TA375 for severe RA to those published in Table 191- TA375 systematic review and economic Evaluation HTA. These TA375 ICERs are in line with the following statement in TAG

375 *"The base case ICERs for the severe active population who can take methotrexate is £41,600"* (TA375).

Table A. 19: Validation of severe RA ICERs between TA 375 and the AbbVie model

	AbbVie Model (using TA375 base case pain VAS scores)	*TA 375 base case model
MTX	Reference	Reference
ADA + MTX	£41,853	£41,567
ETN + MTX	£40,504	£42,494
IFX + MTX	£38,978	£38,503
CTZ + MTX	£41,287	£39,924
GOL + MTX	£42,060	£41,611

Abbreviations: ADA = adalimumab, CTZ = certolizumab pegol, ETN = etanercept, GOL = golimumab, IFX = infliximab, MTX = methotrexate, TCZ = tocilizumab.

To validate the AbbVie model output against TA375 model output in moderate RA patients the following treatment sequence output has been compared: ADA+MTX then MTX then BSC vs MTX then BSC (after two csDMARD failure, moderate RA). The pain VAS score map used in TA375 was used in the AbbVie model without transition to severe RA and using an annual ADA drug acquisition cost of £9187 to align to the settings and parameters used in TA375:

Table A. 20: Validation of moderate RA ICERs between TA 375 and the AbbVie model ADA+MTX versus MTX after two csDMARD-IR)

Population	AbbVie model (ICER per QALY gained)	NICE TA375 report, ICER per QALY gained* (2015 £)
csDMARD-IR, moderately active RA	£63,293	£63,513

Abbreviations: csDMARD= conventional disease-modifying anti-rheumatic drug; ICER= Incremental cost-effectiveness ratio; QALY= quality-adjusted life year; RA= Rheumatoid Arthritis; UPA= upadacitinib

* Referenced to Table 246 p415 of TA375 ERG report

A validation of the 150819 model (which was used as the basis of this addendum analysis) utility and change in HAQ ouput against trial data was provided in response to Clarification Question B23 by AbbVie on 15th August 2019.

B.3.11 Interpretation and conclusions of economic evidence

Table A. 21: Summary of deterministic ICERs for upadacitinib versus most cost-effective comparator

Patient population	Population position	Comparator	Upadacitinib : Upa + MTX or upa mono	Base case ICER (upa vs comparator) (deterministic)
After one csDMARD failure (MTX eligible population)	1b	Int csDMARD	Upa + MTX	£21,631
		Int csDMARD	Upa mono	£22,659
After one csDMARD failure (MTX ineligible population)	1a	Int csDMARD	Upa mono	£16,554
After two csDMARD failure (MTX eligible population)	2b	MTX	Upa + MTX	£13,434
		MTX	Upa mono	£13,568
After two csDMARD failure (MTX ineligible population)	2a	BSC	Upa mono	£8,885
Severe RA (first line advanced therapies MTX eligible population)	3b	CTZ + MTX	Upa + MTX	*£828,052
		CTZ + MTX	Upa mono	*£353,740
Severe RA (first line advanced therapies MTX ineligible population)	3a	TCZ SC	Upa mono	*£501,994
After first line advanced therapy failure (in rituximab eligible patients)	4b	RTX + MTX	Upa + MTX	Dominated
		RTX + MTX	Upa mono	Dominated
After first line advanced therapy failure (in rituximab ineligible patients) (MTX eligible)	5	TCZ IV + MTX	Upa + MTX	*£2,155,336
		TCZ IV + MTX	Upa mono	*£693,604
After first line advanced therapy failure (MTX ineligible)	4a	ADA	Upa mono	Dominant
After RTX + MTX failure	6	TCZ IV + MTX	Upa + MTX	*£419,748
		TCZ IV + MTX	Upa mono	*£297,520

Abbreviations: BSC= best supportive care; csDMARD= conventional disease-modifying anti-rheumatic drug; ICER= Incremental cost-effectiveness ratio; IFX= infliximab; IV= intravenous; MTX= methotrexate; RA= Rheumatoid Arthritis; RTX= rituximab; SC= Subcutaneous; TCZ= tocilizumab; UPA= upadacitinib

*Upadacitinib less costly and less benefits

The base case analysis was carried out using a deterministic analysis for logistical (time related) reasons. Deterministic and probabilistic ICERs were similar.

Both upadacitinib combination and upadacitinib monotherapy were cost effective in moderate RA patients:

- For the moderate, MTX eligible patient population after one csDMARD failure compared to intensive cDMARD, upadacitinib combination therapy and upadacitinib monotherapy were associated with increased benefits associated

with cost per QALYs of £21,631 and £22,659 respectively. The comparable analysis for MTX ineligible patients for upadacitinib monotherapy was associated with increased benefits associated with a cost per QALYs of £16,554.

- For the moderate, MTX eligible patient population after two or more csDMARD failure compared to MTX, upadacitinib combination therapy and upadacitinib monotherapy were associated with increased benefits associated with cost per QALYs of £13,434 and £13,568 respectively. The comparable analysis for MTX ineligible patients for upadacitinib monotherapy was associated with increased benefits associated with a cost per QALYs of £8,885.

In the cDMARD-IR, MTX eligible severe patient population (versus first line advanced therapies) both upadacitinib combination therapy and upadacitinib monotherapy were cost effective. In addition, upadacitinib monotherapy was cost effective in the respective MTX ineligible patients:

- In MTX eligible patients, upadacitinib combination therapy dominated all comparators except certolizumab combination therapy, which provided more benefits at a higher cost (associated with the non cost-effective ICER of £828,052).

- In MTX eligible patients, upadacitinib monotherapy was cost effective against all comparators. The most cost effective, certolizumab combination therapy, provided more benefits at a higher cost but was associated with the non cost-effective ICER of £353,740.

- In MTX ineligible patients, upadacitinib monotherapy was cost effective against all comparators. The most cost-effective comparator, tocilizumab SC monotherapy, provided more benefits at a higher cost but was associated with the non cost-effective ICER of £501,994.

After first line advanced therapy failure, in MTX eligible severe patient population who are not eligible for rituximab + MTX both upadacitinib combination therapy and upadacitinib monotherapy were cost effective. In addition, upadacitinib monotherapy was cost effective in the respective MTX ineligible patients:

- In MTX eligible patients, upadacitinib combination therapy dominated all comparators except tocilzumab IV combination therapy, which provided more benefits at a higher cost (associated with the non cost-effective ICER of £2,155,336).

- In MTX eligible patients, Upadacitinib monotherapy was cost effective against all comparators. The most cost effective, tocilzumab IV combination therapy, provided more benefits at a higher cost but was associated with the non cost-effective ICER of £693,604)

- In MTX ineligible patients, upadacitinib monotherapy dominated all comparators.

After first line advanced therapy failure, in MTX eligible severe patient population who are eligible for rituximab + MTX both upadacitinib combination therapy and monotherapy are dominated by RTX + MTX.

In those failing rituximab + MTX both upadacitinib combination therapy and monotherapy were cost effective:

- For upadacitinib combination therapy, the most cost-effective comparator tocilzumab IV combination therapy provided more benefits at a higher cost but it was associated with the non cost-effective ICER of £419,748.

- For upadacitinib monotherapy, the most cost-effective comparator tocilzumab IV combination therapy provided more benefits at a higher cost but it was associated with the non cost-effective ICER of £297,520.

Probabilistic ICERs were similar to those for the deterministic analysis and all ICERs were robust to sensisitivity analysis. Key probabilistic ICERs are summarised in Table A.17.

Overall, the results of the base case and sensitivity analyses are robust and demonstrate that upadacitinib combination therapy represents a cost-effective option across its expected full marketing authorisation for the treatment of patients with moderate to severe RA.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Upadacitinib for previously treated moderate to severe active rheumatoid arthritis [ID1400]

Clarification questions

July 2019

File name	Version	Contains confidential information	Date
ID1400_ Upadacitinib_RA_ Clarification questions_AbbVie response [ACIC]_FINAL.docx	Version 1	Yes	13/08/2019

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Literature searching

A1. The eligibility criteria for the clinical review (p. 43, Appendix D) includes 'biosimilars to any of the interventions listed above', however, free text search terms were not included for all brand names or biosimilars of comparators. For example, for infliximab, the following terms were not searched: Inflectra, Renflexis, Flixabi, Ixifi, Zessly. Please can you clarify why free text search terms for all brand names or biosimilars for relevant comparators were not included in the search strategy?

AbbVie response: The search strategy was designed to be broad as it included all the generic names in the search. All the intervention terms were exploded as well as searched as free text terms. For example, in OVID, the term infliximab covers all synonyms and drug brand names e.g. Avakine, Flixabi, Inflectra, ixifi, Remicade, Zessly, Remsima, Revellex, pf6438179, pf06438179, infliximab-dyyb. Hence, the current search strategy aimed to be comprehensive enough to cover all branded and biosimilar agents for relevant comparators.

A2. Search strategies have not been provided for searches of ClinicalTrials.gov. Please can you confirm if searches of ClinicalTrials.gov were completed for ongoing trials for upadacitinib and all comparators?

AbbVie response: Search strategies were completed in Clinical trials.gov. Please see details of the search in Table 1.

Table 1 Clinicaltrials.gov search strategies and hits

Conference	Data searched	Source	Year	Search terms	Number of hits
ClinicalTrials.gov (original review)					
ClinicalTrials.gov	03/4/2018	Online search, abstract archives: https://clinicaltrials.gov/	Last 3 years	Rheumatoid Arthritis	667
ClinicalTrials.gov (update review)					
ClinicalTrials.gov	24/4/2019	Online search, abstract archives: https://clinicaltrials.gov/	From last day of original search to 04/01/2018	Rheumatoid Arthritis	429

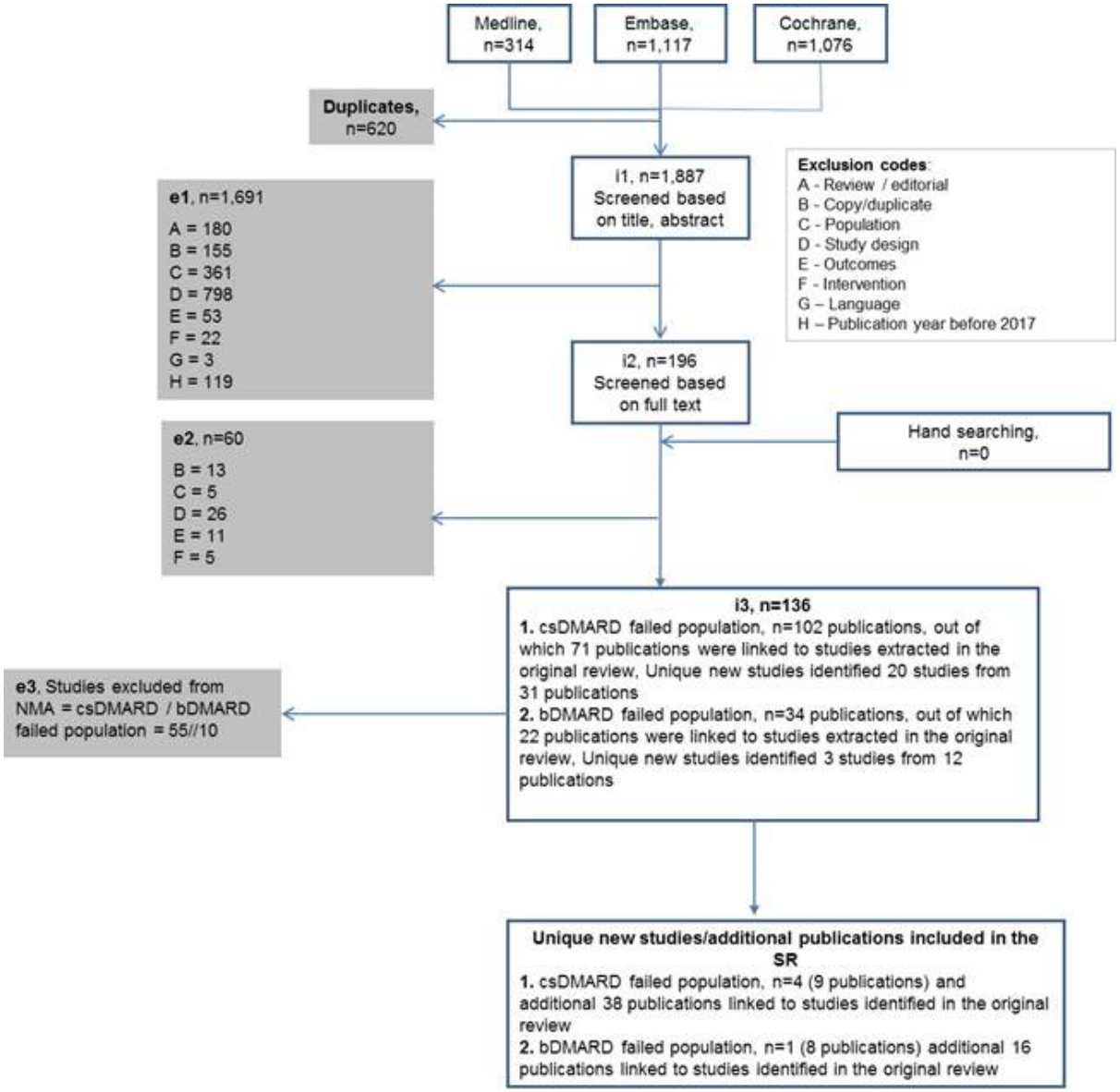
A3. Have searches been completed for literature on adverse reactions associated with upadacitinib?

AbbVie response: Search terms for literature on adverse reactions associated with upadacitinib were included in the clinical literature review. The clinical review encompassed safety outcomes as an outcome of interest in the eligibility criteria. However, only the efficacy data were extracted to inform the network meta-analysis.

A4. The PRISMA flow diagram presented on p. 57 of Appendix D does not clearly incorporate the results from the April 2019 update searches. There is a box for April 2019 (n=136), but it is not clear what source this is from. Please provide further details for the flow of studies for the April 2019 update searches.

AbbVie response: Please see the detailed PRISMA diagram for the April 2019 update search for the clinical review in Figure 1.

Figure 1: Clinical review update (April 2019) PRISMA diagram



Trial population

A5. Please state whether the bracketed quantities of Table 5 (p. 50, Company Submission) are standard deviations or standard errors. Please augment Table 5 with the baseline means, to a minimum of 3 significant figures, and standard deviations or standard errors as appropriate for quantities which are presented in the relevant trials' results tables: e.g. EQ-5D-5L for which the baseline values are not presented in Table 5. Please further augment it with the patient numbers (%) who are severe at baseline in line with the definition of severe in Figure 2 (p. 29). Please also split this augmented Table 5 into the subgroups of (1) moderate at baseline, (2) severe at baseline, as closely aligned with the definition of severe of Figure 2 as is feasible given trial data.

AbbVie response: Please find in Table 2 the updated baseline characteristics of the whole trial populations, as per the request. The bracketed quantities refer to either a proportion of patients or standard deviations, explained in the first column of Table 2**.** In addition, the baseline characteristics for the moderate and severe subgroup populations are listed in Table 3 and Table 4, respectively.

Table 2: Baseline characteristics of trial populations

Study	SELECT-COMPARE			SELECT-NEXT		SELECT-MONOTHERAPY		SELECT-BEYOND	
Treatment	PBO (N=651)	ADA (N=327)	UPA (N=651)	PBO (N=221)	UPA 15 mg (N=221)	MTX (N=216)	UPA 15 mg QD (N=217)	PBO (N=169)	UPA 15 mg (N=164)
Sex, n (%)									
Male	139 (21.4)	68 (20.8)	130 (20.0)	55 (24.9)	39 (17.6)	37 (17.1)	43 (19.8)	26 (15.4)	27 (16.5)
Female	512 (78.6)	259 (79.2)	521 (80.0)	166 (75.1)	182 (82.4)	179 (82.9)	174 (80.2)	143 (84.6)	137 (83.5)
Age (years) Mean (SD)	53.590 (12.2395)	53.737 (11.7028)	54.189 (12.0795)	55.991 (12.2229)	55.339 (11.4700)	55.315 (11.1185)	54.516 (12.1982)	57.645 (11.3946)	56.317 (11.3407)
Race, n (%)									
White	561 (86.2)	292 (89.3)	576 (88.5)	187 (84.6)	188 (85.1)	176 (81.5)	173 (79.7)	143 (84.6)	142 (86.6)
Black or African American	38 (5.84)	17 (5.20)	33 (5.07)	10 (4.53)	13 (5.88)	11 (5.09)	15 (6.91)	21 (12.4)	17 (10.4)
American Indian/Alaska Native	2 (0.307)	1 (0.306)	1 (0.154)	1 (0.452)	0	3 (1.39)	4 (1.84)	0	3 (1.83)
Native Hawaiian or other Pacific Islander	1(0.154)	0	0	0	0	NR	NR	0	0
Asian	39 (5.99)	15 (4.59)	31 (4.76)	19 (8.60)	19 (8.60)	24 (11.1)	24 (11.1)	5 (2.96)	2 (1.22)
Multiple	10 (1.54)	2 (0.612)	10 (1.54)	4 (1.81)	1 (0.452)	2 (0.93)	1 (0.461)	0	0
Ethnicity (Hispanic or Latino), n (%)	206 (31.6)	106 (32.4)	215 (33.0)	27 (12.2)	23 (10.4)	50 (23.1)	52 (24.0)	24 (14.2)	34 (20.7)
BMI (kg/m^2), Mean (SD)	28.675 (6.2040)	28.563 (6.5292)	29.188 (7.0045)	29.565 (6.5967)	29.721 (7.5600)	29.125 (6.9999)	28.202 (6.3166)	29.685 (7.3611)	31.168 (7.3019)
Duration of RA diagnosis (years) – continuous, Mean (SD)	8.274 (7.9966)	8.340 (8.4141)	8.101 (7.7277)	7.183 (7.4550)	7.254 (7.8880)	5.814 (6.6344)	7.458 (8.8794)	14.495 (9.2209)	12.376 (9.3827)
RF positive – categorical, n (%)	517 (79.4)	265 (81.0)	521 (80.0)	164 (74.2)	163 (73.8)	151 (69.9)	155 (71.4)	113 (66.9)	119 (73.0)
Anti-CCP positive – categorical, n (%)	529 (81.5)	264 (80.7)	525 (80.6)	167 (75.9)	174 (79.1)	153 (70.8)	159 (73.3)	117 (69.2)	119 (72.6)
RF and anti-CCP positive, n (%)	475 (73.2)	241 (73.7)	480 (73.7)	150 (67.9)	153 (69.5)	135 (62.5)	142 (65.4)	102 (60.4)	107 (65.6)
DAS28 (CRP) – continuous, Mean (SD)	5.833 (0.9400)	5.867 (0.9556)	5.777 (0.9708)	5.557 (0.8381)	5.653 (0.9709)	5.592 (1.0445)	5.618 (0.9233)	5.829 (1.0014)	5.869 (0.9473)
CDAI – continuous, Mean (SD)	40.028 (12.7322)	39.800 (13.1799)	39.704 (12.9204)	37.764 (11.8121)	38.268 (11.8638)	37.755 (14.3901)	37.986 (13.1208)	40.966 (13.2972)	41.654 (13.2776)
TJC68, Mean (SD)	25.989 (14.3009)	26.373 (15.1555)	26.435 (15.1497)	24.697 (14.9610)	25.158 (13.7952)	25.227 (15.9852)	24.465 (15.0987)	28.491 (15.2749)	27.762 (16.3061)
SJC66, Mean (SD)	16.206 (8.9711)	16.294 (9.1922)	16.571 (10.3089)	15.367 (9.2381)	15.955 (10.0439)	16.912 (11.5242)	16.415 (10.9423)	16.320 (9.5826)	17.037 (10.7509)

Study	SELECT-COMPARE			SELECT-NEXT		SELECT-MONOTHERAPY		SELECT-BEYOND	
Treatment	PBO (N=651)	ADA (N=327)	UPA (N=651)	PBO (N=221)	UPA 15 mg (N=221)	MTX (N=216)	UPA 15 mg QD (N=217)	PBO (N=169)	UPA 15 mg (N=164)
HAQ-DI Mean (SD)	1.609 (0.6082)	1.647 (0.5897)	1.633 (0.6352)	1.425 (0.6343)	1.478 (0.6076)	1.466 (0.6581)	1.471 (0.6603)	1.564 (0.6035)	1.669 (0.6428)
CRP (mg/L), Mean (SD)	17.974 (21.5172)	19.809 (21.5103)	17.896 (22.4855)	12.578 (13.9597)	16.622 (19.1698)	14.526 (17.3302)	13.952 (16.4865)	16.298 (21.1013)	16.246 (18.6238)
Baseline mTSS, Mean (SD)	35.892 (51.6590)	34.534 (47.0621)	34.031 (50.0755)	NR	NR	NR	NR	NR	NR
Baseline joint erosion score Mean (SD)	16.958 (27.4302)	15.414 (23.0983)	16.512 (26.4161)	NR	NR	NR	NR	NR	NR
Baseline JSN score, Mean (SD)	18.948 (26.1216)	19.170 (25.8428)	17.482 (25.0995)	NR	NR	NR	NR	NR	NR
Morning stiffness duration (minutes), Mean (SD)	142.444 (169.7796)	146.083 (184.9339)	141.538 (187.6118)	138.861 (213.9702)	152.406 (241.9026)	153.033 (221.7151)	144.203 (215.0519)	138.426 (178.5935)	140.415 (189.7186)
EUROQOL 5D Index score, Mean (SD)	0.548 (0.2689)	0.540 (0.2741)	0.546 (0.2687)	0.623 (0.2339)	0.603 (0.2454)	0.598 (0.2550)	0.587 (0.2507)	0.573 (0.2571)	0.521 (0.2712)
MTX dose at Baseline (mg), Mean (SD)	16.840 (3.8197)	17.097 (3.7618)	17.019 (4.1669)	NR	NR	16.719 (4.4102)	16.798 (4.2139)	NR	NR
Oral corticosteroid dosing at Baseline, n (%)	392 (60.2)	202 (61.8)	388 (59.6)	NR	NR	115 (53.2)	114 (52.5)	NR	NR
Oral corticosteroid dose (mg), Mean (SD)	6.266 (2.4082)	6.499 (2.4383)	6.226 (2.2715)	NR	NR	6.165 (2.5604)	6.103 (2.5232)	NR	NR
Prior biologic DMARD use, n (%)	63 (9.7)	34 (10.4)	54 (8.3)	29 (13.1)	27 (12.2)	NR	NR	169 (100)	164 (100)
Concomitant csDMARD at baseline, n (%)									
MTX alone	NR	NR	NR	141 (64.1)	122 (55.5)	NR	NR	122 (72.6)	118 (73.3)
MTX and other csDMARD	NR	NR	NR	49 (22.3)	47 (21.4)	NR	NR	17 (10.1)	19 (11.8)
csDMARD other than MTX	NR	NR	NR	30 (13.6)	51 (23.2)	NR	NR	29 (17.3)	24 (14.9)
Missing	NR	NR	NR	1	1	NR	NR	NR	NR
Oral steroid dosing at baseline, n (%)	NR	NR	NR	106 (48.0)	96 (43.4)	NR	NR	NR	NR
Oral steroid dose (mg), Mean (SD)	NR	NR	NR	6.349 (2.5504)	6.000 (2.3606)	6.165 (2.5604)	6.103 (2.5232)	6.257 (2.4245)	5.660 (2.3658)
MTX dose (mg), Mean (SD)	NR	NR	NR	16.263 (4.8913)	17.041 (4.8750)	16.719 (4.4102)	16.798 (4.2139)	NR	NR
Prior failed bDMARDs, n (%)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Stratum 1:1 MOA and ≤ 2 prior bDMARDs	NR	NR	NR	NR	NR	NR	NR	117 (69.2)	116 (70.7)

Study	SELECT-COMPARE			SELECT-NEXT		SELECT-MONOTHERAPY		SELECT-BEYOND	
Treatment	PBO (N=651)	ADA (N=327)	UPA (N=651)	PBO (N=221)	UPA 15 mg (N=221)	MTX (N=216)	UPA 15 mg QD (N=217)	PBO (N=169)	UPA 15 mg (N=164)
Stratum 2:> 1 MOA and/or > 2 prior bDMARDs	NR	NR	NR	NR	NR	NR	NR	52 (30.8)	48 (29.3)
Failed at least 1 anti-TNF, n (%)	NR	NR	NR	NR	NR	NR	NR	152 (89.9)	146 (89.0)
≤5.1 DAS28CRP at baseline (%)	130 (20.0)	71 (21.9)	149 (23.0)	33 (14.9)	20 (9.3)	73 (33.8)	72 (33.3)	38 (22.9)	39 (23.9)
>5.1 DAS28CRP at baseline(%)	519 (80.0)	253 (79.1)	498 (77.0)	188 (85.1)	195 (90.7)	143 (66.2)	144 (66.7)	128 (77.1)	124 (76.1)

Abbreviations: ADA: Adalimumab; bDMARD: biological Disease Modifying Anti-Rheumatic Drugs; BMI: Body Mass Index; CDAI: Crohn's Disease Activity Index; CRP: C-Reactive Protein; DAS28: Disease Activity Score version 28; csDMARD: conventional synthetic Disease Modifying Anti-Rheumatic Drugs; DMARD: Disease Modifying Anti-Rheumatic Drugs; HAQ-DI: Health Assessment Questionnaire Disability Index; JSN: Joint Space Narrowing; mTSS: modified Total Sharp Score; MOA: Mechanism of Action; MTX: Methotrexate; PBO: Placebo; RA: Rheumatoid Arthritis; RF: Rheumatoid Factor; SD: Standard deviation; SJC66: Swollen joint count based on 66 joints; TJC68: Tender joint count based on 68 joints; TNF: Tumor Necrosis Factor; UPA: Upadacitinib;

Table 3: Baseline characteristics of moderate trial population

Study	SELECT-COMPARE			SELECT-NEXT		SELECT-MONOTHERAPY		SELECT-BEYOND	
Treatment	PBO	ADA	UPA	PBO	UPA 15 mg	MTX	UPA 15 mg QD	PBO	UPA 15 mg
Sex, n (%)									
Male									
Female									
Age (years) Mean (SD)									
Race, n (%)									
White									
Black or African American									
American Indian/Alaska Native									
Native Hawaiian or other Pacific Islander									
Asian									
Multiple									
Ethnicity (Hispanic or Latino), n (%)									
BMI (kg/m^2), Mean (SD)									
Duration of RA diagnosis (years) – continuous, Mean (SD)									
RF positive– categorical, n (%)									
Anti-CCP positive – categorical, n (%)									
RF and anti-CCP positive, n (%)									
DAS28 (CRP) – continuous, Mean (SD)									
CDAI – continuous, Mean (SD)									

Study	SELECT-COMPARE			SELECT-NEXT		SELECT-MONOTHERAPY		SELECT-BEYOND	
Treatment	PBO [redacted]	ADA [redacted]	UPA [redacted]	PBO [redacted]	UPA 15 mg [redacted]	MTX [redacted]	UPA 15 mg QD [redacted]	PBO [redacted]	UPA 15 mg [redacted]
TJC68, Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SJC66, Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HAQ-DI Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRP (mg/L), Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline mTSS, Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline joint erosion score Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline JSN score, Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Morning stiffness duration (minutes), Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EUROQOL 5D Index score, Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SF-36 Physical component summary	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Functional assessment of chronic illness therapy-fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue scale	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MTX dose at Baseline (mg), Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oral corticosteroid dosing at Baseline, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oral corticosteroid dose (mg), Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior biologic DMARD use, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Concomitant csDMARD at baseline, n (%)									
MTX alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MTX and other csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
csDMARD other than MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Study	SELECT-COMPARE			SELECT-NEXT		SELECT-MONOTHERAPY		SELECT-BEYOND	
Treatment	PBO [redacted]	ADA [redacted]	UPA [redacted]	PBO [redacted]	UPA 15 mg [redacted]	MTX [redacted]	UPA 15 mg QD [redacted]	PBO [redacted]	UPA 15 mg [redacted]
Oral steroid dosing at baseline, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oral steroid dose (mg), Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MTX dose (mg), Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior failed bDMARDs, n (%)									
Stratum 1:1 MOA and ≤ 2 prior bDMARDs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratum 2:> 1 MOA and/or > 2 prior bDMARDs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Failed at least 1 anti-TNF, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA: Adalimumab; bDMARD: biological Disease Modifying Anti-Rheumatic Drugs; BMI: Body Mass Index; CDAI: Crohn's Disease Activity Index; CRP: C-Reactive Protein; DAS28: Disease Activity Score version 28; csDMARD: conventional synthetic Disease Modifying Anti-Rheumatic Drugs; DMARD: Disease Modifying Anti-Rheumatic Drugs; HAQ-DI: Health Assessment Questionnaire Disability Index; JSN: Joint Space Narrowing; mTSS: modified Total Sharp Score; MOA: Mechanism of Action; MTX: Methotrexate; PBO: Placebo; RA: Rheumatoid Arthritis; RF: Rheumatoid Factor; SD: Standard deviation; SJC66: Swollen joint count based on 66 joints; TJC68: Tender joint count based on 68 joints; TNF: Tumor Necrosis Factor; UPA: Upadacitinib;

Table 4: Baseline characteristics of severe trial population

Study	SELECT-COMPARE			SELECT-NEXT		SELECT-MONOTHERAPY		SELECT-BEYOND	
Treatment	PBO [redacted]	ADA [redacted]	UPA 15 mg [redacted]	PBO [redacted]	UPA 15 mg [redacted]	MTX [redacted]	UPA 15 mg QD [redacted]	PBO [redacted]	UPA 15 mg [redacted]
Sex, n (%)									
Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age (years) Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race, n (%)									
White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
American Indian/Alaska Native	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Study	SELECT-COMPARE			SELECT-NEXT		SELECT-MONOTHERAPY		SELECT-BEYOND	
Treatment	PBO	ADA	UPA 15 mg	PBO	UPA 15 mg	MTX	UPA 15 mg QD	PBO	UPA 15 mg
Native Hawaiian or other Pacific Islander	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Multiple	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ethnicity (Hispanic or Latino), n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI (kg/m^2), Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Duration of RA diagnosis (years) – continuous, Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RF – categorical, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-CCP – categorical, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RF and anti-CCP, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DAS28 (CRP) – continuous, Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CDAI – continuous, Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TJC68, Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SJC66, Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HAQ-DI Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRP (mg/L), Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline mTSS, Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline joint erosion score Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline JSN score, Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Morning stiffness duration (minutes), Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EUROQOL 5D Index score, Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SF-36 PCS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue Scale	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Study	SELECT-COMPARE			SELECT-NEXT		SELECT-MONOTHERAPY		SELECT-BEYOND	
Treatment	PBO [redacted]	ADA [redacted]	UPA 15 mg [redacted]	PBO [redacted]	UPA 15 mg [redacted]	MTX [redacted]	UPA 15 mg QD [redacted]	PBO [redacted]	UPA 15 mg [redacted]
MTX dose at Baseline (mg), Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oral corticosteroid dosing at Baseline, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oral corticosteroid dose (mg), Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior biologic DMARD use, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Concomitant csDMARD at baseline, n (%)									
MTX alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MTX and other csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
csDMARD other than MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oral steroid dosing at baseline, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oral steroid dose (mg), Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MTX dose (mg), Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior failed bDMARDs, n (%)									
Stratum 1:1 MOA and ≤ 2 prior bDMARDs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Others	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Failed at least 1 anti-TNF, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA: Adalimumab; bDMARD: biological Disease Modifying Anti-Rheumatic Drugs; BMI: Body Mass Index; CDAI: Crohn's Disease Activity Index; CRP: C-Reactive Protein; DAS28: Disease Activity Score version 28; csDMARD: conventional synthetic Disease Modifying Anti-Rheumatic Drugs; DMARD: Disease Modifying Anti-Rheumatic Drugs; HAQ-DI: Health Assessment Questionnaire Disability Index; JSN: Joint Space Narrowing; mTSS: modified Total Sharp Score; MOA: Mechanism of Action; MTX: Methotrexate; PBO: Placebo; RA: Rheumatoid Arthritis; RF: Rheumatoid Factor; SD: Standard deviation; SJC66: Swollen joint count based on 66 joints; TJC68: Tender joint count based on 68 joints; TNF: Tumor Necrosis Factor; UPA: Upadacitinib;

A6. Please provide the equivalent of Table 6 (p. 54, Company Submission) for those with moderate disease, as defined by the DAS28.

AbbVie response: The baseline characteristics of the moderate RA (as defined by DAS28) subgroup of patients alongside the BSRBR registry data is presented in Table 5. As would be expected, baseline age and gender can be seen to be comparable to baseline patient characteristics in the BSRBR registry. However, as the BSRBR registry represents a more severe cohort of patients with RA (as it includes data on those patients who are eligible for advanced therapies), the baseline DAS 28 or HAQ score are not comparable.

Table 5. Baseline characteristics of the eligible for bDMARDs patient cohort in the BSRBR registry compared to moderate RA patient subgroup in upadacitinib trials

Characteristic	SELECT-COMPARE			SELECT-NEXT		SELECT-MONOTHERAPY		SELECT-BEYOND		BSRBR registry
	PBO	ADA	UPA	PBO	UPA 15 mg	MTX	UPA 15 mg	PBO	UPA 15 mg	Eligible for bDMARDs
	[redacted]									(N = 11,798)
Age, mean (S.D.), years	[redacted]									56 (12)
Gender, female (%)	[redacted]									8777 (76)
DAS-28, mean (S.D.)	[redacted]									6.5 (1.0)
HAQ score, mean (S.D.)	[redacted]									2.0 (0.6)

Abbreviations: ADA: Adalimumab; DAS28: Disease Activity Score version 28; DMARD: Disease Modifying Anti-Rheumatic Drugs; HAQ: Health Assessment Questionnaire; MTX: Methotrexate; PBO: Placebo; SD: Standard deviation; TNF: tumor necrosis factor; UPA: Upadacitinib;

A7. Please report the baseline characteristics of SELECT-SUNRISE in a format paralleling Table 5, augmented as above

AbbVie response: The baseline patients characteristics of the SELECT-SUNRISE trial population are shown in Table 6.

Table 6: Baseline characteristics of SELECT-SUNRISE trial population

	Placebo (N = 49)	Upadacitinib 15 mg QD (N = 49)
Sex, n (%)		
Male	7 (14.3)	13 (26.5)
Female	42 (85.7)	36 (73.5)
Age (years), Mean (SD)	54.3 (13.04)	56.0 (12.50)
Race, n (%)		
Asian[a]	49 (100)	49 (100)
BMI (kg/m^2), Mean (SD)	22.8 (4.47)	23.2 (3.43)
Duration of RA diagnosis (years), Mean (SD)	4.8 (4.86)	5.9 (7.20)
Rheumatoid factor (RF), n (%)		
Positive	31 (63.3)	36 (73.5)
Negative	18 (36.7)	13(26.5)
Anti-CCP, n (%)		
Positive	40 (81.6)	38 (77.6)
Negative	9 (18.4)	11 (22.4)
RF and anti-CCP, n (%)		
Positive (RF and anti-CCP)	31 (63.3)	35 (71.4)
At least one negative	18 (36.7)	14 (28.6)
Negative (RF and anti-CCP)	9 (18.4)	10 (20.4)
At least one positive	40 (81.6)	39 (79.6)
DAS28 (CRP) – continuous, Mean (SD)	5.2 (0.84)	5.1 (1.07)
CDAI – continuous, Mean (SD)	31.0 (9.92)	32.1 (12.01)
TJC68, Mean (SD)	16.8 (11.42)	17.8 (12.58)
SJC66, Mean (SD)	10.9 (4.65)	14.0 (7.82)
HAQ-DI, Mean (SD)	1.0 (0.67)	1.0 (0.67)
CRP (mg/L), Mean (SD)	17.9 (20.53)	15.8 (18.23)
Morning stiffness - severity, Mean (SD)	4.6 (2.66)	4.9 (2.87)
Morning stiffness - duration (minutes), Mean (SD)	179.7 (302.44)	125.9 (234.12)
Prior biologic DMARD use, n (%)	3 (6.12)	6 (12.2)
Concomitant csDMARD at Baseline, n (%)		
MTX alone	29 (59.2)	28 (57.1)
MTX and other csDMARDs	14 (28.6)	12 (24.5)
csDMARDs other than MTX	6 (12.2)	9 (18.4)
Oral steroid dosing at baseline, n (%)	24 (49.0)	28 (57.1)
Oral steroid dose (mg), Mean (SD)	3.8 (2.05)	3.8 (1.90)
MTX dose (mg), Mean (SD)	10.1 (2.51)	9.2 (1.86)
≤5.1 DAS28CRP at baseline (%)	20 (40.8)	25 (51.0)
>5.1 DAS28CRP at baseline(%)	29 (59.2)	24 (49.0)

Abbreviations : BMI: Body Mass Index; CDAI: Crohn's Disease Activity Index; CRP: C-Reactive Protein; DAS28: Disease Activity Score version 28; csDMARD(s): conventional synthetic Disease Modifying Anti-Rheumatic Drugs; HAQ-DI: Health Assessment Questionnaire Disability Index; MTX: Methotrexate; RA: Rheumatoid Arthritis; RF: Rheumatoid Factor; SD: Standard deviation; SJC66: Swollen joint count based on 66 joints; TJC68: Tender joint count based on 68 joints

[a] Study consisted only of Japanese subjects.

Trial design

A8. Priority question: Was disease severity a stratifying factor at randomisation in any of the SELECT trials? Was disease severity a pre-specified subgroup analysis in any of the SELECT trials?

AbbVie response: Disease severity was not a stratifying factor at randomisation in any of the SELECT trials. The primary efficacy endpoint was examined in the subgroups with baseline DAS28(hsCRP) ≤ 5.1 or > 5.1 as a pre-specified subgroup analysis in SELECT-NEXT, SELECT-MONOTHERAPY, SELECT-COMPARE, SELECT-BEYOND and SELECT-SUNRISE.

A9. Priority question: For clarity, please provide a table for each of the 4 key trials plus SELECT-SUNRISE profiling interventions received in each arm including co-interventions.

AbbVie response: Please see Table 7 for details of all interventions and co-interventions received in the SELECT trials.

Table 7: Interventions and co-interventions received in SELECT trials

Study title	SELECT-COMPARE	SELECT-NEXT	SELECT-MONOTHERAPY	SELECT-BEYOND	SELECT-SUNRISE
Intervention(s)	Upadacitinib 15 mg orally QD (N=600) from Day 1 to Week 48 (Period 1) and thereafter up to 5 years (Period 2)	Upadacitinib 15 mg and 30 mg orally QD (N=200) from Day 1 to Week 12 (Period 1) and thereafter up to 5 years (Period 2)	Upadacitinib 15 mg and 30 mg orally QD (N=200) from Day 1 to Week 14 (Period 1) and thereafter up to Week 226 (Period 2)	Upadacitinib 15 mg and 30 mg orally QD (N=150) from Day 1 to Week 24 (Period 1) and thereafter up to Week 216 (Period 2)	Upadacitinib 7.5mg, 15 mg or 30 mg orally QD (N=48) from Day 1 to Week 12 (Period 1) and thereafter up to regulatory approval of RA indication in Japan (Period 2)
Comparator(s)	Placebo (orally QD or SC eow) from Day 1 to Week 26, followed by Upadacitinib 15 mg QD from Week 26 to Week 48 (Period 1) and thereafter up to 5 years (Period 2) Adalimumab 40 mg SC eow from Day 1 to Week 48 (Period 1) and thereafter up to 5 years (Period 2)	Placebo from Day 1 to Week 12, followed by Upadacitinib 15 mg or 30 mg orally QD at Week 12 and thereafter up to 5 years	MTX once weekly from day 1 to Week 14 (Period 1), followed by Upadacitinib 15 mg or 30 mg orally QD at Week 14 and thereafter up to Week 226 (Period 2)	Placebo from Day 1 to Week 12, followed by Upadacitinib 15 mg or 30 mg orally QD at Week 12 to Week 24 (Period 1) and thereafter up to Week 216 (Period 2)	Placebo from Day 1 to Week 12 (Period 1), followed by Upadacitinib 7.5mg, 15 mg or 30 mg orally QD up to regulatory approval of RA indication in Japan (Period 2)

Study title	SELECT-COMPARE	SELECT-NEXT	SELECT-MONOTHERAPY	SELECT-BEYOND	SELECT-SUNRISE
Co-Interventions	Patients were to continue their weekly stable background therapy of methotrexate. In addition, all subjects were to take a dietary supplement of oral folic acid (or equivalent) throughout study participation. Patients were to continue stable doses of non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen or oral steroids (equivalent to ≤10 mg prednisone or equivalent/day).	Patients were to continue their weekly stable background therapy of csDMARD. Permitted background csDMARDs were oral and parenteral methotrexate (15 – 25 mg per week), chloroquine (≤250 mg per day), hydroxychloroquine (≤400 mg per day), sulfasalazine (≤3000 mg per day), or leflunomide (≤20 mg per day); up to two concomitant background csDMARDs were allowed, with the exception of the combination of methotrexate and leflunomide. csDMARD doses could only be reduced in cases of intolerance or for safety reasons. Subjects taking MTX were to take a dietary supplement of oral folic acid or equivalent. Stable doses of non-steroidal anti-inflammatory drugs, acetaminophen, oral steroids (equivalent to ≤10 mg prednisone or equivalent per day), or inhaled steroids were allowed throughout the study.	Patients were to continue stable doses of non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen or oral steroids (equivalent to ≤10 mg prednisone or equivalent/day) and were to take a dietary supplement of folic acid or an equivalent.	Patients continued stable csDMARD therapy for the first 24 weeks of the study, restricted to oral or parenteral methotrexate (7·5 – 25 mg per week), chloroquine (≤250 mg per day), hydroxychloroquine (≤400 mg per day), sulfasalazine (≤3000 mg per day), or leflunomide (≤20 mg per day). Patients could be taking a maximum of two background csDMARDs, except the combination of methotrexate and leflunomide, which was not allowed. Dose decreases of csDMARDs were permitted for safety reasons only. Subjects taking MTX were to take a dietary supplement of oral folic acid or equivalent. Patients continued stable doses of nonsteroidal anti-inflammatory drugs, acetaminophen, or steroids (prednisone equivalent of ≤10 mg per day).	Patients continued stable csDMARD therapy for the first 24 weeks of the study, restricted to oral or parenteral MTX (7.5 – 25 mg per week), sulfasalazine (≤ 3000 mg/day], leflunomide (≤ 20 mg/day), bucillamine (≤ 300 mg/day), or iguratimod (≤ 50 mg/day); up to two concomitant background csDMARDs were allowed, with the exception of the combination of methotrexate and leflunomide. During the study, the csDMARD dose was only allowed to be decreased for safety reasons. Subjects taking MTX were to take oral folic acid or an equivalent. Patients were to continue stable doses of non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, oral steroids (equivalent to ≤10 mg prednisone or equivalent/day) or inhaled corticosteroids.

Trial results

A10. Please provide the standard errors for the estimates presented in tables 7, 8, 9, 10, 11 (Company Submission). Within this please present the results to a minimum of 3 significant figures. Please also provide these tables split into the subgroups of (1) moderate disease at baseline and (2) severe disease at baseline, as closely aligned with the definition of severe of Figure 2 as is feasible given trial data.

AbbVie response: Please note as standard errors were not available, confidence intervals have been provided in response to this question instead as discussed and agreed during the clarification question call. Please find this detailed in Table 8, Table 11, Table 17, Table 20, and Table 23 for the full trial populations. Table 9, Table 10, Table 12, Table 13, Table 14, Table 15, Table 16, Table 18, Table 19, Table 21, Table 22, Table 24, and Table 25 provide the data split by moderate and severe subgroups for each trial.

Table 8: Summary of clinical effectiveness results for SELECT-COMPARE trial population

Endpoints	Week 12			Week 26		
	PBO (+MTX) (N=651)	ADA (+MTX) (N=327)	UPA 15 mg (+MTX) (N=651)	PBO (+MTX) (N=651)	ADA (+MTX) (N=327)	UPA 15 mg (+MTX) (N=651)
ACR20 response rate (95% CI)	36.4 (32.7, 40.1) ***	63 (57.8, 68.2)#	70.5 (67.0, 74.0)	35.6 (32.0, 39.3) ***	57.2 (51.8, 62.5) ##	67.4 (63.8, 71.0)
ACR50 response rate (95% CI)	14.9 (12.2, 17.6) ***	29.1 (24.1, 34.0) ###	45.2 (41.3, 49.0)	20.9 (17.8, 24.0) ***	41.9 (36.5, 47.2) ###	53.9 (50.1, 57.7)
ACR70 response rate (95% CI)	4.9 (3.3, 6.6) ***	13.5 (9.8, 17.2) ###	24.9 (21.6, 28.2)	9.5 (7.3, 11.8) ***	22.9 (18.4, 27.5) ###	34.7 (31.1, 38.4)
Clinical remission based on DAS28 (CRP) (95% CI)	6.1 (4.3, 8.0) ***	18.0 (13.9, 22.2) ###	28.7 (25.2, 32.2)	9.2 (7.0, 11.4) ***	26.9 (22.1, 31.7) ###	40.9 (37.1, 44.6)
DAS28 (CRP) CFB (95% CI)	-1.140 (-1.275, -1.004) ***	-1.993 (-2.164, -1.822) ###	-2.483 (-2.622, -2.344)	-1.196 (-1.344, -1.048) ***	-2.302 (-2.489, -2.116) ###	-2.810 (-2.959, -2.661)
EQ-5D-5L CFB (95% CI)	0.104 (0.084, 0.125) ***	0.174 (0.149, 0.199) #	0.208 (0.187, 0.229)	0.111 (0.091, 0.132) ***	0.205 (0.179, 0.231) #	0.220 (0.199, 0.241)
FACIT-F CFB (95% CI)	4.808 (3.850, 5.766) ***	7.442 (6.247, 8.637) #	8.954 (7.979, 9.930)	5.483 (4.485, 6.482)***	8.239 (6.981, 9.497) #	9.683 (8.675, 10.692)
HAQ-DI CFB (95% CI)	-0.281 (-0.338, -0.224) ***	-0.492 (-0.563, -0.420)	-0.598 (-0.656, -0.540)	-0.332 (-0.393, -0.270)***	-0.574 (-0.651, -0.496) #	-0.692 (-0.754, -0.629)
LDA CDAI (95% CI)	16.3 (13.4, 19.1) ***	30.0 (25.0, 34.9) ##	40.4 (36.6, 44.2)	22.1 (18.9, 25.3) ***	38.2 (33.0, 43.5) ###	52.7 (48.9, 56.5)
LDA DAS28(CRP) (95% CI)	13.8 (11.2, 16.5) ***	28.7 (23.8, 33.7) ##	45.0 (41.2, 48.8)	18.0 (15.0, 20.9)***	38.5 (33.3, 43.8) ###	54.7 (50.9, 58.5)
LDA DAS28(CRP) - Non - Inferiority (95% CI)	13.8 (11.2, 16.5) ***	28.7 (23.8, 33.7) ##	45.0 (41.2, 48.8)	18.0 (15.0, 20.9)	38.5 (33.3, 43.8) ***	54.7 (50.9, 58.5)
Morning stiffness duration (minutes) change (95% CI)	-50.382 (-60.927, -39.837)***	-83.959 (-97.205, -70.712)	-93.034 (-103.769, -82.300)	-53.875 (-64.683, -43.067) ***	-91.357 (-105.060, -77.653)	-100.253 (-111.171, -89.336)
mTSS CFB	NA	NA	NA	0.9	0.1	0.2***
Patient's global assessment of pain change	-15.692 (-18.149, -13.236) ***	-25.611 (-28.680, -22.542) ###	-32.097 (-34.602, -29.593)	-18.597 (-21.235, -15.959) ***	-31.864 (-35.197, -28.531) ##	-36.745 (-39.415, -34.076)
Proportion of subjects with no radiographic progression	NA	NA	NA	76.0 (72.5, 79.4)	86.8 (83.0, 90.7)	83.5 (80.5, 86.5)
RA-WIS score CFB (95% CI)	-1.982 (-2.865, -1.100) ***	-4.447 (-5.614, -3.280)	-5.162 (-6.096, -4.228)	-2.658 (-3.645, -1.671) ***	-4.621 (-5.958, -3.283)	-5.894 (-6.936, -4.853)
SF-36 PCS CFB (95% CI)	3.559 (2.786, 4.332) ***	6.271 (5.310, 7.233) ##	7.893 (7.109, 8.677)	4.503 (3.650, 5.357) ***	7.841 (6.767, 8.915) ##	9.507 (8.647, 10.367)

Abbreviations: ACR20/50/70 = American College of Rheumatology 20%, 50%, 70% response; CDAI = Clinical Disease Activity Index; CFB = Change From Baseline; CRP = C-reactive protein; DAS28 = Disease Activity Score 28; FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue; HAQ-DI = Health Assessment Questionnaire – Disability Index; LDA = low disease activity; PCS = physical component summary; QD = once daily; SF-36 = Short Form-36
***, **, * Statistically significant at 0.001, 0.01, and 0.05 level, respectively UPA vs placebo
###, ##, # Statistically significant at 0.001, 0.01, and 0.05 level, respectively UPA vs placebo

Table 9: Summary of clinical effectiveness results for SELECT-COMPARE: moderate trial patients

Endpoints	Week 12			Week 26		
	PBO (+MTX)	ADA (+MTX)	UPA 15 mg (+MTX)	PBO (+MTX)	ADA (+MTX)	UPA 15 mg (+MTX)
ACR20 response rate (95% CI)	[redacted]					
ACR50 response rate (95% CI)						
ACR70 response rate (95% CI)						
Clinical remission based on DAS28 (CRP) (95% CI)						
DAS28 (CRP) CFB (95% CI)						
EQ-5D-5L CFB (95% CI)						
FACIT-F CFB (95% CI)						
HAQ-DI CFB (95% CI)						
LDA CDAI (95% CI)						
LDA DAS28(CRP) (95% CI)						
LDA DAS28(CRP) - Non -Inferiority (95% CI)						
Morning stiffness duration (minutes) change (95% CI)						
mTSS CFB (95% CI)						

Patient's global assessment of pain change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of subjects with no radiographic progression (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RA-WIS score CFB (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SF-36 PCS CFB (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ACR20/50/70 = American College of Rheumatology 20%, 50%, 70% response; CDAI = Clinical Disease Activity Index; CFB = Change From Baseline; CRP = C-reactive protein; DAS28 = Disease Activity Score 28; FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue; HAQ-DI = Health Assessment Questionnaire – Disability Index; LDA = low disease activity; PCS = physical component summary; QD = once daily; SF-36 = Short Form-36 ***, **, * Statistically significant at 0.001, 0.01, and 0.05 level, respectively UPA vs placebo						

Table 10: Summary of clinical effectiveness results for SELECT-COMPARE: severe trial patients

Endpoints	Week 12			Week 26		
	PBO (+MTX)	ADA (+MTX)	UPA 15 mg (+MTX)	PBO (+MTX)	ADA (+MTX)	UPA 15 mg (+MTX)
ACR20 response rate (95% CI)	[redacted]					
ACR50 response rate (95% CI)						
ACR70 response (95% CI)						
Clinical remission based on DAS28 (CRP) (95% CI)						
DAS28 (CRP) CFB (95% CI)						
EQ-5D-5L CFB (95% CI)						
FACIT-F CFB (95% CI)						
HAQ-DI CFB (95% CI)						
LDA CDAI (95% CI)						
LDA DAS28(CRP) (95% CI)						
LDA DAS28(CRP) - Non - Inferiority (95% CI)						
Morning stiffness duration (minutes) change (95% CI)						
mTSS CFB (95% CI)						
Patient's global assessment of pain change (95% CI)						
Proportion of subjects with no radiographic progression (95% CI)						

RA-WIS score CFB (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SF-36 PCS CFB (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ACR20/50/70 = American College of Rheumatology 20%, 50%, 70% response; CDAI = Clinical Disease Activity Index; CFB = Change From Baseline; CRP = C-reactive protein; DAS28 = Disease Activity Score 28; FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue; HAQ-DI = Health Assessment Questionnaire – Disability Index; LDA = low disease activity; PCS = physical component summary; QD = once daily; SF-36 = Short Form-36
***, **, * Statistically significant at 0.001, 0.01, and 0.05 level, respectively UPA vs placebo

Table 11: Summary of clinical effectiveness results for SELECT-NEXT trial patients

Endpoints	Week 12	
	PBO (+csDMARDs) (N=221)	UPA 15 mg (+ csDMARDs) (N=221)
ACR20 response rate (95% CI)	35.7 (29.4, 42.1)	63.8 (57.5, 70.1)***
ACR50 response rate (95% CI)	14.9 (10.2, 19.6)	38.0 (31.6, 44.4)***
ACR70 response rate (95% CI)	5.9 (2.8, 9.0)	20.8 (15.5, 26.2)***
Clinical remission based on DAS28 (CRP) (95% CI)	10.0 (6.0, 13.9)	30.8 (24.7, 36.9)***
DAS28 (CRP) CFB (95% CI)	-1.022 (-1.206, -0.838)	-2.255 (-2.441, -2.069)***
EQ-5D-5L CFB (95% CI)	0.078 (0.052, 0.105)	0.186 (0.159, 0.213)***
FACIT-F CFB (95% CI)	2.959 (1.620, 4.299)	7.912 (6.558, 9.266)***
HAQ-DI CFB (95% CI)	-0.257 (-0.334, -0.180)	-0.606 (-0.683, -0.528)***
LDA CDAI (95% CI)	19.0 (13.8, 24.2)	40.3 (33.8, 46.7)***
LDA DAS28(CRP) (95% CI)	17.2 (12.2, 22.2)	48.4 (41.8, 55.0)***
Morning stiffness duration (minutes) change (95% CI)	-34.270 (-54.633, -13.907)	-85.279 (-105.609, -64.948)***
RA-WIS CFB (95% CI)	-1.554 (-2.686, -0.422)	-4.276 (-5.413, -3.139)***
SF-36 PCS CFB (95% CI)	3.030 (1.884, 4.177)	7.585 (6.430, 8.740)***

Abbreviations: ACR20/50/70 = American College of Rheumatology 20%, 50%, 70% response; CDAI = Clinical Disease Activity Index; CFB = Change From Baseline; CRP = C-reactive protein; DAS28 = Disease Activity Score 28; FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue; HAQ-DI = Health Assessment Questionnaire – Disability Index; LDA = low disease activity; PCS = physical component summary; QD = once daily; SF-36 = Short Form-36
*** Statistically significant at 0.001 level

Table 12: Summary of clinical effectiveness results for SELECT-NEXT moderate trial patients

Endpoints	Week 12	
	PBO (+csDMARDs)	UPA 15 mg (+ csDMARDs)
ACR20 response rate (95% CI)		
ACR50 response rate (95% CI)		
ACR70 response rate (95% CI)		
Clinical remission based on DAS28 (CRP) (95% CI)		
DAS28 (CRP) CFB (95% CI)		
EQ-5D-5L CFB (95% CI)		
FACIT-F CFB (95% CI)		
HAQ-DI CFB (95% CI)		
LDA CDAI (95% CI)		
LDA DAS28(CRP) (95% CI)		
Morning stiffness duration (minutes) change (95% CI)		
RA-WIS CFB (95% CI)		
SF-36 PCS CFB (95% CI)		

Abbreviations: ACR20/50/70 = American College of Rheumatology 20%, 50%, 70% response; CDAI = Clinical Disease Activity Index; CFB = Change From Baseline; CRP = C-reactive protein; DAS28 = Disease Activity Score 28; FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue; HAQ-DI = Health Assessment Questionnaire – Disability Index; LDA = low disease activity; PCS = physical component summary; QD = once daily; SF-36 = Short Form-36
***, **, * Statistically significant at 0.001, 0.01, and 0.05 level, respectively

Table 13: Summary of clinical effectiveness results for SELECT-NEXT severe trial patients

Endpoints	Week 12	
	PBO (+csDMARDs)	UPA 15 mg (+ csDMARDs)
ACR20 response rate (95% CI)		
ACR50 response rate (95% CI)		
ACR70 response rate (95% CI)		
Clinical remission based on DAS28 (CRP) (95% CI)		
DAS28 (CRP) CFB (95% CI)		
EQ-5D-5L CFB (95% CI)		
FACIT-F CFB (95% CI)		
HAQ-DI CFB (95% CI)		
LDA CDAI (95% CI)		
LDA DAS28(CRP) (95% CI)		
Morning stiffness duration (minutes) change (95% CI)		
RA-WIS CFB (95% CI)		
SF-36 PCS CFB (95% CI)		

Abbreviations: ACR20/50/70 = American College of Rheumatology 20%, 50%, 70% response; CDAI = Clinical Disease Activity Index; CFB = Change From Baseline; CRP = C-reactive protein; DAS28 = Disease Activity Score 28; FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue; HAQ-DI = Health Assessment Questionnaire – Disability Index; LDA = low disease activity; PCS = physical component summary; QD = once daily; SF-36 = Short Form-36
*** Statistically significant at 0.001 level

Table 14: Least squared mean (LSM) changes from baseline and percentage of responders for MCID and for normative values at week 12 after upadacitinib initiation

PRO	Change from baseline		% responders			
	LSM		Reporting scores ≥MCID, n (%)		Reporting scores ≥normative values, n (%)	
	PBO N=221	UPA 15 mg N=221	PBO N=221	UPA 15 mg N=221	PBO N=221	UPA 15 mg N=221
HAQ-DI	-0.26	-0.61*	109 (49.3)	156 (72.2) *	30 (13.6)	56 (25.9) *
Tag	-10.36	-29.67*	94 (42.5)	153 (70.5) *	32 (14.5)	78 (35.9) *
Pain VAS	-10.26	-29.92*	97 (43.9)	158 (72.8) *	-	-
FACIT-F	2.96	7.91*	91 (41.2)	138 (63.9) *	35.8 (15.8)	60 (27.8) *
Duration morning stiffness[a]	-34.27	-85.28*	29 (13.4)	57 (26.3) *, b	-	-
Severity morning stiffness[b]	-1.38	-2.88*	130 (60.2)	165 (76.0) *, b	-	-
SF-36 PCS	3.03	7.58*	106 (48.0)	152 (69.4) *	18 (8.1)	39 (17.8) *
SF-36 MCS	2.58	4.69*	91 (41.2)	120 (54.8) *	102 (46.2)	114 (52.1)
Abbreviations: HAQ-DI = Health Assessment Questionnaire – Disability Index; MCID = minimum clinically important differences; MCS= Mental component summary; PCS = physical component summary; PtGA = Patient's Global Assessment of Disease Activity QD = once daily; SF-36 = Short Form-36; VAS = Visual Analogue Scale						

***, **, * Statistically significant at 0.001, 0.01, and 0.05 level, respectively for upadacitinib versus placebo.
[a]Duration in minutes.
[b]% responders reporting scores minimal important difference.
cAssessed on a numeric scale of 1–10, 10 being the worst level.

Table 15: Least squared mean (LSM) changes from baseline and percentage of responders for MCID and for normative values at week 12 after upadacitinib initiation: moderate patients

PRO	Change from baseline	
	LSM (95% CI)	
	PBO [redacted]	UPA 15 mg [redacted]
HAQ-DI	[redacted]	[redacted]
Tag	[redacted]	[redacted]
Pain VAS	[redacted]	[redacted]
FACIT-F	[redacted]	[redacted]
Duration morning stiffness[a]	[redacted]	[redacted]
Severity morning stiffness[b]	[redacted]	[redacted]
SF-36 PCS	[redacted]	[redacted]
SF-36 MCS	[redacted]	[redacted]

Source: (61) ***, **, * Statistically significant at 0.001, 0.01, and 0.05 level, respectively for upadacitinib versus placebo.
[a]Duration in minutes.
[b]% responders reporting scores minimal important difference.
cAssessed on a numeric scale of 1–10, 10 being the worst level.

Table 16: Least squared mean (LSM) changes from baseline and percentage of responders for MCID and for normative values at week 12 after upadacitinib initiation: severe patients

PRO	Change from baseline	
	LSM (95% CI)	
	PBO	UPA 15 mg
HAQ-DI	[redacted]	[redacted]
Tag	[redacted]	[redacted]
Pain VAS	[redacted]	[redacted]
FACIT-F	[redacted]	[redacted]
Duration morning stiffness[a]	[redacted]	[redacted]
Severity morning stiffness[b]	[redacted]	[redacted]
SF-36 PCS	[redacted]	[redacted]
SF-36 MCS	[redacted]	[redacted]

***, **, * Statistically significant at 0.001, 0.01, and 0.05 level, respectively for upadacitinib versus placebo.
aDuration in minutes.
b% responders reporting scores minimal important difference.
cAssessed on a numeric scale of 1–10, 10 being the worst level.

Table 17: Summary of clinical effectiveness results for SELECT-MONOTHERAPY trial patients

Endpoints	Week 14	
	cMTX (N=216)	UPA 15 mg QD (N=217)
ACR20 response rate (95% CI)	41.2 (34.6, 47.8)	67.7 (61.5, 74.0)***
ACR50 response rate (95% CI)	15.3 (10.5, 20.1)	41.9 (35.4, 48.5)***
ACR70 response rate (95% CI)	2.8 (0.6, 5.0)	22.6 (17.0, 28.1)***
Clinical remission based on DAS28 (CRP) (95% CI)	8.3 (4.6, 12.0)	28.1 (22.1, 34.1)***
DAS28 (CRP) CFB (95% CI)	-1.233 (-1.421, -1.044)	-2.318 (-2.506, -2.130)***
EQ-5D-5L CFB (95% CI)	0.079 (0.050, 0.108)	0.159 (0.130, 0.187)***
HAQ-DI CFB (95% CI)	-0.321 (-0.405, -0.238)	-0.652 (-0.735, -0.568)***
LDA DAS28(CRP) (95% CI)	19.4 (14.2, 24.7)	44.7 (38.1, 51.3)***
Morning stiffness duration (minutes) change (95% CI)	-53.031 (-72.180, -33.881)	-94.558 (-113.574, -75.541)**
SF-36 PCS CFB (95% CI)	4.315 (3.189, 5.442)	8.285 (7.170, 9.399)***
Abbreviations: ACR20/50/70 = American College of Rheumatology 20%, 50%, 70% response; CFB = Change From Baseline; CRP = C-reactive protein; DAS28 = Disease Activity Score 28; HAQ-DI = Health Assessment Questionnaire – Disability Index; LDA = low disease activity; PCS = physical component summary; PBO =Placebo; QD = once daily; SF-36 = Short Form-36; UPA = Upadacitinib ***, **, * Statistically significant at 0.001, 0.01, and 0.05 level, respectively		

Table 18: Summary of clinical effectiveness results for SELECT-MONOTHERAPY moderate trial patients

Endpoints	Week 14	
	cMTX [redacted]	UPA 15 mg QD [redacted]
ACR20 response rate (95% CI)	[redacted]	[redacted]
ACR50 response rate (95% CI)	[redacted]	[redacted]
ACR70 response rate (95% CI)	[redacted]	[redacted]
Clinical remission based on DAS28 (CRP) (95% CI)	[redacted]	[redacted]
DAS28 (CRP) CFB (95% CI)	[redacted]	[redacted]
EQ-5D-5L CFB (95% CI)	[redacted]	[redacted]
HAQ-DI CFB (95% CI)	[redacted]	[redacted]
LDA DAS28(CRP) (95% CI)	[redacted]	[redacted]
Morning stiffness duration (minutes) change (95% CI)	[redacted]	[redacted]
SF-36 PCS CFB (95% CI)	[redacted]	[redacted]

Abbreviations: ACR20/50/70 = American College of Rheumatology 20%, 50%, 70% response; CFB = Change From Baseline; CRP = C-reactive protein; DAS28 = Disease Activity Score 28; HAQ-DI = Health Assessment Questionnaire – Disability Index; LDA = low disease activity; PCS = physical component summary; PBO =Placebo; QD = once daily; SF-36 = Short Form-36; UPA = Upadacitinib
***, **, * Statistically significant at 0.001, 0.01, and 0.05 level, respectively

Table 19: Summary of clinical effectiveness results for SELECT-MONOTHERAPY severe trial patients

Endpoints	Week 14	
	cMTX [redacted]	UPA 15 mg QD [redacted]
ACR20 response rate (95% CI)	[redacted]	[redacted]
ACR50 response rate (95% CI)	[redacted]	[redacted]
ACR70 response rate (95% CI)	[redacted]	[redacted]
Clinical remission based on DAS28 (CRP) (95% CI)	[redacted]	[redacted]
DAS28 (CRP) CFB (95% CI)	[redacted]	[redacted]
EQ-5D-5L CFB (95% CI)	[redacted]	[redacted]
HAQ-DI CFB (95% CI)	[redacted]	[redacted]
LDA DAS28(CRP) (95% CI)	[redacted]	[redacted]
Morning stiffness duration (minutes) change (95% CI)	[redacted]	[redacted]
SF-36 PCS CFB (95% CI)	[redacted]	[redacted]

Abbreviations: ACR20/50/70 = American College of Rheumatology 20%, 50%, 70% response; CFB = Change From Baseline; CRP = C-reactive protein; DAS28 = Disease Activity Score 28; HAQ-DI = Health Assessment Questionnaire – Disability Index; LDA = low disease activity; PCS = physical component summary; PBO =Placebo; QD = once daily; SF-36 = Short Form-36; UPA = Upadacitinib
***, **, * Statistically significant at 0.001, 0.01, and 0.05 level, respectively

Table 20: Summary of clinical effectiveness results for SELECT-BEYOND trial patients

Endpoints	Week 12		Week 24
	PBO (+ csDMARDs) (N = 169)	UPA 15 mg (+ csDMARDs) (N = 164)	UPA 15 mg (+ csDMARDs) (N = 69)
ACR20 response rate (95% CI)	28.4 (21.6, 35.2)	64.6 (57.3, 72.0)***	61.6 (54.1, 69.0)
ACR20 response rate at Week 1 (95% CI)	10.7 (6.0, 15.3)	27.4 (20.6, 34.3)***	27.4 (20.6, 34.3)
ACR50 response rate (95% CI)	11.8 (7.0, 16.7)	34.1 (26.9, 41.4)***	42.7 (35.1, 50.3)
ACR70 response rate (95% CI)	6.5 (2.8, 10.2)	11.6 (6.7, 16.5)*	22.0 (15.6, 28.3)
Clinical remission (DAS28- CRP ≤2.6) (95% CI)	9.5 (5.1, 13.9)	28.7 (21.7, 35.6)***	32.3 (25.2, 39.5)
CDAI CFB (95% CI)	-13.315 (-15.561, -11.069)	-24.376 (-26.579, -22.174)***	-27.487 (-29.417, -25.557)
DAS28 (CRP) CFB (95% CI)	-1.006 (-1.218, -0.795)	-2.367 (-2.575, -2.159)***	-2.571 (-2.775, -2.366)
EQ-5D-5L CFB (95% CI)	0.076 (0.043, 0.110)	0.149 (0.116, 0.182)**	0.172 (0.140, 0.203)
HAQ-DI change from baseline (95% CI)	-0.163 (-0.249, -0.078)	-0.412 (-0.497, -0.327)***	-0.440 (-0.531, -0.350)
LDA based on DAS28 (CRP) ≤ 3.2 (95% CI)	14.2 (8.9, 19.5)	43.3 (35.7, 50.9)***	52.4 (44.8, 60.1)
SDAI CFB (95% CI)	-13.515 (-15.835, -11.195)	-25.567 (-27.844, -23.289)***	-28.442 (-30.415, -26.470)
SF-36 PCS CFB (95% CI)	2.391 (1.141, 3.640)	5.828 (4.605, 7.051)***	7.146 (5.837, 8.455)

Abbreviations: ACR20/50/70 = American College of Rheumatology 20%, 50%, 70% response; CDAI = Clinical Disease Activity Index; CFB = Change From Baseline; CRP = C-reactive protein; DAS28 = Disease Activity Score 28; FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue; HAQ-DI = Health Assessment Questionnaire – Disability Index; LDA = low disease activity; PCS = physical component summary; QD = once daily; SF-36 = Short Form-36
***, **, * Statistically significant at 0.001, 0.01, and 0.05 level, respectively

Table 21: Summary of clinical effectiveness results for SELECT-BEYOND moderate trial patients

Endpoints	Week 12		Week 24
	PBO (+ csDMARDs) [redacted]	UPA 15 mg (+ csDMARDs) [redacted]	UPA 15 mg (+ csDMARDs) [redacted]
ACR20 response rate (95% CI)	[redacted]	[redacted]	[redacted]
ACR20 response rate at Week 1 (95% CI)	[redacted]	[redacted]	[redacted]
ACR50 response rate (95% CI)	[redacted]	[redacted]	[redacted]
ACR70 response rate (95% CI)	[redacted]	[redacted]	[redacted]
Clinical remission (DAS28- CRP ≤2.6) (95% CI)	[redacted]	[redacted]	[redacted]
CDAI CFB (95% CI)	[redacted]	[redacted]	[redacted]
DAS28 (CRP) CFB (95% CI)	[redacted]	[redacted]	[redacted]
EQ-5D-5L CFB (95% CI)	[redacted]	[redacted]	[redacted]
HAQ-DI change from baseline (95% CI)	[redacted]	[redacted]	[redacted]
LDA based on DAS28 (CRP) ≤ 3.2 (95% CI)	[redacted]	[redacted]	[redacted]
SDAI CFB (95% CI)	[redacted]	[redacted]	[redacted]
SF-36 PCS CFB (95% CI)	[redacted]	[redacted]	[redacted]

Abbreviations: ACR20/50/70 = American College of Rheumatology 20%, 50%, 70% response; CDAI = Clinical Disease Activity Index; CFB = Change From Baseline; CRP = C-reactive protein; DAS28 = Disease Activity Score 28; FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue; HAQ-DI = Health Assessment Questionnaire – Disability Index; LDA = low disease activity; PCS = physical component summary; QD = once daily; SF-36 = Short Form-36
***, **, * Statistically significant at 0.001, 0.01, and 0.05 level, respectively

Table 22: Summary of clinical effectiveness results for SELECT-BEYOND severe trial patients

Endpoints	Week 12		Week 24
	PBO (+ csDMARDs) [redacted]	UPA 15 mg (+ csDMARDs) [redacted]	UPA 15 mg (+ csDMARDs) [redacted]
ACR20 response rate (95% CI)	[redacted]	[redacted]	[redacted]
ACR20 response rate at Week 1 (95% CI)	[redacted]	[redacted]	[redacted]
ACR50 response rate (95% CI)	[redacted]	[redacted]	[redacted]
ACR70 response rate (95% CI)	[redacted]	[redacted]	[redacted]
Clinical remission (DAS28- CRP ≤2.6) (95% CI)	[redacted]	[redacted]	[redacted]
CDAI CFB (95% CI)	[redacted]	[redacted]	[redacted]
DAS28 (CRP) CFB (95% CI)	[redacted]	[redacted]	[redacted]
EQ-5D-5L CFB (95% CI)	[redacted]	[redacted]	[redacted]
HAQ-DI change from baseline (95% CI)	[redacted]	[redacted]	[redacted]
LDA based on DAS28 (CRP) ≤ 3.2 (95% CI)	[redacted]	[redacted]	[redacted]
SDAI CFB (95% CI)	[redacted]	[redacted]	[redacted]
SF-36 PCS CFB (95% CI)	[redacted]	[redacted]	[redacted]

Abbreviations: ACR20/50/70 = American College of Rheumatology 20%, 50%, 70% response; CDAI = Clinical Disease Activity Index; CFB = Change From Baseline; CRP = C-reactive protein; DAS28 = Disease Activity Score 28; FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue; HAQ-DI = Health Assessment Questionnaire – Disability Index; LDA = low disease activity; PCS = physical component summary; QD = once daily; SF-36 = Short Form-36
***, **, * Statistically significant at 0.001, 0.01, and 0.05 level, respectively

Table 23: Summary of clinical effectiveness results for SELECT-SUNRISE

Endpoints	Week 12	
	PBO (N=49)	Upadacitinib 15 mg QD (N=49)
ACR20 response rate	42.9	83.7***
ACR50 response rate (95% CI)	16.3 (6.0, 26.7)	65.3 (52.0, 78.6)***
ACR70 response rate (95% CI)	2.04 (0.0, 6.0)	34.7 (21.4, 48.0)***
Clinical remission (DAS28- CRP ≤2.6) (95% CI)	6.12 (0.0, 12.8)	57.1 (43.3, 71.0)***
FACIT-F CFB (95% CI)	1.811 (-0.346, 3.967)	3.601 (1.528, 5.675)
HAQ-DI CFB (95% CI)	-0.147 (-0.287, -0.008)	-0.497 (-0.633, -0.361)***
LDA based on DAS28 (CRP) ≤ 3.2 (95% CI)	18.4 (7.5, 29.2)	69.4 (56.5, 82.3)***
Morning stiffness (minutes) CFB (95% CI)	-10.733 (-68.786, 47.321)	-92.577 (-150.088, -35.065)*
SF-36 PCS CFB (95% CI)	2.876 (1.027, 4.724)	6.376 (4.604, 8.148)**
RA-WIS CFB (95% CI)	-0.686 (-2.585, 1.212)	-2.743 (-4.749, -0.736)

Abbreviations: ACR20/50/70 = American College of Rheumatology 20%, 50%, 70% response; CFB = Change From Baseline; CRP = C-reactive protein; DAS28 = Disease Activity Score 28; FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue; HAQ-DI = Health Assessment Questionnaire – Disability

Index; LDA = low disease activity; PBO = Placebo; PCS = physical component summary; RA-WIS = Rheumatoid Arthritis-Work Instability Scale; QD = once daily; SF-36 = Short Form-36
***, **, * Statistically significant at 0.001, 0.01, and 0.05 level, respectively

Table 24: Summary of clinical effectiveness results for SELECT-SUNRISE moderate trial patients

Endpoints	Week 12	
	PBO	Upadacitinib 15 mg QD
ACR20 response rate (95% CI)	[redacted]	[redacted]
ACR50 response rate (95% CI)	[redacted]	[redacted]
ACR70 response rate (95% CI)	[redacted]	[redacted]
Clinical remission (DAS28- CRP ≤2.6) (95% CI)	[redacted]	[redacted]
FACIT-F CFB (95% CI)	[redacted]	[redacted]
HAQ-DI CFB (95% CI)	[redacted]	[redacted]
LDA based on DAS28 (CRP) ≤ 3.2 (95% CI)	[redacted]	[redacted]
Morning stiffness (minutes) CFB (95% CI)	[redacted]	[redacted]
SF-36 PCS CFB (95% CI)	[redacted]	[redacted]
RA-WIS CFB (95% CI)	[redacted]	[redacted]

Abbreviations: ACR20/50/70 = American College of Rheumatology 20%, 50%, 70% response; CFB = Change From Baseline; CRP = C-reactive protein; DAS28 = Disease Activity Score 28; FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue; HAQ-DI = Health Assessment Questionnaire – Disability Index; LDA = low disease activity; PBO = Placebo; PCS = physical component summary; RA-WIS = Rheumatoid Arthritis-Work Instability Scale; QD = once daily; SF-36 = Short Form-36
***, **, * Statistically significant at 0.001, 0.01, and 0.05 level, respectively

Table 25: Summary of clinical effectiveness results for SELECT-SUNRISE severe trial patients

Endpoints	Week 12	
	PBO	Upadacitinib 15 mg QD
ACR20 response rate (95% CI)	[redacted]	[redacted]
ACR50 response rate (95% CI)	[redacted]	[redacted]
ACR70 response rate (95% CI)	[redacted]	[redacted]
Clinical remission (DAS28- CRP ≤2.6) (95% CI)	[redacted]	[redacted]
FACIT-F CFB (95% CI)	[redacted]	[redacted]
HAQ-DI CFB (95% CI)	[redacted]	[redacted]
LDA based on DAS28 (CRP) ≤ 3.2 (95% CI)	[redacted]	[redacted]
Morning stiffness (minutes) CFB (95% CI)	[redacted]	[redacted]
SF-36 PCS CFB (95% CI)	[redacted]	[redacted]
RA-WIS CFB (95% CI)	[redacted]	[redacted]

Abbreviations: ACR20/50/70 = American College of Rheumatology 20%, 50%, 70% response; CFB = Change From Baseline; CRP = C-reactive protein; DAS28 = Disease Activity Score 28; FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue; HAQ-DI = Health Assessment Questionnaire – Disability Index; LDA = low disease activity; PBO = Placebo; PCS = physical component summary; RA-WIS = Rheumatoid Arthritis-Work Instability Scale; QD = once daily; SF-36 = Short Form-36
***, **, * Statistically significant at 0.001, 0.01, and 0.05 level, respectively

A11. Please report the results of SELECT-SUNRISE in a format paralleling Table 7 (p. 57, Company Submission), augmented as above.

AbbVie response: Please see detailed response below. Where it has not been possible to report the outcomes to three significant figures, two significant figures have been reported instead.

Clinical effectiveness results

SELECT SUNRISE

SELECT-SUNRISE compared the efficacy of upadacitinib 15 mg QD versus placebo for the treatment of signs and symptoms of Japanese subjects with moderately to severely active RA who were on a stable dose of csDMARDs and have an inadequate response to csDMARDs.

The clinical effectiveness results demonstrated the superiority of upadacitinib 15 mg vs placebo, as assessed by the proportion of patients who achieved an ACR20 response at Week 12. The following secondary outcomes are also presented: change in FACIT-F, ACR 20 response rate at week 1, ACR50/70 response, change in HAQ-DI score, change in RA-WIS, change in SF-36 PCS, clinical remission based on DAS28 (CRP), proportion of patients achieving LDA (DAS28 CRP ≤3.2) and change in morning stiffness severity. A summary of the outcomes is presented in Table 26.

Table 26: Summary of clinical effectiveness results for SELECT-SUNRISE

Endpoints	Week 12	
	PBO (N=49)	Upadacitinib 15 mg QD (N=49)
ACR20 response	42.9	83.7***
ACR50 response	16.3	65.3***
ACR70 response	2.04	34.7***
Clinical remission (DAS28- CRP ≤2.6)	6.12	57.1***
FACIT-F CFB	1.81	3.60
HAQ-DI CFB	-0.10	-0.45***
LDA based on DAS28 (CRP) ≤ 3.2	18.4	69.4***
Morning stiffness (severity) CFB	-1.02	-2.84
SF-36 PCS CFB	2.88	6.38**
RA-WIS CFB	-0.69	-2.74
Abbreviations: ACR20/50/70 = American College of Rheumatology 20%, 50%, 70% response; CFB = Change From Baseline; CRP = C-reactive protein; DAS28 = Disease Activity Score 28; FACIT-F = Functional		

Endpoints	Week 12	
	PBO (N=49)	Upadacitinib 15 mg QD (N=49)
Assessment of Chronic Illness Therapy – Fatigue; HAQ-DI = Health Assessment Questionnaire – Disability Index; LDA = low disease activity; PBO = Placebo; PCS = physical component summary; RA-WIS = Rheumatoid Arthritis-Work Instability Scale; QD = once daily; SF-36 = Short Form-36 ***, ** Statistically significant at 0.001 and 0.01 level, respectively		

Primary endpoints

The primary outcomes showed that at week 12, a significantly greater proportion of patients receiving upadacitinib achieved an ACR20 response compared with patients receiving placebo (83.7% versus 42.9% respectively, p<0.001) (Table 26).

Secondary endpoints

Study findings demonstrated the superiority of upadacitinib 15mg over placebo for all ranked secondary endpoints that compared both groups in Japanese population (Table 26).

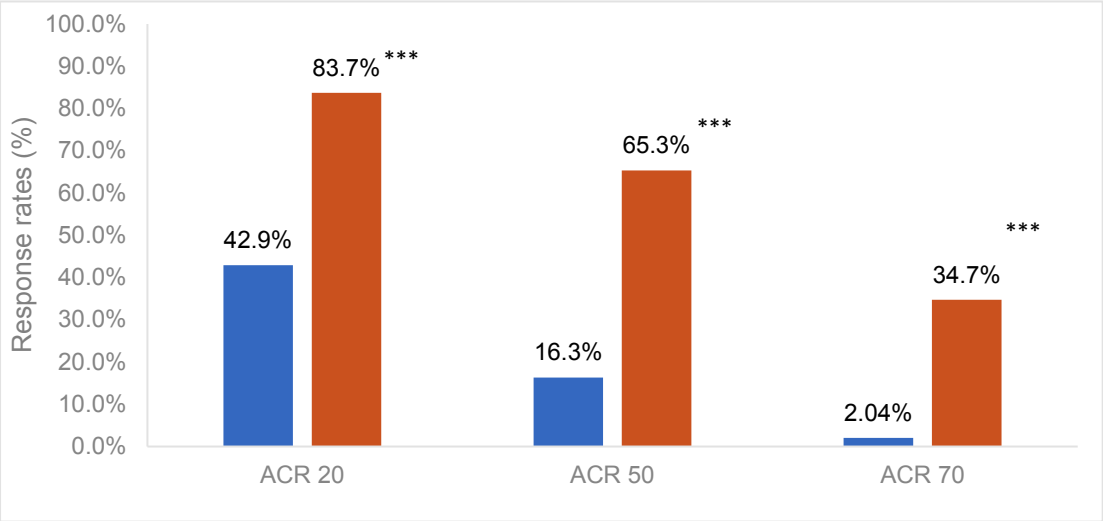
Clinical remission

A significantly greater proportion of patients receiving upadacitinib 15 mg QD achieved clinical remission compared with placebo (57.1% versus 6.1% at week 12, p<0.001) (Table 26).

ACR50 and ACR70

At week 12, a significantly greater proportion of patients receiving upadacitinib 15 mg QD achieved an ACR50 response compared with patients receiving placebo (65.3% versus 16.3% respectively, p<0.001). Similarly, a significantly greater proportion of patients receiving upadacitinib 15 mg QD achieved an ACR70 response compared to patients receiving placebo (34.7% versus 2.0% respectively, p<0.001) (see Figure 2).

Figure 2: ACR response rates at week 12 in SELECT-SUNRISE[a]



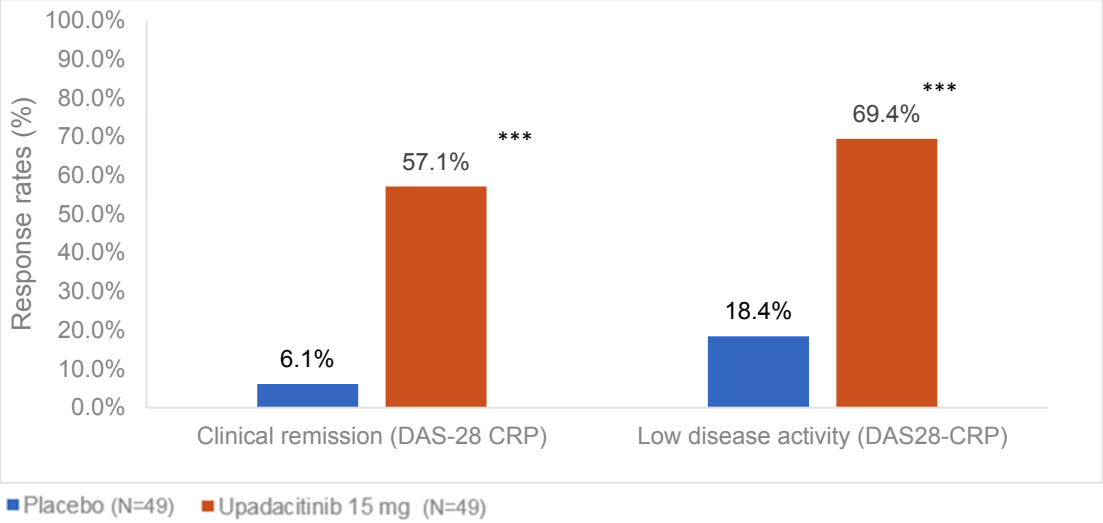
*All week 12 endpoints shown in the bar graph achieved p-values of <0.001 versus placebo for both doses except for the 15 mg ACR70 value.

ACR50 and ACR70 were not ranked secondary endpoints. Not all ranked and non-ranked secondary endpoints shown.

[a]ACR20/50/70 is defined as American College of Rheumatology 20 percent/50 percent/70 percent improvements in tender and swollen joint counts, patient assessments of pain, global disease activity and physical function, physician global assessment of disease activity and acute phase reactant.

Abbreviations: ACR20/50/70 = American College of Rheumatology 20%, 50%, 70% response

Figure 3: Clinical remission and LDA results at week 12 in SELECT-SUNRISE[a,b]



*All week 12 endpoints shown in the bar graph achieved p-values of <0.001 versus placebo for both. Not all ranked and non-ranked secondary endpoints shown

[a]LDA was defined by a clinical response DAS28 CRP less than or equal to 3.2

[b]Clinical remission was based on DAS28 (CRP) less than 2.6.

Abbreviations: DAS28 = Disease Activity Score 28

LDA (based on DAS28(CRP)≤3.2)

At week 12, a significantly greater proportion of patients receiving upadacitinib 15 mg QD achieved LDA (based on DAS28(CRP)≤3.2) compared with patients receiving placebo (69.4% versus 18.4% respectively, p<0.001) (see Figure 3).

HAQ-DI change from baseline

At week 12, patients receiving upadacitinib 15 mg QD had significant improvements in the ability to function in daily life, as measured by Health Assessment Questionnaire (HAQ-DI) compared with patients receiving placebo (mean change from baseline of -0.45 versus -0.10 respectively, p≤0.001]) (Table 26).

Severity of morning joint stiffness

At week 12, patients receiving upadacitinib 15 mg QD had significant improvements in the severity of morning stiffness (mean change from baseline of -2.84 versus -1.02 respectively, p<0.001) (Table 26).

Medical outcomes study 36-Item Short Form Health Survey

Treatment with upadacitinib 15 mg QD versus placebo resulted in an improved quality of life (SF-36 PCS) at week 12 (Table 26).

Adverse reactions

A summary of the safety events reported during the controlled period (Period 1) for the SELECT-SUNRISE study are outlined in Table 27.

Through Week 12 (Period 1), the percentage of subjects with TEAEs was numerically higher in the upadacitinib 15 mg (57.1%) group compared with the placebo (49.0%) group (Table 27). The percentage of subjects with a severe AE was slightly higher in the upadacitinib 15 mg (2.04%) compared with the placebo groups (0.0%). No deaths were reported through Week 12.

Table 27: Summary of key safety events from SELECT-SUNRISE

	Week 12	
	PBO (N=49)	**UPA 15 mg QD (N=49)**
Any AE, n (%)	24 (49.0)	28 (57.1)
Any SAE, n (%)	0	1 (2.04)
Any AE leading to discontinuation of study drug, n (%)	0	1 (2.04)
Any severe AE, n (%)	0	2 (4.08)
Any AE with reasonable possibility of being related to study drug[a], n (%)	8 (16.3)	16 (32.7)
Any AE leading to death, n (%)	0	0
Deaths[b], n (%)	0	0

Abbreviations: AE: Adverse event; PBO: Placebo; SAE: Serious adverse event; UPA: Upadacitinib; QD = once daily
a: As assessed by investigator
b: Any death including non-treatment-emergent deaths

Through Week 12 (Period 1), the most frequently reported TEAEs (≥ 5% of subjects in any treatment group) were nasopharyngitis, blood creatine phosphokinase (CPK) increased, herpes zoster, headache, nausea, liver function test increased, stomatitis, and hypertension.

A12. Please augment Table 9 (p. 67, Company Submission) with the EQ-5D-5L values. Please also provide an account of how the EQ-5D-5L values reported in the clinical effectiveness section have been calculated.

AbbVie response: EQ-5D-5L values have been added and can be seen in Table 28.

Table 28. Least squared mean (LSM) changes from baseline and percentage of responders for MCID and for normative values at week 12 after upadacitinib initiation

PRO	Change from baseline		% responders			
	LSM		Reporting scores ≥MCID, n (%)		Reporting scores ≥normative values, n (%)	
	PBO N=221	UPA 15 mg N=221	PBO N=221	UPA 15 mg N=221	PBO N=221	UPA 15 mg N=221
HAQ-DI	-0.26	-0.61*	109 (49.3)	156 (72.2) *	30 (13.6)	56 (25.9) *
Tag	-10.36	-29.67*	94 (42.5)	153 (70.5) *	32 (14.5)	78 (35.9) *
Pain VAS	-10.26	-29.92*	97 (43.9)	158 (72.8) *	-	-
FACIT-F	2.96	7.91*	91 (41.2)	138 (63.9) *	35.8 (15.8)	60 (27.8) *
Duration morning stiffness[a]	-34.27	-85.28*	29 (13.4)	57 (26.3) *, [b]	-	-
Severity morning stiffness[b]	-1.38	-2.88*	130 (60.2)	165 (76.0) *, [b]	-	-
SF-36 PCS	3.03	7.58*	106 (48.0)	152 (69.4) *	18 (8.1)	39 (17.8) *
SF-36 MCS	2.58	4.69*	91 (41.2)	120 (54.8) *	102 (46.2)	114 (52.1)
EQ-5D-5L CFB	0.08	0.19***	NR	NR	NR	NR

Abbreviations: HAQ-DI = Health Assessment Questionnaire – Disability Index; MCID = minimum clinically important differences; MCS= Mental component summary; PCS = physical component summary; PtGA = Patient's Global Assessment of Disease Activity QD = once daily; SF-36 = Short Form-36; VAS = Visual Analogue Scale

*p<0.05 for upadacitinib versus placebo.

[a]Duration in minutes.

[b]% responders reporting scores minimal important difference.

[c]Assessed on a numeric scale of 1–10, 10 being the worst level.

The EQ-5D self-report questionnaire (EQ-5D) essentially consists of two modules comprising the EQ-5D descriptive system and the EQ VAS. The EQ-5D-5L descriptive system is comprised of 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort anxiety/depression) to describe the patient's current health state. Each dimension comprises five levels (no problems, slight problems, moderate problems, severe problems, unable to perform activity) with corresponding numeric scores 1, 2, 3, 4 and 5. Only a single response is required for each dimension. A unique EQ-5D health state is defined by combining 1 level from each of the 5 dimensions. The index score will not be calculated when responses are missing for one or more of the dimensions.

Each state is referred to in terms of a 5-digit code. For example, state 11111 indicates no problem on any of the fine dimensions, while state 11335 indicates no problems with mobility or self-care, some problems with performing usual activities,

moderate pain or discomfort, and extreme anxiety or depression. If a score of other than 1 is chosen for an item, then the weights below should be subtracted from the constant. The weighted average of slope (a fixed coefficient 0.9675) should be multiplied by the sum of the five decrements while calculating values for all health states.

Table 29: Item weights to calculate EQ-5D-5L

	Item Weights				
Dimensions	1	2	3	4	5
Constant	1				
Mobility	0	0.051	0.063	0.212	0.275
Self-Care	0	0.057	0.076	0.181	0.217
Usual Activities	0	0.051	0.067	0.174	0.190
Pain/Discomfort	0	0.060	0.075	0.276	0.341
Anxiety/Depression	0	0.079	0.104	0.296	0.301

To make it clearer, on this scoring system, the predicted value for state 23245 is calculated as follow:

1-0.9675(0.051+0.076+0.051+0.276+0.301) =0.270*

The EQ VAS records the respondents self-rated health status on a vertical graduated (0-100) visual analogue scale with 0 being the “Worst Imaginable Health State” and 100 being “Best Imaginable Health State”. It generates a self-rating of current health-related quality of life. It was used with the 5-digit health state classification to build a composite picture of the respondent’s health status.

Network meta-analysis

A13. Please clarify why additional ACR timepoints were not included when a continuous meta-regressor for time could have been used to account for these, and how many trials were excluded on this basis.

AbbVie response: The 12-week and 24-week time points are the most commonly used timepoints to evaluate ACR outcomes in almost all key RA randomized controlled trials. The specific timepoints considered may vary slightly across trials. Therefore, to more comprehensively include all available evidence in the network meta-analysis (NMA), trials that reported ACR outcomes between 9 and 15 weeks or between 20 and 30 weeks were included. A similar approach has been used in prior NICE technology appraisals (TA375, TA466, and TA480) in RA[1-3]. Additionally, the

base case model included a meta-regressor that allowed the simultaneous evaluation of the week 12 and week 24 outcomes.

The requirement for the specified ACR timepoints have very limited impact on the inclusion/exclusion of trials. The majority of the trials that did not report data for the specified timepoints would be excluded based on other reasons. Some phase II trials evaluated clinical outcomes over a shorter time horizon (e.g., 6 weeks)[4]. However, these trials would have been excluded based on study design. On the other hand, some open-label extension studies of phase II or phase III trials evaluated clinical outcomes over longer timer horizon (e.g., 1 year, 5 years)[5]. However, the open-label extension phase typically did not include a randomised comparator arm, and therefore would be excluded due to the lack of comparator data.

A14. Priority question: Please clarify what counted as 'appropriate imputation of data' for trials where early escape was employed, and how many trials were excluded because this was not undertaken.

AbbVie response: Due to the heterogeneity of the early escape rules and proportion of patients who early escaped in various trials, different imputation methods were used in different trials to account for the missing measurements. Non-responder imputation (NRI) and last observation carried forward (LOCF) are the two most commonly used imputation methods in RA trials. Both were deemed appropriate imputation methods, and therefore no trials were excluded based on the type of imputation method used. A detailed description of imputation method and early escape rules for all included RA trials are described in Tables 10, 11, 30 and 31 of the appendix in the original submission.

A15. Please clarify the definition of a 'Phase III' study design used to include studies in the NMA.

AbbVie response: The Phase III study design was based on the information specified in the trial publication or provided on clinicaltrials.gov. If there was no explicit statement for a "Phase III" study in the trial publication or other traceable public sources, the trial would not be considered a 'Phase III' study and would be excluded from the NMA. We did not impose any criteria to manually classify the

identified publication as a ‘Phase III’ study if this information was not readily available.

A16. Please clarify whether MTX was required as a previous csDMARD for all trials, as Figure 1 in Appendix D suggests that trials were excluded because populations were MTX naïve.

AbbVie response: MTX was not required as a previous csDMARD for included trials. Trials were only excluded if the results of the subgroup of csDMARD-experienced patients were not reported. All 8 trials excluded due to having a MTX-naïve population did not report results for the subgroup of csDMARD-experienced patients (Appendix Table 4). For example, the COMET trial publication which included 20% csDMARD-experienced patients[6] does not report ACR outcomes results for the subgroup of csDMARD-experienced patients and was therefore excluded from the NMA.

A17. Priority question: Please clarify whether subgroup data from trials with potentially includable ‘subpopulations’ were sought.

AbbVie response: Subgroup data reported from trials were included in the NMA where applicable. Specifically, three trials (i.e., REALISTIC, MOBILITY, and BREVACTA) reported data for both csDMARD-IR and bDMARD-IR populations in the subgroup analysis, and were included in the NMAs for both populations.[7-10]

A18. Priority question: Please send the WinBUGS files (e.g. in .odc format), including data, used to estimate the NMAs.

Response: The code to estimate NMAs for both csDMARD-IR and bDMARD-IR populations are attached below. JAGS was used instead of WinBUGS to implement the NMAs. The R code used to implement the NMAs are attached in the files below.


csDMARD.zip


Bio-IR.zip

A19. Please confirm that no additional NMAs were undertaken besides ACR for csDMARD-IR and ACR for bDMARD-IR.

AbbVie response: This is correct. No additional NMAs were conducted besides the evaluation of ACR outcomes for the csDMARD-IR and bDMARD-IR populations.

A20. Priority question: Please provide evidence that convergence was reached for each NMA estimated.

AbbVie response: The Gelman-Rubin diagnostic was used to evaluate MCMC convergence for the base-case model for both csDMARD-IR and bDMARD-IR populations. The potential scale reduction factors were all close to 1, indicating that convergence was reached (Table 30).

Table 30: Convergence results for base-case NMA models

Model	Gelman-Rubin diagnostic results
Base-case model for csDMARD-IR	1.000415
Base-case model for bDMARD-IR	1.000943

A21. Please provide surface under the cumulative ranking curve (SUCRA) values to justify the numerical ranking of treatments.

Response: The surface under the cumulative ranking curve (SUCRA) values are presented in Table 31 and Table 32 below. The SUCRA values were added to the existing results output from the NMA. Overall, the SUCRA values support the numeric rankings of treatments as indicated in the NMA.

Please note, in responding to this question, AbbVie noticed that the incorrect tables were included in the original submission for the combined 12/24 week NMA. Tables 26 and 27 (pages 105 and 106 of Document B) present the 12 week results rather than the 24 week results from the combined bDMARD model. The correct values are presented in Table 31 and Table 32.

Table 31: Base case: Combined model with random effects in csDMARD experienced RA: absolute probabilities of achieving ≥20, ≥50 or ≥70 ACR response for each treatment – week 24

Treatment	SUCRA value	ACR 20		ACR 50		ACR 70	
		Posterior Median	(95% CrI)	Posterior Median	(95% CrI)	Posterior Median	(95% CrI)
csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abatacept 10 mg/kg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abatacept 125 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab 40 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab 40 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baricitinib 2 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baricitinib 4 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Certolizumab 200 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept 50 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept 50 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab 50 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab 3 mg/kg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Intensive csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rituximab 2000 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sarilumab 150 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sarilumab 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sarilumab 200 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tocilizumab 8 mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tocilizumab 8 mg/kg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tocilizumab 162 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tofacitinib 10 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tofacitinib 5 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tofacitinib 5 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Upadacitinib 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Upadacitinib 15 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ACR, American College of Rheumatology; csDMARD, conventional synthetic disease modifying antirheumatic drug; CrI, credible interval; RA, rheumatoid arthritis; SUCRA, surface under the cumulative ranking curve

Table 32: Base case: Combined model with random effects in bDMARD experienced RA: absolute probabilities of achieving ≥20, ≥50 or ≥70 ACR response for each treatment – week 24

Treatment	SUCRA value	ACR 20		ACR 50		ACR 70	
		Posterior Median	(95% CrI)	Posterior Median	(95% CrI)	Posterior Median	(95% CrI)
csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abatacept 10 mg/kg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baricitinib 2 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baricitinib 4 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Certolizumab 200 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab 50 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rituximab 2000 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sarilumab 150 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sarilumab 200 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tocilizumab 8 mg/kg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tocilizumab 162 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tofacitinib 10 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tofacitinib 5 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Upadacitinib 15 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ACR, American College of Rheumatology; csDMARD, conventional synthetic disease modifying antirheumatic drug; CrI, credible interval; RA, rheumatoid arthritis; SUCRA, surface under the cumulative ranking curve

A22. Priority question: NMA model structure. Please clarify:

- what is meant in B.2.9.7 by 'treatment effects can be considered exchangeable between trials' (p. 91, Company Submission);

AbbVie response: The trial-specific treatment effects are assumed to be exchangeable, meaning that the information the trials provided is independent of the order in which they were carried out, over the population of interest. The trial-specific treatment effects are assumed to come from a common distribution.

- whether the same between-study variance estimate (tau-squared) was assumed for all contrasts in each model;

AbbVie response: This is the correct understanding.

- what the term 'random effects' is used to describe; i.e. were random effects assumed only for the relative treatment effects, or also for the thresholds (e.g. z_j) as described in NICE DSU TSD 2 (noting however that 'category cut-offs/thresholds […] were assumed to be fixed across trials' [p. 91, Company Submission]);

AbbVie response: The term "random effects" used in the report assumes that the trial-specific relative treatment effects is a sample from a common random effects distribution. The z_j terms (i.e. the average differences in the probability of achieving <50% vs. <20% improvement and in achieving <70% vs. <20% improvement on the probit scale) was assumed to have a "fixed effect" across trials ($z_{ij} = z_j$) for each of the categories over all trials i.

- by corollary, whether differences between random effects and fixed effects NMAs as compared on the basis of DIC relate only to the use of a between-study variance parameter different from 0;

AbbVie response: Yes, if the between-study variance parameter is estimated to be zero in the random effects model, the random effects model becomes the fixed effects model, which is more parsimonious but not robust to between-trial heterogeneity. The random-effects model and fixed-effects model were compared using DIC, which is a measure that balances goodness of fit and model complexity.

- whether trial-specific baselines were treated as nuisance parameters, as is standard, or whether another method was used;

AbbVie response: The trial-specific baselines μ_i were treated as nuisance parameters that were estimated in the model but were of no further interest, as is standard.

- whether the meta-regression coefficient for three months vs. six months was assumed to be equal across all relative treatment effects.

AbbVie response: The average difference in three months vs. six month (ζ_l) was assumed to be equal across all relative treatment effects. An additional random effects term $\eta_{i,k}$ was used in the model to capture the correlations that arise from the fact that trial i contributes two time points of data.

A23. Priority question: Please clarify how response estimates were generated for placebo arms in the NMA, including how this relates to the handling of trial-specific baselines.

AbbVie response: In the NMA among both the csDMARD-IR population and the bDMARD-IR population, csDMARD was used as the reference arm. The trial-specific baselines were modelled using as nuisance parameters for each trial (as mentioned in A22).

After the NMA is estimated, the ACR20 non-response for the csDMARD arm was estimated using the maximum likelihood estimator based on the observed ACR20 non-response data from observed data of all csDMARD arms. The estimated distribution of ACR20 non-response rate was further combined with NMA model parameters to estimate the ACR20/50/70 response rates for all treatments.

A24. Priority question: Please clarify the status of the 'baseline risk-adjusted NMA' referenced in B.2.9.11 (p. 109, Company Submission), as this is not described elsewhere in the submission.

AbbVie response: This was a typographical error, it was not described elsewhere in the submission, because a baseline risk-adjusted NMA was not conducted.

A25. Priority question: What is the effect upon the NMA results of excluding the SELECT-SUNRISE trial results?

AbbVie response: In the NMA, Japanese-specific trials were not excluded and therefore SELECT-SUNRISE was included in the NMA to be consistent with the general inclusion/exclusion criteria considered for all RA treatments. This was to ensure consistency with the approach used by the ScHARR academic group for TA375.

To address this question, we ran a scenario analysis for the csDMARD-IR population excluding SELECT-SUNRISE. Overall, the results are consistent with the base-case NMA and show only minimal differences (for example in the base case upadacitinib combination therapy good and moderate responders are [redacted] and in the NMA excluding SELECT-SUNRISE they are [redacted]). Please see Table 33 and Table 34 for details.

Table 33: Table Base case: Combined model with random effects in csDMARD experienced RA: absolute probabilities of achieving ≥20, ≥50 or ≥70 ACR response for each treatment – week 24 (Excluding SELECT-SUNRISE)

	ACR 20		ACR 50		ACR 70	
Treatment	**Posterior Median**	**(95% CrI)**	**Posterior Median**	**(95% CrI)**	**Posterior Median**	**(95% CrI)**
csDMARD	[redacted]					
Abatacept 10 mg/kg + csDMARD						
Abatacept 125 mg + csDMARD						
Adalimumab 40 mg						
Adalimumab 40 mg + csDMARD						
Baricitinib 2 mg + csDMARD						
Baricitinib 4 mg + csDMARD						
Certolizumab 200 mg + csDMARD						
Etanercept 50 mg						
Etanercept 50 mg + csDMARD						
Golimumab 50 mg + csDMARD						
Infliximab 3 mg/kg + csDMARD						
Intensive csDMARD						
Placebo						
Rituximab 2000 mg + csDMARD						
Sarilumab 150 mg + csDMARD						
Sarilumab 200 mg						
Sarilumab 200 mg + csDMARD						
Tocilizumab 8 mg/kg						
Tocilizumab 8 mg/kg + csDMARD						
Tocilizumab 162 mg + csDMARD						
Tofacitinib 10 mg + csDMARD						
Tofacitinib 5 mg						
Tofacitinib 5 mg + csDMARD						
Upadacitinib 15 mg						
Upadacitinib 15 mg + csDMARD						

Abbreviations: ACR, American College of Rheumatology; csDMARD, conventional synthetic disease modifying antirheumatic drug; CrI, credible interval; RA, rheumatoid arthritis.

Table 34: Table Base case: Treatment comparison of six month estimated EULAR response mapped from the network meta-analysis ACR outcomes in csDMARD-experienced RA from combined three/six month network (Excluding SELECT-SUNRISE)

	No response		Moderate Response		Good Response	
Treatment	**Posterior Median**	**(95% CrI)**	**Posterior Median**	**(95% CrI)**	**Posterior Median**	**(95% CrI)**
csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abatacept 10 mg/kg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abatacept 125 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab 40 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab 40 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baricitinib 2 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baricitinib 4 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Certolizumab 200 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept 50 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept 50 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab 50 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab 3 mg/kg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Intensive csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rituximab 2000 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sarilumab 150 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sarilumab 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sarilumab 200 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tocilizumab 8 mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tocilizumab 8 mg/kg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tocilizumab 162 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tofacitinib 10 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tofacitinib 5 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tofacitinib 5 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Upadacitinib 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Upadacitinib 15 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EULAR, European League Against Rheumatism; csDMARD, conventional synthetic disease modifying antirheumatic drug; CrI, credible interval; RA, rheumatoid arthritis.

A26. As the HAQ is central to the health economic analysis, why was it not considered in the NMA?

AbbVie response: The NMA focused on the core outcomes that were most commonly reported across all eligible RCTs to increase the overall stability of the estimates. Because HAQ was not as commonly reported as ACR response categories, there may not be data for all interventions of interest and may not provide a comprehensive picture of the comparative effectiveness in HAQ across all relevant interventions. For example, a recently published NMA was able to include much fewer interventions in the HAQ NMA (i.e., 8 interventions) compared to the ACR NMA (i.e., 14 interventions)[11]. This evidence highlights the data gap for a comprehensive evaluation of HAQ in the NMA.

The achievement of ACR/EULAR response and reduction in HAQ are highly correlated. Based on the British Society of Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR-RA) database, patients with good EULAR response at 6 months were associated with a mean reduction in HAQ of 0.673, and patients with moderate EULAR responses were associated with a mean reduction in HAQ of 0.317. These data were further validated using the upadacitinib clinical data (EULAR good responders were associated with a HAQ reduction of 0.755, and EULAR moderate responders were associated with a HAQ reduction of 0.481). Therefore, the relative rankings as estimated from the NMA of ACR/EULAR response categories would likely be similar to the relative rankings as estimated from the NMA of HAQ.

The CEA model estimated the initial reduction in HAQ based on the estimated EULAR response categories from the NMA result and predicted long-term HAQ progression based on literature.

A27. Please provide an account of the NMA results for the comparison of upadacitinib with adalimumab and how this compares and relates to the results of SELECT-COMPARE. The NICE reference case states a preference for the results of head-to-head trials.

AbbVie response: To address this question, we compared the 6-month ACR response rates estimated in the base-case NMA vs. the results from the SELECT-COMPARE trial. The observed response rates from the SELECT-COMPARE trial for

csDMARD, adalimumab 40 mg + csDMARD and upadacitinib 15 mg + csDMARD are similar to the response rate estimated from the NMA (Table 35).

Table 35: Table. ACR response at 6 months: SELECT-COMPARE vs. NMA

Treatment	ACR response at 6 months	SELECT-COMPARE	NMA
Adalimumab 40 mg + csDMARD	ACR20	57.20%	[redacted]
	ACR50	41.90%	[redacted]
	ACR70	22.90%	[redacted]
Upadacitinib 15 mg + csDMARD	ACR20	67.40%	[redacted]
	ACR50	53.90%	[redacted]
	ACR70	34.70%	[redacted]
csDMARD	ACR20	35.60%	[redacted]
	ACR50	20.90%	[redacted]
	ACR70	9.50%	[redacted]

[1]In SELECT-COMPARE trial, all the patients received MTX as a background therapy. Thus, the three treatment arms are treated as "csDMARD", "Adalimumab 40 mg + csDMARD" and "Upadacitinib 15 mg + csDMARD", respectively, in the NMA.

Table 36 also displays the EULAR responses at 6 months from the SELECT-COMPARE trial, in comparison with the NMA estimates for upadacitinib and adalimumab among the csDMARD-IR RA patients. Both NRI and LOCF values are presented although it should be noted that the NRI approach is more comparable to the NMA input as the the ACR response is estimated using the NRI approach.

Table 36: Table. EULAR response at 6 months: SELECT-COMPARE vs .NMA

Treatment	EULAR response at 6 months	SELECT-COMPARE (NRI)	SELECT-COMPARE (LOCF)	NMA
Adalimumab 40mg + csDMARD	Good	39.2%	43.3%	[redacted]
	Moderate	24.8%	39.8%	[redacted]
	None	36.1%	16.9%	[redacted]
Upadacitinib 15 mg + csDMARD	Good	54.2%	58.9%	[redacted]
	Moderate	19.0%	30.5%	[redacted]
	None	26.8%	10.6%	[redacted]
csDMARD	Good	17.3%	18.4%	[redacted]
	Moderate	24.0%	35.7%	[redacted]
	None	58.7%	46.0%	[redacted]

Abbreviations: LOCF=last observation carried forward, NRI=non-responder imputation

A28. Following on from question A27, what is the effect of applying the results of SELECT-COMPARE upon the cost effectiveness estimate(s) for pairwise comparison(s) of upadacitinib with adalimumab?

AbbVie response: Using the LOCF and NRI data at 3 months and 6 months from Table 37 and Table 38 of moderate and severe RA patients in SELECT-COMPARE

(and an annual drug acquisition cost for upadacitinib of [redacted]) results in the outputs shown in Table 42 to Table 45.

Table **41** also shows the output resulting from using the base case HE model using base case NMA results. All results are using the re-submitted HE model provided in response to the clarification questions.

Table 37: EULAR response at 3 months in moderate and severe RA patients in SELECT-COMPARE

		NRI Imputation Method		LOCF Imputation Method		Base case NMA results (used in HE model)
Treatment	**EULAR Response at 3 Months**	**Count**	**Percent**	**Count**	**Percent**	**Percent**
Adalimumab 40mg q2wk + csDMARD	Good	90	28%	99	31%	[redacted]
	Moderate	156	49%	172	54%	[redacted]
	None	73	23%	48	15%	[redacted]
Upadacitinib 15 mg QD + csDMARD	Good	281	44%	300	47%	[redacted]
	Moderate	240	37%	269	42%	[redacted]
	None	120	19%	72	11%	[redacted]
csDMARD (used for MTX in treatment sequence run)	Good	84	13%	85	13%	[redacted]
	Moderate	250	39%	274	43%	[redacted]
	None	308	48%	283	44%	[redacted]

Table 38: EULAR response at 6 months in moderate and severe RA patients in SELECT-COMPARE

		NRI Imputation Method		LOCF Imputation Method		Base case NMA results (used in HE model)
Treatment	**EULAR Response at 6 Months**	**Count**	**Percent**	**Count**	**Percent**	**Percent**
Adalimumab 40mg q2wk + csDMARD	Good	125	39%	138	43%	[redacted]
	Moderate	79	25%	127	40%	[redacted]
	None	115	36%	54	17%	[redacted]
Upadacitinib 15 mg QD + csDMARD	Good	348	54%	378	59%	[redacted]
	Moderate	122	19%	196	31%	[redacted]
	None	172	27%	68	11%	[redacted]
csDMARD (used for MTX in treatment sequence run)	Good	111	17%	118	18%	[redacted]
	Moderate	154	24%	229	36%	[redacted]
	None	377	59%	295	46%	[redacted]

Treatment sequences used in the pairwise analyses are shown in Table 39:

Table 39: Treatment sequences used in pairwise analyses

First-line treatment	Second-line treatment	Third-line treatment	Fourth-line treatment	Fifth-line treatment
UPA + MTX	RTX + MTX	TCZ IV + MTX	MTX	BSC
ADA + MTX	RTX + MTX	TCZ IV + MTX	MTX	BSC

Table 40: Summary of incremental costs with upadacitinib combination therapy as reference case for base case compared to scenario analyses

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case (using NMA results)	[redacted]	[redacted]	Dominant
Using EULAR 3 month data (NRI)	[redacted]	[redacted]	Dominant
Using EULAR 3 month data (LOCF)	[redacted]	[redacted]	Dominant
Using EULAR 6 month data (NRI)	[redacted]	[redacted]	Dominant
Using EULAR 6 month data (LOCF)	[redacted]	[redacted]	Dominant

Table 41: 3b. csDMARD-IR, MTX eligible, severe RA – versus UPA 15mg + MTX versus ADA + MTX (deterministic results) – base case HE model using base case NMA results

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
UPA 15mg + MTX	[redacted]	[redacted]	14.196	[redacted]	[redacted]	Reference
ADA + MTX	[redacted]	[redacted]	14.196	-	-	Dominated

Table 42: 3b. csDMARD-IR, MTX eligible, severe RA – versus UPA 15mg + MTX versus ADA + MTX (deterministic results) – response data using COMPARE EULAR response data 3 months LOCF

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
UPA 15mg + MTX	[redacted]	[redacted]	14.196	[redacted]	[redacted]	Reference
ADA + MTX	[redacted]	[redacted]	14.196			Dominated

Table 43: 3b. csDMARD-IR, MTX eligible, severe RA – versus UPA 15mg + MTX versus ADA + MTX (deterministic results) – response data using COMPARE EULAR response data 3 months NRI

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
UPA 15mg + MTX	[redacted]	[redacted]	14.196	[redacted]	[redacted]	Reference
ADA + MTX	[redacted]	[redacted]	14.196			Dominated

Table 44: 3b. csDMARD-IR, MTX eligible, severe RA – versus UPA 15mg + MTX versus ADA + MTX (deterministic results) – response data using COMPARE EULAR response data 6 months LOCF

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
UPA 15mg + MTX	[redacted]	[redacted]	14.196	[redacted]	[redacted]	Reference
ADA + MTX	[redacted]	[redacted]	14.196			Dominated

Table 45: 3b. csDMARD-IR, MTX eligible, severe RA – versus UPA 15mg + MTX versus ADA + MTX (deterministic results) – response data using COMPARE EULAR response data 6 months NRI

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
UPA 15mg + MTX	[redacted]	[redacted]	14.196	[redacted]	[redacted]	Reference
ADA + MTX	[redacted]	[redacted]	14.196			Dominated

The results show that both the incremental cost savings and the QALY gain are increased for upadacitinib combination therapy compared to adalimumab combination therapy using the EULAR 3 month and 6 month data (both NRI and LOCF approaches) in place of the base case NMA results.

Although not requested specifically as a response to A28, EULAR response rates derived directly from SELECT-COMPARE for the severe RA subgroup are shown in Table 46 and Table 47. These show similar results for both adalimumab and upadacitinib combination therapy for their respective severe subgroups compared to the corresponding moderate and severe datasets; for example, non-responder percentages are similar between the severe subgroup and the moderate and severe dataset for both therapy arms.

Table 46: Severe RA subgroup of SELECT COMPARE 3-month data compared to base case NMA results

		NRI Imputation Method		LOCF Imputation Method		Base case NMA results (used in HE model)
Treatment	**EULAR Response at 3 Months**	**Count**	**Percent**	**Count**	**Percent**	**Percent**
Adalimumab 40mg q2wk + csDMARD	Good	57	23%	63	25%	[redacted]
	Moderate	133	53%	147	59%	[redacted]
	None	60	24%	40	16%	[redacted]
Upadacitinib 15 mg QD + csDMARD	Good	199	40%	209	42%	[redacted]
	Moderate	208	42%	230	46%	[redacted]
	None	89	18%	57	11%	[redacted]
csDMARD (used for MTX in treatment sequence run)	Good	51	10%	52	10%	[redacted]
	Moderate	216	42%	236	46%	[redacted]
	None	251	48%	230	44%	[redacted]

Table 47: Severe RA subgroup of SELECT COMPARE 6-month data compared to base case NMA results

		NRI Imputation Method		**LOCF Imputation Method**		**Base case NMA results (used in HE model)**
Treatment	**EULAR Response at 6 Months**	**Count**	**Percent**	**Count**	**Percent**	**Percent**
Adalimumab 40mg q2wk + csDMARD	Good	89	36%	94	38%	[redacted]
	Moderate	74	30%	115	46%	[redacted]
	None	87	35%	41	16%	[redacted]
Upadacitinib 15 mg QD + csDMARD	Good	260	52%	273	55%	[redacted]
	Moderate	105	21%	169	34%	[redacted]
	None	132	27%	55	11%	[redacted]
csDMARD (used for MTX in treatment sequence run)	Good	80	15%	85	16%	[redacted]
	Moderate	130	25%	196	38%	[redacted]
	None	308	59%	237	46%	[redacted]

A29. For the NMA results, please tabulate:

The p-values for a treatment effect difference for the active treatments relative to placebo for tables 23 and 25 (p. 100, 102) using a similar format to these tables (2 tables).

The p-values for a treatment effect difference for UPA15mg relative to the other treatments for tables 23 and 25 (p. 100, 102) using a similar format to these tables (2 tables).

The p-values for a treatment effect difference for the active arms relative to csDMARDs for tables 23, 25, 26 and 27 (Company Submission using a similar format to these tables (4 tables).

The p-values for a treatment effect difference for UPA15mg+csDMARDS relative to the other treatments for tables 23, 25, 26 and 27 (Company Submission) in a similar format to these tables (4 tables).

AbbVie response: The requested analyses were performed for tables 23, 25, 26, and 27. The posterior probabilities that the other treatments have a lower ACR response rate than the placebo, other treatments have a lower response rate than csDMARD, other treatments have a lower ACR response than UPA 15 mg, and other treatments have a lower response rate than UPA 15 mg + csDMARDs were calculated and presented in Table 48 to Table 51.

Table 48: Base case: Combined model with random effects in csDMARD experienced RA: absolute probabilities of achieving ≥20, ≥50 or ≥70 ACR response for each treatment – week 24

	ACR 20		ACR 50		ACR 70		Posterior probability of treatment effect difference			
Treatment	Posterior Median	(95% CrI)	Posterior Median	(95% CrI)	Posterior Median	(95% CrI)	Pr (Trt < PBO)	Pr (Trt < csDMARD)	Pr (Trt < UPA 15 mg)	Pr (Trt < UPA 15 mg + csDMARDs)
csDMARD	[redacted]									
Abatacept 10 mg/kg + csDMARD	[redacted]									
Abatacept 125 mg + csDMARD	[redacted]									
Adalimumab 40 mg	[redacted]									
Adalimumab 40 mg + csDMARD	[redacted]									
Baricitinib 2 mg + csDMARD	[redacted]									
Baricitinib 4 mg + csDMARD	[redacted]									
Certolizumab 200 mg + csDMARD	[redacted]									
Etanercept 50 mg	[redacted]									
Etanercept 50 mg + csDMARD	[redacted]									
Golimumab 50 mg + csDMARD	[redacted]									
Infliximab 3 mg/kg + csDMARD	[redacted]									
Intensive csDMARD	[redacted]									
Placebo	[redacted]									
Rituximab 2000 mg + csDMARD	[redacted]									
Sarilumab 150 mg + csDMARD	[redacted]									
Sarilumab 200 mg	[redacted]									
Sarilumab 200 mg + csDMARD	[redacted]									
Tocilizumab 8 mg/kg	[redacted]									

Tocilizumab 8 mg/kg + csDMARD	[redacted]									
Tocilizumab 162 mg + csDMARD	[redacted]									
Tofacitinib 10 mg + csDMARD	[redacted]									
Tofacitinib 5 mg	[redacted]									
Tofacitinib 5 mg + csDMARD	[redacted]									
Upadacitinib 15 mg	[redacted]									
Upadacitinib 15 mg + csDMARD	[redacted]									

Abbreviations: ACR, American College of Rheumatology; csDMARD, conventional synthetic disease modifying antirheumatic drug; CrI, credible interval; PBO: placebo; RA, rheumatoid arthritis; Trt: treatment; UPA: upadacitinib

Notes:

1. Posterior probability of treatment effect difference is presented in this table. For example, Pr (Trt < PBO) is the posterior probability that treatment effect difference between active treatment and placebo is less than 0.
2. The posterior probability of treatment effect difference is the same for ACR 20, ACR 50 and ACR 70.

Table 49: Base case: Treatment comparison of six month estimated EULAR response mapped from the network meta-analysis ACR outcomes in csDMARD-experienced RA from combined three/six month network

Treatment	No Response (95% CrI)	Moderate Response (95% CrI)	Good Response (95% CrI)	Posterior probability of treatment effect difference			
				Pr (Trt < PBO)	Pr (Trt < csDMARD)	Pr (Trt < UPA 15 mg)	Pr (Trt < UPA 15 mg + csDMARDs)
csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abatacept 10 mg/kg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abatacept 125 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab 40 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab 40 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baricitinib 2 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baricitinib 4 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Certolizumab 200 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept 50 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept 50 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab 50 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab 3 mg/kg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Intensive csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rituximab 2000 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sarilumab 150 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Sarilumab 200 mg	[redacted]									
Sarilumab 200 mg + csDMARD	[redacted]									
Tocilizumab 8 mg/kg	[redacted]									
Tocilizumab 8 mg/kg + csDMARD	[redacted]									
Tocilizumab 162 mg + csDMARD	[redacted]									
Tofacitinib 10 mg + csDMARD	[redacted]									
Tofacitinib 5 mg	[redacted]									
Tofacitinib 5 mg + csDMARD	[redacted]									
Upadacitinib 15 mg	[redacted]									
Upadacitinib 15 mg + csDMARD	[redacted]									

Abbreviations: csDMARD, conventional synthetic disease modifying antirheumatic drug; CrI, credible interval; EULAR, European League Against Rheumatism; PBO: placebo; RA, rheumatoid arthritis; Trt: treatment; UPA: upadacitinib

Notes:

1. Posterior probability of treatment effect difference is presented in this table. For example, Pr (Trt < PBO) is the posterior probability that treatment effect difference between active treatment and placebo is less than 0.
2. The posterior probability of treatment effect difference is the same for EULAR response categories

Table 50: Combined model with random effects in bDMARD experienced RA: absolute probabilities of achieving ≥20, ≥50 or ≥70 ACR response for each treatment – 24 weeks

	ACR 20		ACR 50		ACR 70		Posterior probability of treatment effect difference	
Treatment	Posterior Median	(95% CrI)	Posterior Median	(95% CrI)	Posterior Median	(95% CrI)	Pr (Trt < csDMARD)	Pr (Trt < UPA 15 mg + csDMARDs)
csDMARD	[redacted]							
Abatacept 10 mg/kg + csDMARD	[redacted]							
Baricitinib 2 mg + csDMARD	[redacted]							
Baricitinib 4 mg + csDMARD	[redacted]							
Certolizumab 200 mg + csDMARD	[redacted]							
Golimumab 50 mg + csDMARD	[redacted]							
Rituximab 2000 mg + csDMARD	[redacted]							
Sarilumab 150 mg + csDMARD	[redacted]							
Sarilumab 200 mg + csDMARD	[redacted]							
Tocilizumab 8 mg/kg + csDMARD	[redacted]							
Tocilizumab 162 mg + csDMARD	[redacted]							
Tofacitinib 10 mg + csDMARD	[redacted]							
Tofacitinib 5 mg + csDMARD	[redacted]							
Upadacitinib 15 mg + csDMARD	[redacted]							

Abbreviations: ACR, American College of Rheumatology; csDMARD, conventional synthetic disease modifying antirheumatic drug; CrI, credible interval; PBO: placebo; RA, rheumatoid arthritis; Trt: treatment; UPA: upadacitinib

Notes:

1. Posterior probability of treatment effect difference is presented in this table. For example, Pr (Trt < csDMARD) is the posterior probability that treatment effect difference between active treatment and csDMARD is less than 0.
2. The posterior probability of treatment effect difference is the same for ACR 20, ACR 50 and ACR 70.

Table 51: Treatment comparison of six month estimated EULAR response mapped from the network meta-analysis ACR outcomes in bDMARD-experienced RA from combined three/six month network

Treatment	No Response (95% CrI)		Moderate Response (95% CrI)		Good Response (95% CrI)		Posterior probability of treatment effect difference	
							Pb (Trt < csDMARD)	Pr (Trt < UPA 15 mg + csDMARDs)
csDMARD	[redacted]		[redacted]		[redacted]		[redacted]	[redacted]
Abatacept 10 mg/kg + csDMARD	[redacted]		[redacted]		[redacted]		[redacted]	[redacted]
Baricitinib 2 mg + csDMARD	[redacted]		[redacted]		[redacted]		[redacted]	[redacted]
Baricitinib 4 mg + csDMARD	[redacted]		[redacted]		[redacted]		[redacted]	[redacted]
Certolizumab 200 mg + csDMARD	[redacted]		[redacted]		[redacted]		[redacted]	[redacted]
Golimumab 50 mg + csDMARD	[redacted]		[redacted]		[redacted]		[redacted]	[redacted]
Rituximab 2000 mg + csDMARD	[redacted]		[redacted]		[redacted]		[redacted]	[redacted]
Sarilumab 150 mg + csDMARD	[redacted]		[redacted]		[redacted]		[redacted]	[redacted]
Sarilumab 200 mg + csDMARD	[redacted]		[redacted]		[redacted]		[redacted]	[redacted]
Tocilizumab 8 mg/kg + csDMARD	[redacted]		[redacted]		[redacted]		[redacted]	[redacted]
Tocilizumab 162 mg + csDMARD	[redacted]		[redacted]		[redacted]		[redacted]	[redacted]
Tofacitinib 10 mg + csDMARD	[redacted]		[redacted]		[redacted]		[redacted]	[redacted]
Tofacitinib 5 mg + csDMARD	[redacted]		[redacted]		[redacted]		[redacted]	[redacted]
Upadacitinib 15 mg + csDMARD	[redacted]		[redacted]		[redacted]		[redacted]	[redacted]

Abbreviations: ACR, American College of Rheumatology; csDMARD, conventional synthetic disease modifying antirheumatic drug; CrI, credible interval; EULAR, European League Against Rheumatism; PBO: placebo; RA, rheumatoid arthritis; Trt: treatment; UPA: upadacitinib

Notes:

1. Posterior probability of treatment effect difference is presented in this table. For example, Pr (Trt < PBO) is the posterior probability that treatment effect difference between active treatment and placebo is less than 0.
2. The posterior probability of treatment effect difference is the same for EULAR response categories.

Section B: Clarification on cost-effectiveness data

Literature searching

B1. The PRISMA flow diagram presented on p. 305 of Appendix G includes an error in the number of records from the original MEDLINE search (n=127, but the database search results show 217). The rest of the flow diagram appears to be incorrect as a result. Please can you provide an updated version of the PRISMA flow diagram?

AbbVie response: The search number of 127 within PRISMA diagram is correct, there is a typo within recording final number for search strategy. Please find below the text file of all records for MEDLINE and the corrected search strategy in Table 52.

Medline_1-127.txt

Table 52: MEDLINE search stratey and hits

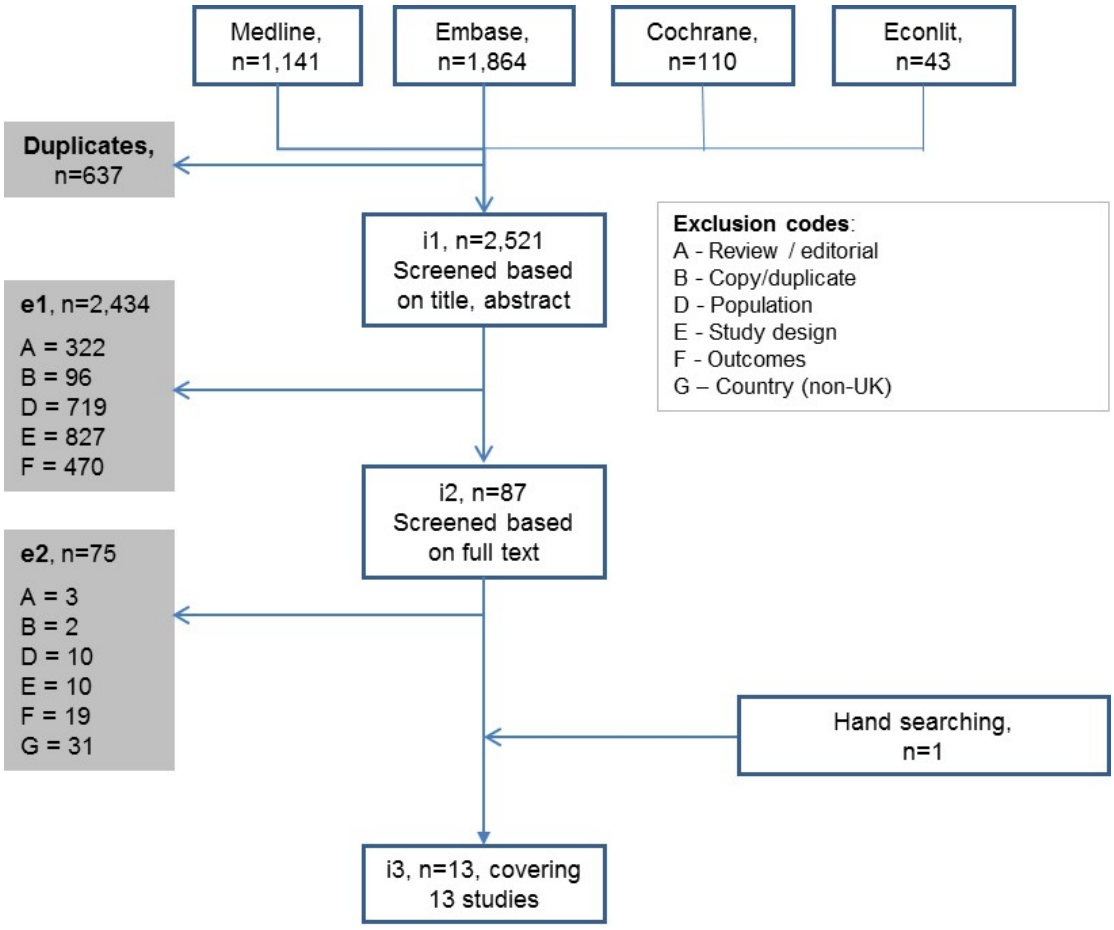
	Searches	Results
1	exp rheumatoid arthritis/	115821
2	rheumatoid arthritis.mp.	105218
3	1 or 2	148522
4	exp upadacitinib/ or (upadacitinib or ABT-494).af.	12
5	exp adalimumab/ or (adalimumab or Humira or trudexa).af.	7245
6	exp etanercept/ or (etanercept or Enbrel or Benepali or SB4 or 185243-69-0 or 200013-86-1).af.	8608
7	exp infliximab/ or (infliximab or Remicade or Remsima or CT-P10 or CT-P13 or 170277-31-3).af.	14115
8	exp golimumab/ or (golimumab or Simponi or CNTO 148 or cnto-148 or 476181-74-5).af.	973
9	exp certolizumab pegol/ or (certolizumab or Cimzia or CDP870 or 428863-50-7).af.	1073
10	exp tocilizumab/ or (tocilizumab or Actemra or RoActemra or 375823-41-9).af.	2473
11	exp abatacept/ or (abatacept or Orencia or CTLA-4Ig or 332348-12-6).af.	3647
12	exp tofacitinib/ or (tofacitinib or tasaocitinib or CP-690550 or Xeljanz or 540737-29-9).af.	824
13	exp rituximab/ or (rituximab or Rituxan or Mabthera or 174722-31-7).af.	21203
14	anakinra/ or (anakinra or Kineret or 143090-92-0).af.	5848
15	baricitinib/ or (baricitinib or Olumiant or LY3009104 or LY 3009104 or 1187594-09-7).af.	93
16	exp sarilumab/ or (sarilumab or Kevzara or SAR 153191 or SAR153191 or REGN 88 or REGN88 or 1189541-98-7).af.	49
17	exp sirukumab/ or (sirukumab or CNTO-136 or CNTO136 or 1194585-53-9).af.	40
18	exp filgotinib/ or (Filgotinib or GLPG0634 or GLPG-0634).af.	35
19	exp peficitinib/ or (Peficitinib or ASP015K).af.	23
20	or/4-19	53336
21	(cost minimi?ation analys* or (cost-minimi?ation adj1 analys*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	712

	Searches	Results
22	exp cost benefit analysis/	79357
23	((cost benefit adj1 analys*) or (cost-benefit adj1 analys*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	81410
24	(cost utility analys* or (cost-utility adj1 analys*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	2825
25	(cost consequence analys* or (cost-conseq* adj1 analys*)).mp.	221
26	((cost-effective* adj1 analys*) or "cost adj1 effectiveness adj1 analys*").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	11634
27	"cost effectiveness analysis"/	79357
28	or/21-27	85796
29	((economic or pharmacoeconomic) adj1 (evaluation or assessment or analys?s or stud*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	17612
30	("CEA" or "CMA" or "CBA" or "CUA" or "CCA").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	61984
31	exp decision theory/ or exp decision tree/	12087
32	decision tree.mp.	5835
33	models, economic/	9694
34	(markov or deterministic).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	36425
35	((transition adj1 probabilit*) or (health adj1 stat*) or (sensitivity adj1 analys*) or (health adj1 outcome)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	198318
36	((patient level or patient-level or discrete event or discrete-event) adj1 simulat*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	737
37	(incremental-cost or incremental cost).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	10145
38	(ICER or QALY or DALY or WTP or TTO).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	12800
39	or/30-38	319949
40	29 and 39	6395
41	28 or 40	87627
42	3 and 20 and 41	127

B2. Please can you provide a PRISMA flow diagram for the original search for the cost and resource use systematic review (p. 470, Appendix I). The PRISMA flow diagram for the April 2019 update search has been included twice.

AbbVie response: Please find in Figure 4 the detailed PRISMA diagram for the original review of cost and resource use.

Figure 4: Cost and resource use systematic review - original search



B3. The PRISMA flow diagram on p. 470 of Appendix I suggests that 131 studies from the April 2019 searches were excluded because the publication year was 2017. Could these records have been newly added to the databases after the original search despite having a 2017 publication date? Was this checked?

AbbVie response: In Appendix I, 131 studies were excluded on the basis that these were published before 2017. All these studies were checked and these were duplicates of the studies which were identified in the original search.

Model structure

B4. Please present a more detailed model schematic that includes the possible transitions from moderate to severe disease and from severe disease to moderate, and outline which analyses/results tables permit which of these transitions. Also:

Within the modelling of moderate RA patients, if these patients transition to severe RA but subsequently transition back to moderate RA, what is assumed in terms of their treatment sequence from the point at which they have returned to moderate RA?

Similarly, within the modelling of severe RA patients, if these patients transition to moderate RA what is assumed in terms of their treatment sequence from the point at which they transition to moderate RA?

Amended question from ERG: "Within the modelling of moderate RA patients, these patients can transition to severe RA. We would be grateful for more information about how this is modelled, particularly in the light of the model apparently being driven by the evolution of HAQ. Please describe how the model decides when a moderate patient becomes severe, and whether any patient variables in addition to the HAQ need to be tracked for this estimation. Please provide the required functional forms that are required to model estimating if and when a moderate patient becomes severe, together with full referencing to the original source data. Please provide the alternative functional forms that were also estimated (if any) together with the reasons for their rejection (as applicable) and the reasons for the selection of the final functional form. Please provide an excel spreadsheet with worked examples of the modelling of time to worsening from moderate to severe for hypothetical patient(s) sufficient to provide a clear understanding of the inputs and how they are applied within this modelling to estimate both if and when a patient transitions from moderate to severe. The ERG would also be grateful if this spreadsheet could be further augmented with worked examples in Excel of the resulting EULAR responses, given the NMA results of tables 25 and 27, and HAQ changes at each change of treatment specifically for sequence 1 and sequence 2 for the 1a Tables 36 and 37 patient population"

AbbVie response: AbbVie will provide a response to this question by 15th August.

B5. Priority question: Please provide an intuitive account of how the economic modelling of EULAR and ACR differ, together with answers to the following:

Does the EULAR modelling probabilistically assign a EULAR response to individual patients based upon the EULAR proportions of the NMA as reported in the clinical effectiveness section, as mapped from the ACR proportions?

AbbVie response: When EULAR is the selected response criteria, the model probabilistically assigns a EULAR response to individual patients based on the EULAR proportions of the NMA, as reported in the clinical effectiveness section. To derive the EULAR response results in the NMA, the mapping algorithm was applied to each individual's simulated ACR results to calculate the EULAR proportions for each iteration. The NMA result for EULAR response was estimated based on all simulated iterations. In the cost-effectiveness model, the EULAR response was probabilistically sampled from the simulated EULAR proportions from the NMA (i.e. the CODA).

Does the ACR modelling probabilistically assign an ACR response to individual patients based upon ACR proportions of the NMA as reported in the clinical effectiveness section, and then probabilistically sample from the same ACR to EULAR mapping function to assign a EULAR response to the patient?

AbbVie response: When ACR is the selected response criteria, the model probabilistically assigns an ACR response to individual patients based upon ACR proportions of the NMA as reported in the clinical effectiveness section. In the cost-effectiveness model, the ACR response was probabilistically sampled from the simulated ACR proportions from the NMA (i.e. the CODA). ACR proportions was directly used as input for the cost-effectiveness model with the following assumption: 1) Individuals with an ACR 20-50 were assumed to be the same as those with a EULAR moderate response, 2) Individuals with an ACR 50-100 were assumed to be the same as those with a EULAR good response, and 3) individuals with an ACR<20 were assumed to be the same as EULAR non-responders. There is no further conversion from ACR to EULAR within the CEA model. All other steps are the same between ACR and EULAR response modelling scenarios. ACR response modelling should be considered only as a sensitivity analysis, given ACR response categories

do not correspond to EULAR response categories in 1:1 manner. In the submission document, all results tables are using EULAR responses, which has taken into consideration of the conversion between ACR and EULAR using the mapping function reported in Table 165 of the Stevenson et al. HTA monograph [Vol 20, Issue 35, April 2016].

Does the ACR to EULAR mapping function correspond to that implied by Table 165 of the Stevenson et al HTA monograph [Vol 20, Issue 35, April 2016], and if so to what extent has this been differentiated by the Table 165 values reported for all patients, for severe patients and the implied values for non-severe patients.

AbbVie response: The algorithm to convert ACR to EULAR was based on the VARA data used in TA375 [1]. The same conversion algorithm was used for all patients regardless of the RA severity, given the NMA populations are moderate-to-severe RA patients. The conversion matrix from ACR response categories to EULAR response categories is presented in Table 53 below.

Table 53: Conversion matrix from ACR response categories to EULAR response categories

From\To	EULAR None (%)	EULAR Moderate	EULAR Good
Less than ACR20	79.641%	14.346%	6.013%
ACR20-50	4.651%	58.140%	37.209%
ACR50-70	20.000%	0.000%	80.000%
ACR70	0.000%	50.000%	50.000%

Please provide within an excel spreadsheet worked examples of the mapping applied within the NMA and within the economics from ACR to EULAR response for (1) all patients, (2) severe patients and (3) moderate patients for a hypothetical ACR response pattern of 70% less than ACR20, 30% ACR20, 15% ACR50 and 5% ACR70 to the extent that they have been applied in the NMA and/or any of the economics.

AbbVie response:

To address these comments, we explored EULAR conversion of the hypothetical ACR response pattern of 70% less than ACR20, 30% ACR20, 15% ACR50 and 5% ACR70. Please refer to the submitted Excel file's *B5. ACR to EULAR map example* worksheet for the worked example. The hypothetical ACR response pattern provided by the ERG can be converted into the following ACR categories:

- Less than ACR20: 70%
- ACR20-50: 15%
- ACR50-70: 10%
- ACR70: 5%

Using the conversion algorithm included in the matrix above, we could estimate the following EULAR response pattern

- EULAR none: 58.4%
- EULAR moderate: 21.3%
- EULAR good: 20.3%

This same conversion from ACR to EULAR will apply to 1) all patients, (2) severe patients and (3) moderate patients.

In the cost-effectiveness model, when EULAR is the selected response criteria, the following response will be used:

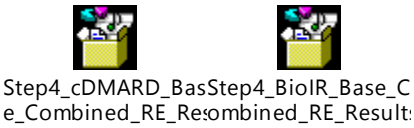
- EULAR none: 58.4%
- EULAR moderate: 21.3%
- EULAR good: 20.3%

In the cost-effectiveness model, when ACR is the selected response criteria, the following response will be used:

- Less than ACR20: 70% - treated as EULAR non-responders in the model
- ACR20-50: 15% - treated as EULAR moderate responder in the model
- ACR50-100: 15% - treated as EULAR good responder in the model

Please provide the WINBUGS code that underlies the mapping from ACR to EULAR within the NMA.

AbbVie response: Please find the code that underlies the mapping from ACR to EULAR attached below. The code can be used in conjunction with what is provided in question A18 to generate the EULAR result.



B6. Please clarify the treatment of HAQ among those discontinuing a csDMARD. For a patient with a baseline HAQ of W, who experiences a treatment effect of X but subsequent to the treatment effect and while remaining on the csDMARD worsens by Y, what is their HAQ if they:

(a) discontinue the csDMARD and switch to a treatment which is estimated to reduce their HAQ by Z?

(b) discontinue the CSDMARD and switch to BSC?

What is assumed for HAQ evolution after having switch to BSC? Does it follow the same possible evolution as for those on csDMARDs with the same input parameters to the probabilities of worsening and degree of worsening? Please provide within an Excel spreadsheet a worked example of the arithmetic of the time to HAQ worsening and the HAQ worsening at this point with full referencing for the input values to this for those on csDMARDs, and for those on BSC to the extent that it differs. Where are these parameters in the electronic model?

AbbVie response: The submission model assumes that HAQ will rebound to baseline HAQ upon treatment discontinuation. The same assumption was applied to all treatments. In the example above, right before discontinuation of the csDMARD, the patient's HAQ will equal W – X + Y. At the time of discontinuation and before switching to the next treatment (regardless of whether the next treatment is active treatment or BSC), the patient's HAQ will revert back to W. This assumption is consistent with the assumption used in the baricitinib submission TA466[3].

(a) After discontinuation of the csDMARD, if the patient initiates a new treatment which can reduce their HAQ by Z, the patient's HAQ will become W-Z after the new treatment.

(b) After discontinuation of the csDMARD, if the patient switches to BSC, the patient's HAQ will progress based on Norton et al. (2014)[12]. Patients who switch to BSC will revert to baseline HAQ.

The same algorithm is used to model HAQ progression for patients on csDMARD and those on BSC. In both cases, HAQ progression is based on a latent class growth model described in Norton et al. (2014). As the first step, the probability of belonging to each of the four latent classes is estimated using the coefficients specified in the supplementary Table 4 in Norton et al. (2014) for each patient simulated in the model. Probability weighted HAQ trajectory is then calculated and used to estimate time to experience a HAQ progression event, which is defined as having an increase in HAQ of more than 0.125. Consistent with the approach used in TA375[1], patients on csDMARDs or BSC could experience a non-linear HAQ progression for the first 15 years on treatment based on the Norton approach, after which HAQ was assumed to remain flat.

The worked example, along with the parameters of the Norton latent class growth model and the digitized trajectories of HAQ over time for the four latent classes reported in the Norton study, were documented in the *HAQ progression* worksheet in the HE model re-submitted in response to the clarification questions. Time to HAQ progression is carried out by the VBA function "HAQ_trajectory" located in the fnct_haq_adjust module.

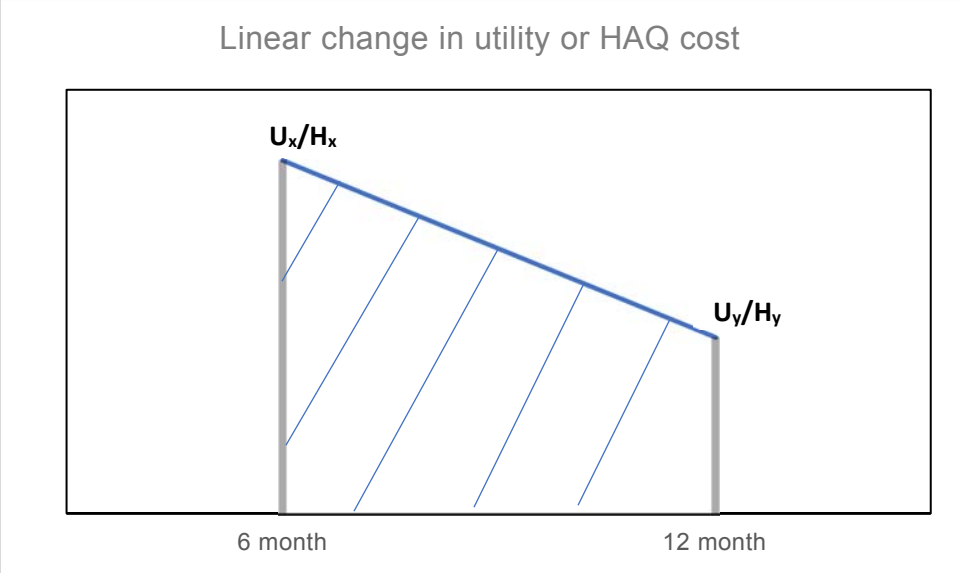
B7. The submission, in section B.3.3 (p. 145), states that "*At each progression event, utility and costs were estimated assuming a linear change in HAQ costs and utility*". Please clarify this, with reference to how costs and QALYs would be calculated for month 6 to month 12 for a csDMARD patient whose HAQ was X at month 6 and worsened to Y at month 12, preferably with worked examples which can be provided in an Excel spreadsheet if more convenient.

AbbVie response: The statement regarding the assumption of linear change in HAQ costs and utility refers to the algorithm used to calculate the total utility and HAQ

costs incurred during the time between two discrete events. With regard to the situation outlined in the question, first, HAQ at month 6 and month 12 would be used to estimate the corresponding utility (based on the mapping processed described in section B.3.4.2) and HAQ costs (converted to monthly costs based on the annual cost reported in Table 63 in section B.3.5.3). Assuming that a HAQ of X corresponds to an estimated utility of U_x and (monthly) HAQ cost of H_x, while a HAQ of Y corresponds to utility of U_y and (monthly) HAQ cost of H_y, the total utility and HAQ costs over the 6 month period would be calculated based on the following equation and is illustrated in Figure 5 below:

- Total utility of the 6 month period = ($|U_x + U_y| \div 2$) x 6 months
- Total HAQ cost of the 6 month period = ($|H_x + H_y| \div 2$) x 6 months

Figure 5: Illustration of linear change in utility of HAQ cost



Model inputs

B8. Within the ACR modelling, what ACR response rates are assumed for BSC, and what EULAR response rates would these imply using the ACR to EULAR response mapping function? Within the EULAR modelling, what EULAR response rates are assumed for BSC?

AbbVie response: For both EULAR and ACR modelling, the response rate of BSC is assumed to be zero and patients do not experience any HAQ benefit. Once

patients start receiving BSC, they will experience HAQ progression based on the latent class growth model described in Norton et al. (referred to in response B6). This assumption is consistent with TA375[1], in which patients treated with BSC (named as non-biologic therapy in TA375) were also assumed to experience no response.

B9. Priority question: Please present within an Excel spreadsheet the data underlying Figure 42 of Appendix J, coupled with the functional forms and input values for the predicted EQ-5D trial based mapping and the predicted EQ-5D literature reported mapping with full referencing for the functional forms and input values. If possible, please provide worked examples of each of these within the Excel. Given the nature of the mappings please provide full details of any and all interim steps, including those used to derive Document B Table 58 (p. 149) and including the role of the 4 classes of Table 78 of Appendix J.

AbbVie response: The analysis presented in Figure 42 of Appendix J was performed to evaluate the impact of using different pain inputs on predicted EQ-5D results. Please refer to Table 54 in the response to B10 for the underlying data. In this analysis, we compared the EQ-5D values observed in the SELECT trials with two versions of predicted EQ-5D values. Both predicted EQ-5D sets used the Hernandez mapping approach to estimate EQ-5D utility values[13]. The Hernandez approach uses a mixture model to predict EQ-5D utility values based on patients' HAQ score, pain on a visual analogue scale (pain VAS), age, and sex. The mixture model was developed based on the US National Data Bank for Rheumatic Diseases (NDB) data. In total, 16,011 unique patients were included in the analysis, representing 103,867 observations. The Hernandez study fit multiple statistical models to the data, including linear regression with random effects, as well as a four-class bespoke mixture model. The four-component mixture model was selected as the optimal model, and included both HAQ and pain VAS as separate covariates. Probability class assignment depends on patient's HAQ, pain VAS and sex. The utility for each latent class is informed by the linear and squared terms of standardized age, the linear and squared terms of HAQ scores, pain VAS/100, and sex (Table 78 of Appendix J).

As described above, the Hernandez approach requires pain VAS inputs over time in order to map HAQ to EQ-5D. However, pain is not directly tracked in the model. Given the strong correlation between pain and HAQ, an algorithm (referred to as "mapping" in the submission document) was used to estimate pain based on HAQ (which is tracked over time in the model), consistent with the approach used in the TA375[1] and baricitinib submission[3].

The only difference between the two predicted EQ-5D sets in Figure 42 Appendix J is the pain input. The pain input in both sets was estimated using a HAQ value: one is estimating pain from HAQ based on the relationship observed in the SELECT trial data (referred to as trial-based HAQ-to-pain mapping), and the other is estimating pain from HAQ using the HAQ and pain relationship reported in the TA375 Figure 114[1] (referred to as literature-reported HAQ-to-pain mapping).

In particular, the three curves reported in Figure 42 Appendix J were derived as follows:

1. The observed EQ-5D curve presented in Figure 42 of Appendix J were based on an analysis of patients with moderately and severely active RA (DAS28 at baseline >3.2) from the SELECT-NEXT, SELECT-COMPARE, SELECT-MONO, SELECT-SUNRISE, and SELECT-BEYOND. Patients with missing DAS28 at baseline were not included in the analysis. Non-missing HAQ and EQ-5D values at baseline, 3 months, and 6 months (for SELECT-COMPARE only) were used for the analyses. Observed data without imputation were used. The SELECT trials collected EQ-5D-5L; the EQ-5D-5L values were converted to EQ-5D-3L using EuroQol mapping. UK values sets were then applied to estimate utilities. Mean EQ-5D utility values were summarized and plotted by HAQ scores (scores range from 0-3, in 0.125 increments) in the Figure 42 Appendix J.

2. The predicted EQ-5D (trial-based HAQ-to-pain map) curve presented in Figure 42 of Appendix J is based on the Hernandez approach applied to the SELECT trial populations with the pain VAS score informed by trial-based HAQ-to-pain map. As a first step, the relationship between pain VAS and HAQ is informed from an analysis of patients with moderately and severely

active RA (DAS28 at baseline >3.2) from the SELECT-NEXT, SELECT-COMPARE, SELECT-MONO, SELECT-SUNRISE, and SELECT-BEYOND trials. To inform the relationship, observed HAQ and pain VAS data from the same patient at baseline, 3 months, and 6 months (for SELECT-COMPARE only) were used for the analyses. Patients with missing either baseline HAQ or pain data were excluded. For each HAQ score (score range 0-3, in 0.125 increments), pain VAS score values were summarized using the mean and standard error. This data was presented in Document B Table 58 (p. 149) - base-case (Phase III upadacitinib trials) column. As the second step, these values were then applied using the Hernandez approach to estimate utilities for the SELECT trial populations. In particular, the same population used to generate observed EQ-5D data was used. As described previously, the Hernandez approach estimates EQ-5D utility values based on patients' HAQ score, pain VAS score, age, and sex. The HAQ score, age, and sex were based on observed values from the SELECT trials, whereas the pain VAS score was informed by the HAQ score based on the relationship informed from the first step. The parameters used in the Hernandez approach were presented in Table 78 of Appendix J.

3. The predicted EQ-5D (literature reported HAQ-to-pain map) curve presented in Figure 42 of Appendix J is based on the Hernandez approach applied to the SELECT trial populations with the pain VAS score informed from literature-based HAQ-to-pain map. The literature reported HAQ-to-pain mapped pain scores were based on the pain by HAQ mapping detailed in TA375 Figure 114[1]. The pain scores in TA375 were estimated using data from the National Data Bank for Rheumatic Diseases, with the mean pain score (and standard error) estimated for each valid HAQ score. The extracted values from the TA375 Figure 114 were reported in the baricitinib submission Table 115[3], which were used in the analysis. This data was presented in Document B Table 58 (p. 149) - Sensitivity (TA375) column. These values were then applied using the Hernandez approach to estimate utilities for the SELECT trial populations as discussed above

The predictive properties of the two sets of EQ-5D estimates in Figure 42 are presented in Table 75 in Appendix J. Given the smaller mean absolute error (MAE) and root mean squared error (RMSE), the trial-derived HAQ-to-pain mapping is selected as the base-case approach in the CEA model to estimate utility. This is in line with the trial derived HAQ to pain mapping identified in the tofacitinib NICE appraisal as providing the best fit to observed data and agreed as the most appropriate approach to use by the NICE Appraisal Committee.

A worked example of utility allocation is shown in the "Utility" worksheet in the version of the HE model re-submitted in response to the clarification questions.

B10. Priority question: Following on from question B9, what alternative functional forms were explored for the predicted EQ-5D trial-based mapping and why were they rejected? Please present a graph of (1) the HAQ to QoL function of the base case and (2) the HAQ to QoL function prior to any of the rescaling based upon Dolan et al, alongside the corresponding function of TA375 if possible and also alongside those presented in Figure 115 of the Stevenson et al HTA monograph if possible, together with an excel spreadsheet of the underlying calculations for (1) the base case and (2) the HAQ to QoL function prior to any of the rescaling based upon Dolan et al with full input source referencing.

AbbVie response: No alternative HAQ-to-QoL mapping approaches beyond the Hernandez approach[14] were explored to estimate utilities for the cost-effectiveness model because the Hernandez approach was determined to be the most appropriate function to estimate utilities by TA375[1], compared with alternatives. When utilizing the Hernandez approach, two alternative approaches were used to estimate pain VAS from HAQ, as described in the response to B9 and in Document B Section B.3.4.2 Mapping. No other HAQ-to-pain mapping approaches were explored beyond these two. Given that the EQ-5D values estimated from the Hernandez approach[14] using the trial-based HAQ-to-pain map validate well against the observed EQ-5D values and that these values do not deviate from the EQ-5D value estimated from the Hernandez approach[14] using the literature-derived HAQ-to-pain map (Figure 42 in Appendix J), we have not explored alternative approaches.

Figure 6 and Table 54 below illustrate that the HAQ-to-QoL functions with and without rescaling. As evident from the figure and table, the rescaling has limited to no

impact on the QoL (i.e. EQ-5D) utility values. The small differences were only observed when HAQ values and the estimated EQ-5D values were at their extremes. The RMSE comparing the observed EQ-5D values with the estimated EQ-5D values from the Hernandez approach using the trial-based and literature-derived HAQ-to-pain map, respectively, were similar without rescaling (trial-based RMSE: 0.172, literature-reported RMSE: 0.179) and with rescaling (trial-based RMSE: 0.172, literature-reported RMSE: 0.180). Similar to the situation with rescaling, the EQ-5D utilities estimated from the Hernandez approach[14] using the trial-based HAQ-to-pain map without rescaling validate better with the observed EQ-5D values, compared to the EQ-5D utilities estimated from the Hernandez approach[14] using the literature-reported HAQ-to-pain map without rescaling. This evaluation indicates that the EQ-5D utilities estimated from the Hernandez approach[14] using the trial-based HAQ-to-pain map are robust.

To address the ERG's request, Figure 7 was generated to present the curves in Figure 6 curves without rescaling alongside Figure 115 of the Stevenson et al. HTA monograph. This overlay shows that EQ-5D utilities estimated based on the Hernandez approach[14] using the trial-based HAQ-to-pain map were most similar to the observed EQ-5D values, compared to alternative functions to estimate utilities. A caveat is that Figure 115 of the Stevenson et al. HTA monograph was not tailed to the SELECT trial populations.

Figure 6: EQ-5D by HAQ, with and without rescaling

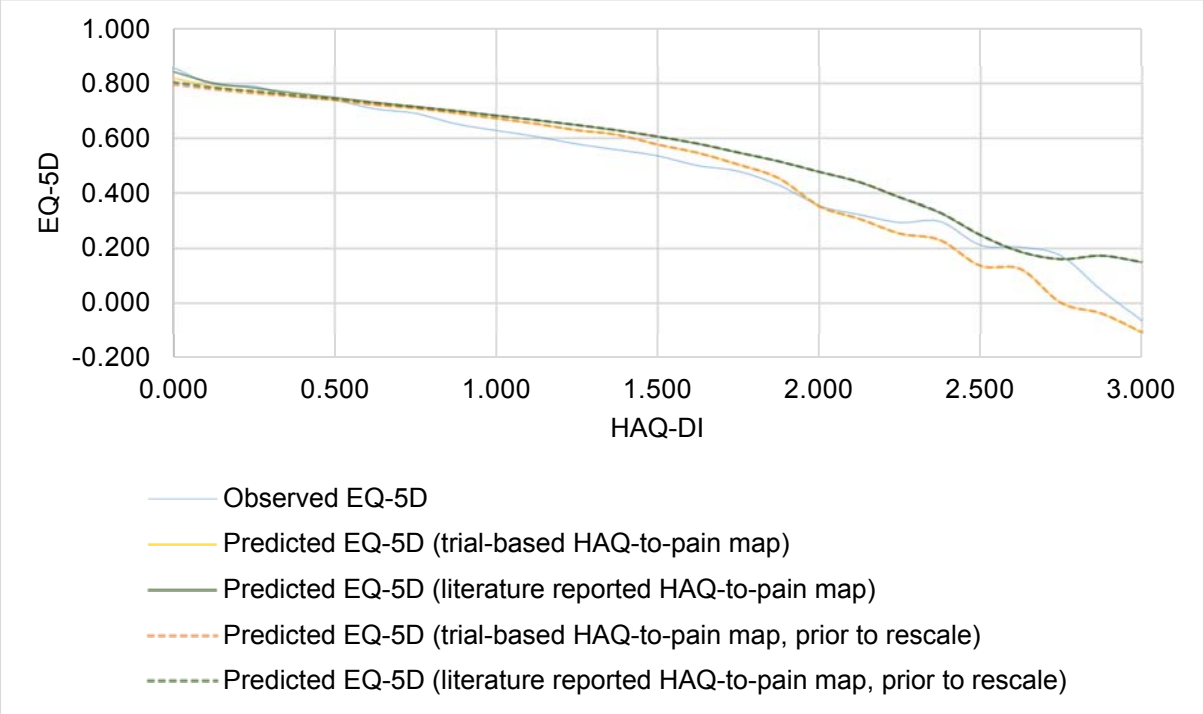


Figure 7: Trial-based EQ-5D estimates and literature reported EQ-5D estimates

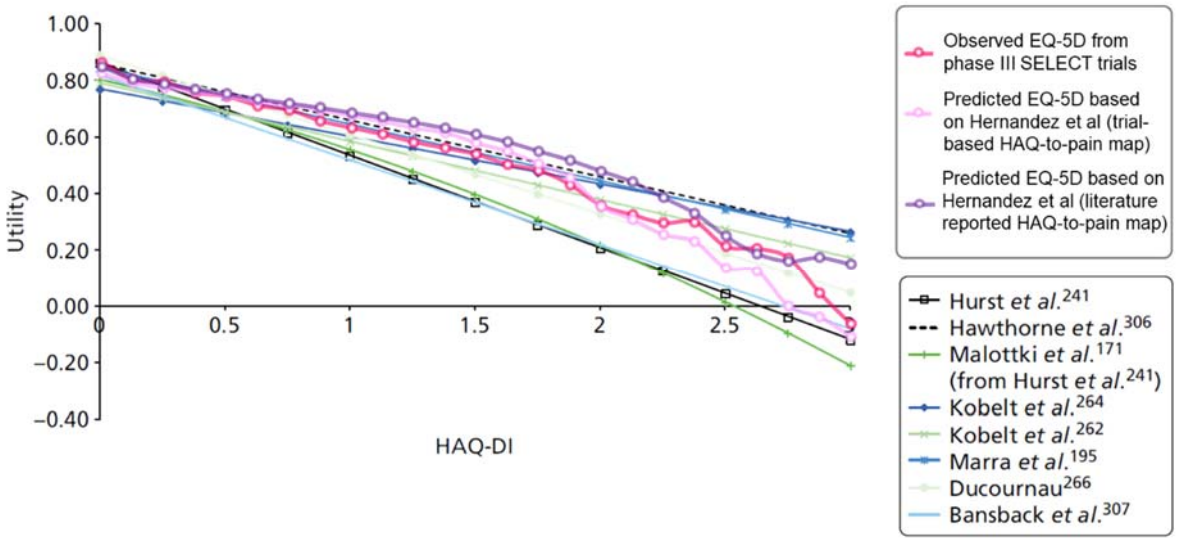


Table 54: Underlying data for trial-based EQ-5D estimates presented in Figure 6

HAQ	Observed EQ-5D	Predicted EQ-5D (trial-based HAQ-to-pain map)	Predicted EQ-5D (literature reported HAQ-to-pain map)	Predicted EQ-5D (trial-based HAQ-to-pain map, prior to rescale)	Predicted EQ-5D (literature reported HAQ-to-pain map, prior to rescale)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

B11. In the model, please disaggregate G5:G38 of the *Raw – baseline characteristics* worksheet in a format similar to that of cells E3:E30 of the *Raw – baseline chars (old)* worksheet, and further disaggregate this to be specific to columns D, E and F if necessary. Why has SELECT-SUNRISE been included in this and what is the effect of excluding it?

AbbVie response: Please refer to the submitted Excel file's *B11. Baseline with & without SUNRISE* worksheet for the baseline characteristics table presented with disaggregated sources. Of note, the *Raw – baseline chars (old)* worksheet is out of date and was not used in the model. It was developed before all the SELECT trial data became available. The *Raw – baseline characteristics* worksheet is used in the model. It reflects an analysis of patient-level data for the trials SELECT-NEXT, SELECT-MONO, SELECT-COMPARE, SELECT-SUNRISE, and SELECT-BEYOND.

The baseline characteristics table sources are disaggregated as detailed below:

- Moderate, csDMARD-IR population (column C) is based on patient-level data analysis of the trials including csDMARD-IR patients (SELECT-NEXT, SELECT-MONO, SELECT-COMPARE, and SELECT-SUNRISE), restricted to patients who had moderate RA at baseline per DAS28 score (>3.2 and ≤ 5.1)
- Severe, csDMARD-IR population (column D) is based on patient-level data analysis of the trials including csDMARD-IR patients (SELECT-NEXT, SELECT-MONO, SELECT-COMPARE, and SELECT-SUNRISE), restricted to patients who had severe RA at baseline per DAS28 score (>5.1)
- Severe, bDMARD-IR population (RTX- eligible and ineligible) (column E) is based on patient-level data analysis of the trial including bDMARD-IR patients (SELECT-BEYOND), restricted to patients who had severe RA at baseline per DAS28 score (>5.1)

SELECT-SUNRISE was included in this csDMARD-IR moderate and severe population patient-level data analyses (columns C and D). It was included in the analysis because the patient population in SELECT-SUNRISE included moderate to

severe RA patients, which was consistent with the populations in the SELECT-NEXT, SELECT-MONO, and SELECT-COMPARE trials. In the NMA, Japan-specific trials were not excluded and therefore SELECT-SUNRISE was included to be consistent with the general inclusion/exclusion criteria considered for all RA treatments.

To evaluate the effect of excluding the SELECT-SUNRISE clinical trial, the baseline characteristics, the NMA results (referred to in A.25 response), and the cost-effectiveness analysis results were re-evaluated after exclusion.

- Please refer to the submitted Excel file's *B11: Baseline with & without SUNRISE worksheet* for the baseline characteristics generated with (C and D columns) and without (H and I columns) SELECT-SUNRISE. As demonstrated in the Excel, excluding SELECT-SUNRISE has minimal impact on the baseline characteristics of moderate and severe csDMARD-IR populations.
- Please refer to our responses to A.25. for the impact of excluding the SELECT-SUNRISE on the NMA results. Overall, the impact was minimal.

B12. The ERG has to date only been able to source the HAQ to annual hospitalisation costs from figure 113 of the Stevenson et al monograph. Please clarify how Table 63 (p. 155, Company Submission) was sourced, together with any additional referencing as necessary.

AbbVie response: Detailed values for hospitalization costs by HAQ Table 63 (p. 155) were sourced in the baricitinib NICE submission ID979, Table 115[3]: Summary of variables applied in the economic model. The costs were inflated to 2018 GBP. The study was performed and originally reported in detail by Roche[15], as cited in TA 375 and in our submission.

B13. Please provide in an excel spreadsheet the digitized pseudo IPD and Kaplan Meier data (t, n at risk, n events, n censored, S(t)) that underlies the curves of Figure 20 (p. 127, Company Submission). Please clarify if e.g. the Figure 20 good responder proportion at day 4,000 of around 45% suggests that of 100 good responders at day 0 there will be 45 remaining alive and on treatment at day 4,000,

or of 100 patients remaining alive at day 4,000 there will be 45 remaining on treatment. It is unclear how treatment discontinuation has been modelled among those with a good or a moderate response. Is this solely governed by the generalised gammas of Figure 20, or is it also governed by e.g. HAQ scores worsening beyond some threshold? Are those receiving csDMARDs modelled as continuing csDMARDs until the sampled gamma determines they cease their csDMARD, regardless of their HAQ?

AbbVie Response: Figure 20 presents the time on treatment by good and moderate EULAR responses reported from TA375[1]. At day 4,000 the 45% refers to the proportion of patients still on treatment. In a cohort of 100 good responders, at day 4,000, on average 45 patients would be using the treatment whereas the other 55 would have already discontinued treatment.

The time to treatment discontinuation curves presented in Figure 20 were extracted to reconstruct pseudo-IPDs based on the Guyot approach[16]. Pseudo-IPDs (one each by EULAR response) were used to fit parametric survival models. Please refer to the submitted Excel file's *B13. Pseudo IPD EULAR Moderate* and *B13. Pseudo IPD EULAR Good* worksheets for the digitized pseudo-IPD data. The original Kaplan-Meier data only reported the initial number of patients without number at risk and censoring information. In the preparation of the clarification questions response, we noticed there was an issue in exporting the pseudo-IPD from R software. The issue involves exporting an extra number of censored patients to the pseudo-IPD and resulted in an underestimation of the discontinuation rate for all treatment arms in the CEA model. This issue was fixed, and parametric functions were refitted based on the updated IPD data and presented in Figure 8 and Figure 9 below. The re-submission model and the IPD data in the submitted Excel file *B13. Pseudo IPD EULAR Moderate* and *B13. Pseudo IPD EULAR Good* worksheets incorporated this update. The AIC and BIC values for each parametric fit is presented in *Table 55.* The log normal model and generalized gamma model provides the best fit for EULAR moderate and good responses, respectively. As the generalized gamma model fit for moderate EULAR response is almost identical to the log normal model (best fit), for simplicity and consistency with the TA375 approach, the generalized gamma model was used in the CEA model to simulate time to treatment discontinuation for both moderate and good EULAR responders. Essentially, there are two sets of

generalized gamma parameter estimates, one for good EULAR response and another for moderate EULAR response. In the health economics model, the time to treatment discontinuation for each individual on each active treatment was probabilistically estimated based on the corresponding distribution by response.

The results from the cost-effectiveness analyses presented in the original submission Documents A and B are updated based on the corrected parametric functions for treatment discontinuation.

In the model, treatment discontinuation is solely governed by the generalised gammas of Figure 20 and it is not governed by worsening HAQ scores unless when we are evaluating the moderate population, where they could progress to severe RA. In this case, in addition to the discontinuation governed by the discontinuation curve, once patients' DAS28 (estimated from HAQ) exceeds 5.1, patients would discontinue the moderate treatment sequence and start the severe treatment sequence.

Figure 8: Time to treatment discontinuation digitized TA375 vs. parametric fitted curves (EULAR moderate response)

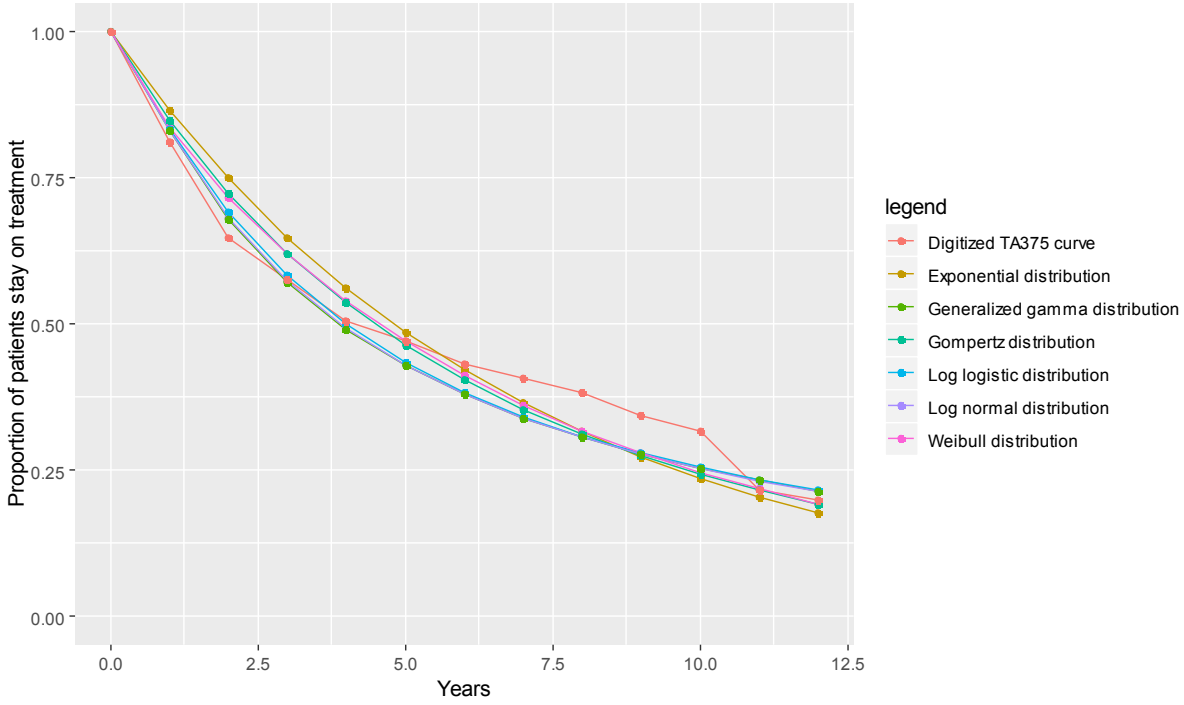


Figure 9: Time to treatment discontinuation digitized TA375 vs. parametric fitted curves (EULAR good response)

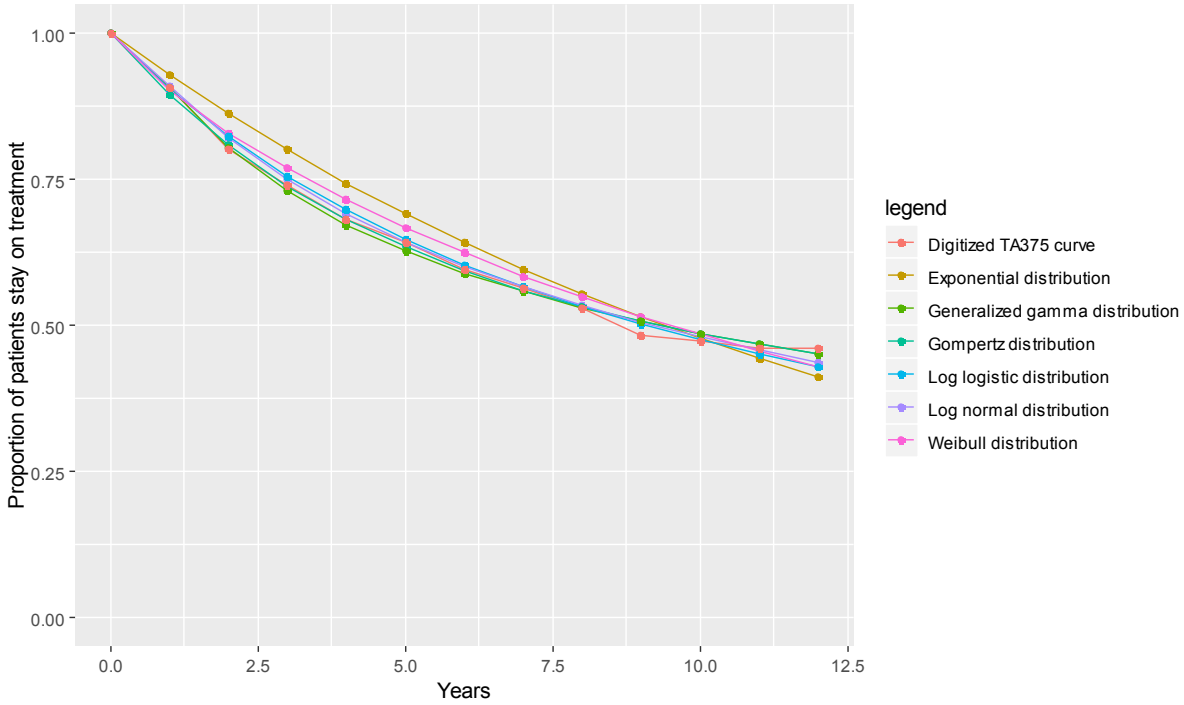


Table 55: Parameters of parametric functions for treatment discontinuation

EULAR Response	Distribution	Parameter[1]	Estimate	SE	AIC	BIC
Good	Generalized gamma	Location	1.704	0.106	9180	9198
		Scale	1.832	0.039		
		Shape	-0.808	0.138		
	Weibull	Shape	0.843	0.021	9345	9357
		Scale	14.626	0.518		
	Log normal	Mean	2.220	0.040	9211	9223
		SD	1.665	0.036		
	Log logistic	Shape	1.022	0.024	9272	9283
		Scale	9.052	0.343		
	Gompertz	Shape	-0.107	0.009	9251	9263
		Rate	0.118	0.005		
	Exponential	Rate	0.074	0.002	9393	9399
Moderate	Generalized gamma	Location	1.337	0.046	25575	25595
		Scale	1.418	0.019		
		Shape	-0.033	0.068		
	Weibull	Shape	0.895	0.011	25774	25787
		Scale	6.834	0.115		
	Log normal	Mean	1.357	0.020	25573	25587
		SD	1.413	0.016		
	Log logistic	Shape	1.170	0.014	25807	25820
		Scale	3.980	0.081		
	Gompertz	Shape	-0.033	0.005	25805	25819
		Rate	0.167	0.004		
	Exponential	Rate	0.145	0.002	25850	25857

Abbreviations: AIC=Akaike information criterion, BIC=Bayesian information criterion, SD=standard deviation, SE=standard error.

[1]Treatment discontinuation parameter estimates were performed in the scale of years using flexsurv package in R (https://cran.r-project.org/web/packages/flexsurv/flexsurv.pdf [Last accessed: March 12 2018]).

B14. Please specify which SELECT trials contribute data to the calculation of Table 56 (p. 144, Company Submission), what their data contributions are, and how this data has been combined to result in the values of Table 56. Please also provide this data split by those with moderate disease at baseline and those with severe disease at baseline.

AbbVie response: The trials with csDMARD-IR patients (SELECT-NEXT, SELECT-MONO, SELECT-COMPARE, and SELECT-SUNRISE) contributed data to the analysis. SELECT trial patients with moderately and severely active RA (DAS28 at baseline >3.2) at baseline were included in the analysis. Patients with missing DAS28 at baseline were not included. Further, included patients had non-missing

HAQ and DAS28 (for estimating EULAR score) data at baseline and at 3 months. EULAR response was calculated based on DAS28 values at 3 months (Week 12/14 [all trials reported at Week 12 except SELECT-MONO, which reported results at Week 14]). Observed data without imputation were used. Patients were classified into good, moderate, or no EULAR responses based on their month 3 response. Change in HAQ score from baseline at 3 months was then summarized for each group using descriptive statistics. Please see below for the results from the csDMARD trials (SELECT-NEXT, SELECT-MONO, SELECT-COMPARE, and SELECT-SUNRISE), presented by disease severity at baseline.

A new analysis was conducted to include SELECT-BEYOND (bDMARD population). The inclusion of SELECT-BEYOND data had a minimal impact on the results. Please see Table 56 for the results from csDMARD and bDMARD trials (SELECT-NEXT, SELECT-MONO, SELECT-COMPARE, SELECT-SUNRISE, and SELECT-BEYOND), presented by disease severity at baseline.

Table 56: Initial HAQ reduction by EULAR response at 3 months

	EULAR response at 3 months	Mean reduction in HAQ	SE
csDMARD-IR patients in SELECT-NEXT, SELECT-MONO, SELECT-COMPARE, and SELECT-SUNRISE			
csDMARD-IR Moderate + Severe RA at baseline (presented in Table 56, p. 144, Company Submission)	Good	0.755	0.019
	Moderate	0.481	0.016
csDMARD-IR Moderate RA at baseline	Good	[redacted]	[redacted]
	Moderate	[redacted]	[redacted]
csDMARD-IR Severe RA at baseline	Good	[redacted]	[redacted]
	Moderate	[redacted]	[redacted]
csDMARD-IR + bDMARD-IR patients in SELECT-NEXT, SELECT-MONO, SELECT-COMPARE, SELECT-SUNRISE and SELECT-BEYOND			
csDMARD-IR + bDMARD-IR Moderate + Severe RA at baseline	Good	0.740	0.018
	Moderate	0.461	0.015
csDMARD-IR + bDMARD-IR Moderate RA at baseline	Good	[redacted]	[redacted]
	Moderate	[redacted]	[redacted]
csDMARD-IR + bDMARD-IR Severe RA at baseline	Good	[redacted]	[redacted]
	Moderate	[redacted]	[redacted]

Abbreviation: SE=standard error.

Table 56 (p. 144, Company Submission) in the company submission was used in a scenario analysis in the cost-effectiveness model. The base-case model informs the initial HAQ changes by EULAR response based on the analysis of the BSRBR-RA database, which was used in TA375.

Model set-up

B15. How should the model be set up to run a cohort of identical patients with characteristics equal to the means? Is it sufficient to set the SD and/or SE of cells D6:F38 of the *Raw – baseline characteristics* worksheet to zero?

AbbVie response: Because the model also considers a variance-covariance matrix between the baseline characteristics, setting the SD and SE values of the baseline characteristics to zero in the *Baseline characteristics* worksheet (or the *Raw - baseline characteristics* worksheet) is not sufficient to create a cohort of identical patients with characteristics equal to the mean values. Instead, to create a cohort of identical patients, the following approach is suggested:

- Select the desired settings on the *Model settings* worksheet (e.g., population, transition from moderate to severe RA).
- On the *Baseline characteristics* worksheet, change the SE for "Female" in cell E16 to zero. This is to ensure that the gender distribution in the final cohort approximates the mean proportion that is reported on this worksheet.
- Return to the *Model settings* worksheet and click the "Generate baseline cohort" button. This creates a patient cohort on the *Cohort* worksheet.
- Next, copy the mean value for each of the baseline characteristics on the *Baseline characteristics* worksheet and paste these values into the relevant columns on the *Cohort* worksheet for each patient. The gender distribution of the cohort will already reflect the mean proportion that is in the *Baseline characteristics* worksheet.
- In cell H6 in the *Cohort* worksheet, which contains the "Time to death" value for the first patient in the cohort, replace the content of this cell with the following formula: "=function_survival(sex, haq, age) * days_per_year". In the formula, replace "sex" with cell E6, replace "haq" with C6, replace "age" with B6, and replace "days_per_year" with 365.25. The resulting formula should look like the following: "=function_survival(E6, C6, B6) *365.25". Drag this formula down column H for all of the patients in the cohort. This uses the

"function_survival" function written in VBA to calculate the patient's time to death with the desired mean values for the relevant baseline characteristics.

- Finally, return to the *Model settings* sheet and click the "Run simulation" button. This run of the model will use the cohort of identical patients with characteristics equal to the means.

B16. Priority question: Ignoring running the DSA and the PSA, which cells within the *Raw - efficacy (12 weeks)* worksheet and the *Raw - efficacy (12 and 24)* worksheet does the VBA model rely upon for (1) the EULAR response estimates for the base case and (2) the ACR response estimates? To explore the effect of differing responses is it sufficient to revise these cells and run the model, and if not what else should be changed? Within the VBA, which if any of the EULAR response categories is treated as a residual to ensure summation to 100% and likewise which if any of the ACR response categories is treated as a residual? To abstract from adverse events is it sufficient to set cells D4:D6 of the *Raw – AEs* worksheet to zero? To change drug and administration costs of a particular treatment is it sufficient to revise the drug specific row entries of columns F, Z and AA of the *Drug costs* worksheet?

AbbVie response: For the EULAR and ACR response estimates, the base case relies upon data pulled from the *Efficacy* worksheet, which in turn pulls data from the following cells within the *Raw - efficacy (12 weeks)* and the *Raw - efficacy (12 and 24)* worksheets:

- For the csDMARD populations:
    - EULAR
        - *Raw - efficacy (12 and 24)* worksheet cells N10:V40
        - *Raw - efficacy (12 weeks)* worksheet cells N10:V34
    - ACR
        - *Raw - efficacy (12 and 24)* worksheet cells C97:O127
        - *Raw - efficacy (12 weeks)* worksheet cells C80:O104
- For the bDMARD populations:

- EULAR
    - *Raw - efficacy (12 and 24)* worksheet cells C10:K24
    - *Raw - efficacy (12 weeks)* worksheet cells C10:K26
- ACR
    - *Raw - efficacy (12 and 24)* worksheet cells C66:O80
    - *Raw - efficacy (12 weeks)* worksheet cells C57:O72

To explore the effect of differing efficacy responses, please use the *Efficacy* worksheet to revise values as desired. The light blue cells are user-modifiable inputs. Revising the inputs on this worksheet and running the model will be sufficient to explore the effects of differing responses. Among the EULAR response categories, the “No Response” category is treated as the residual, which, when added to the “Good Response” and “Moderate Response” categories sums to 100%. Among the ACR response categories, the “<20 ACR” response category, which is calculated as one minus the median ACR20 response, is treated as the residual.

To revise the efficacy inputs, the following approach is suggested:

- Step 1. Confirm model settings: Before updating the efficacy inputs, please ensure that you have specified the scenario settings and treatment sequences in the *Model setting* worksheet.
- Step 2. Confirm efficacy input source: In the *Efficacy* worksheet, please confirm that the “Base-case NMA” option is selected in the “Source of efficacy inputs” dropdown.
- Step 3. Refresh efficacy table to reflect treatment sequence settings: In the *Efficacy* worksheet, press the “Refresh sequences” button to view default efficacy values for all treatments specified in the *Model setting* worksheet.
- Step 4. Enter user-defined efficacy inputs: In the *Efficacy* worksheet, revise the efficacy values directly in the blue cells.

- Step 5. Run scenario analysis: Press the “Run simulation” button in the *Model setting* worksheet to initiate the simulation for the desired scenario.

To abstract from adverse events, it is sufficient to set the light blue cells from D18:D68 on the *Adverse Events* worksheet to zero. These cells are user-modifiable and will be used in the running of the model once revised.

To change drug and administration costs of a particular treatment, it would be sufficient to revise the light blue cells on both the *Drug costs* (for first 6 months costs: Z11:Z76, or for subsequent annual costs: AA11:AA67) and *Admin costs* (cells E5:E7) worksheets. These blue cells are user-modifiable inputs, which, once revised, will be considered in the running of the model.

B17. Priority question: Please provide an account of the model settings and what changes need to be made to the submitted model to replicate the results of tables 66 to 81, Table 86 scenarios 2, 3, 87 and 88, separately for each table of results. If any of these cannot be implemented by changing the submitted model please provide additional electronic models, outlining how these differ from the submitted model with full cell and/or VB code referencing. When running the model deterministically are all sampled values replicated between model runs, or may sampling lead to some variation in results between model runs with the same model settings?

AbbVie response: In order to replicate the deterministic base case model results, please use the submitted model, set up the base case model settings (listed below), and select the treatment sequences as listed in Table 34 to 47. Every time when you switch the patient population, please click on “Generate baseline cohort” button before running the model simulations. A patient cohort will be created according to the baseline characteristics of the selected patient population. All sampled values were replicated between model runs, so the baseline characteristics for the generated patient cohort and model results will always be the same with the same model settings. The deterministic results are reproducible, and all of these can be implemented by changing the submitted model.

The model settings used to generate deterministic results (Table 66 to Table 81) are listed below:

- Transition from moderate to severe RA – “Consider transition to severe RA” for moderate RA patient population, “Do not consider transition to severe RA” for severe RA patient population.
- Time horizon – 45 years
- Response criteria – EULAR
- Size of cohort – 10,000
- Discount rate- 3.5% for both costs and efficacy
- Change in HAQ during first 6 months – Change occurs at 6 months
- Indirect costs – Do not consider indirect costs
- Treatment discontinuation distribution – Gamma
- Monitoring cost for BSC – Yes
- Switch cDMARD severe population to moderate-to-severe population – No

To generate scenario analysis results for scenario 2 and 3 (Table 86), the inputs need to be changed manually in the submitted model.

- Scenario 2: please change the efficacy data in the “Efficacy” tab (col K:L) using the efficacy data listed in the table below (also saved in the “Raw – DSA EULAR response (trial)” tab):

Treatment	EULAR good response	EULAR moderate response
cDMARD	[redacted]	[redacted]
Intensive cDMARD	[redacted]	[redacted]
MTX	[redacted]	[redacted]
UPA 15mg	[redacted]	[redacted]
UPA 15mg + MTX	[redacted]	[redacted]

Source: SELECT trials

- Scenario 3: please change the pain to HAQ mapping algorithm in the “Utility” tab (G3:J29) using mapping algorithm listed in the table below:

Pain to HAQ mapping			
HAQ score	**Pain score (VAS)**	**SE**	**Pain score (VAS) used in DSA**
0	11.83	0.76	11.83
0.125	18.32	1.45	18.32
0.25	19.38	1.33	19.38
0.375	22.57	1.37	22.57
0.5	24.95	1.29	24.95
0.625	27.64	1.35	27.64
0.75	30.46	1.18	30.46
0.875	32.40	1.21	32.40
1	35.20	1	35.20
1.125	37.55	1.01	37.55
1.25	41.38	1.06	41.38
1.375	44.07	1.03	44.07
1.5	46.83	0.98	46.83
1.625	50.07	0.93	50.07
1.75	53.29	0.89	53.29
1.875	55.40	0.95	55.40
2	57.41	0.82	57.41
2.125	58.93	1.1	58.93
2.25	61.82	1.22	61.82
2.375	63.94	1.46	63.94
2.5	67.75	1.44	67.75
2.625	69.33	2.01	69.33
2.75	67.73	1.98	67.73
2.875	61.37	2.71	61.37
3	58.02	2.62	58.02

Source: TA375

Further clarification requested following clarification question call: Could the company double check and confirm that nothing other than the changes outlined in the response to B17 needs revision in the submitted model to enable the ERG to generate the results reported for all the base cases and for the scenario analyses requested?

• The upadacitinib PAS has to be entered in Y67 of the Drug Costs worksheet. To the ERG this suggests that the company may not have run through the submitted

model and cross checked that the changes outlined under its response to B17 do actually result in the results reported in Document B.

• The ERG has not managed to replicate the results of Table 71. There are three QALY gains suggests: 0.795 within the text, a different CIC value within table 71 and a third CIC value within table 84 of the appendices. ERG work suggests that the 0.795 estimate is correct, but that this is within the context of a model with an ICER that differs from that of table 71.

• The ERG had previously not managed to replicate the results of Table 80, but following the instructions in the response to B17 does yield the results of Table 80 in the Model Results worksheet. But the results in the Efficiency Frontier worksheet fails to update. This may be in part due to the model running sequences 12, 13 and possibly beyond despite these sequences having been set to be empty in the relevant drop downs of the Model Settings worksheet (rows 54 onwards). The ERG would be grateful if this could be checked, and also if the company could confirm how to revise a model run with e.g. 10 sequences to have fewer e.g. only 5 sequences and the other sequences (6-10) set to be empty and not to run.

• Prior to receipt of the response to B17, when replicating the results of tables 66-81, excluding those of tables 71 and 72, the ERG has previously had to revise the clinical effectiveness estimates within the Efficacy worksheet to reflect the assumptions of equivalent clinical efficacy as stated in the footers to tables 34-47. The ERG would be grateful if the company could confirm that within the submitted model all clinical effectiveness estimates are updated automatically to reflect the assumptions of equivalent clinical efficacy as stated in the footers to tables 34-47 when the treatment sequences of tables 34-47 are applied, the appropriate population selected and the cohort generated; i.e. to generate the results of tables 66-81 there is no requirement to alter any values in the Efficacy worksheet

AbbVie response to further clarification:

- The drug costs for upadacitinib need to be changed in the "Drug Costs" worksheet. To set to a cost of [redacted] (original submission) set Z67 to [redacted] and AA67 to [redacted] and to set a cost of [redacted] (price used in clarification questions and cost effectiveness analysis to be re-submitted by 30th August 2019) set Z67 to [redacted] and AA67 to [redacted].

- The CIC in Table 71 is correct – 0.826. The CIC in the text and in the appendix are wrong. The model has now been updated according to the clarification questions, please refer to the answers to question B22 where the updated model results for moderate patients are presented.

- All the results should be updated in the efficiency frontier table after each simulation. However, sometimes the efficiency frontier table doesn't show all the comparators, and the user would need to manually unhide all the rows.

- Currently, the efficacy assumptions cannot be automatically updated. The users need to manually change the efficacy data to reflect the assumptions.

B18. How should the model be set up to prevent HAQ worsening for those on csDMARDs? How should the model be set up to prevent HAQ worsening for those on BSC if this differs?

AbbVie response: AbbVie will provide a response to this question by 15th August.

Model results

B19. Please provide an excel spreadsheet that graphs (a) the modelled proportion of surviving patients and (b) the modelled proportion of surviving patients on BSC for each sequence modelled, grouping these as per the results tables of Document B; i.e. 2 graphs per results table, together with the underlying graph data.

AbbVie response: In the re-submission model, updates were made to plot (a) the modelled proportion of surviving patients, and (b) the modelled proportion of surviving patients on BSC. In particular, two VBA functions, "tte_calc" and "tte_plot" were added in the simulation_run module to generate trajectories of the proportion of survived patients and the proportion of patients remaining on their first-line

treatment, and the proportion remaining on BSC. After running the simulation model for a selected population and treatment sequences, these proportions will be available for all treatment sequences and stored in the *tte plot data* worksheet. A figure with the survival and pair-wise time on treatment trajectories was added to the *Model Results* worksheet. The comparator and reference dropdown menus in the *Model Results* worksheet can be used to dynamically view the pair-wise trajectory plot.

The plots and underlying data are shown in the Excel spreadsheet submitted alongside the response to the clarification questions.

B20. For the modelling of moderate RA patients, for each treatment sequence please graph over time and present the graph data within an excel spreadsheet the proportion of surviving patients modelled as having severe RA.

AbbVie response: In the re-submission model, VBA functions “tte_calc” and “tte_plot” described in B19 response, can be used to plot the proportion of patients who have transitioned from moderate to severe RA. The data is stored in the *tte plot data* worksheet after simulating the moderate RA population. For the moderate RA population, the trajectories of the proportion who transitioned to severe RA was also plotted in the dynamic figure described in B19 response in the *Model Results* worksheet.

The plots and underlying data are shown in the Excel spreadsheet submitted alongside the response to the clarification questions.

B21. Please augment Table 84 (p. 179, Company Submission) with the probabilities of cost effectiveness at £20k/Q and at 30k/Q for the most cost-effective comparator at each population position evaluated.

AbbVie response: AbbVie will include this analysis as part of the addendum to the original submission.

B22. Priority question: The company submission Document A section A13 presents the numerical outputs of the modelling among moderate RA patients, but Document A section A17 does not appear to provide any company interpretation of these results. Please provide this. Given the model estimates, does the company accept that when judged solely on cost-effectiveness criteria UPA and UPA+MTX are not cost effective at conventional NICE thresholds across moderate RA patients as a group?

AbbVie response: The submission included a PAS price equating to an annual drug acquisition cost for upadacitinib of [redacted]. Considering the question of cost-effectiveness and given the high unmet need for patient access to effective treatment options in moderate RA, access to upadacitinib for these patients is essential. AbbVie has therefore revised the PAS price to an annual drug acquisition cost for upadacitinib of [redacted] in an effort to expand patient access and increase healthcare professionals treatment options to a cost-effective medicine for moderate RA. At this price, using the base case analysis approach presented in the NICE submission, both upadacitinib monotherapy and combination therapy are cost effective across all moderate RA patient groups.

The revised analyses based on this price will be submitted as an addendum as per the discussion with NICE.

Model validation

B23. Please present 3-month and 6-month model validation data for the change in HAQ and change in EQ-5D modelled for UPA, UPA+csDAMRD, ADA, ADA+csDAMRD alongside ≈3 month (control cross-over) and 6 month data for the SELECT trials arms: UPA, UPA+csDAMRD, control, control+csDMARD and placebo as available.

AbbVie response: AbbVie will provide a response to this question by 15th August.

B24. Priority question: What additional assumptions are necessary to arrive at the estimates of tables 78 and 79 (p. 171, Company Submission) compared to the other modelling among severe RA patients? For model validation purposes, to what extent can the same assumptions that have been made for upadacitinib at this position also be made for (1) baracitinib and (2) tofaticitinib? What are the resulting deterministic cost-effectiveness estimates from making these assumptions for (1) baracitinib and (2) tofaticitinib?

AbbVie response: The treatment sequences outlined in Table 57 below are used to generate the ICERs presented in Tables 78 and 79 in the original submission. These relate to third line therapy for severe RA patients who fail first line advanced therapy and being eligible for rituximab receive that second line. The only two therapies to date to be recommended by NICE for third line treatment are sarilumab and tocilizumab both as combination therapy.

Table 57: 6. Treatment sequences considered in severely active RA, RTX- IR population

Sequence	First-line treatment	Second-line treatment	Third-line treatment
1	UPA + MTX	MTX	BSC
2	UPA*	MTX	BSC
3	SRL + MTX	MTX	BSC
4	TCZ + MTX	MTX	BSC

Abbreviations: BSC=best supportive care; IR=inadequate response; IV=intravenous infusion; MTX=methotrexate; N/A=not applicable; RTX=rituximab; SC=subcutaneous injection; SRL=sarilumab; TCZ=tocilizumab; UPA=upadacitinib.

*Assume same efficacy as BRC+MTX (from bDMARD-IR NMA)

Different treatment sequences (shown below in Table 58) were used for the ICERs generated for Tables 76 and 77 in the original submission. The ICERs in Tables 76 and 77 were for first line advanced therapy failure patients in those not eligible for rituximab combination therapy (ie. It was contraindicated or patients were intolerant to it) as opposed to those who had taken rituximab combination therapy and had discontinued for efficacy reasons.

Table 58: 4b. Treatment sequences considered after failure of first line advanced therapy in MTX eligible patients (RTX ineligible)

Sequence	First-line treatment	Second-line treatment	Third-line treatment	Fourth-line treatment
1	UPA + MTX	TCZ IV + MTX	MTX	BSC

Sequence	First-line treatment	Second-line treatment	Third-line treatment	Fourth-line treatment
2	UPA	TCZ IV + MTX	MTX	BSC
3	ABT IV + MTX	TCZ IV + MTX	MTX	BSC
4	ABT SC + MTX*	TCZ IV + MTX	MTX	BSC
5	ADA + MTX**	TCZ IV + MTX	MTX	BSC
6	BRC + MTX	TCZ IV + MTX	MTX	BSC
7	CTZ + MTX	TCZ IV + MTX	MTX	BSC
8	GOL + MTX	TCZ IV + MTX	MTX	BSC
9	ETN + MTX	TCZ IV + MTX	MTX	BSC
10	IFX + MTX	TCZ IV + MTX	MTX	BSC
11	SRL + MTX	TCZ IV + MTX	MTX	BSC
12	TCZ IV + MTX	SRL + MTX	MTX	BSC
13	TCZ SC + MTX	SRL + MTX	MTX	BSC
14	TFC + MTX	TCZ IV + MTX	MTX	BSC

For the rituximab failure patient analysis the population chosen in the model settings was “bDMARD-IR RTX eligible”. The baseline characteristics of these patients though is the same as for “bDMARD-IR RTX ineligible” patients.

ICERs for following cost-effectiveness analysis including baricitinib are shown Table 59 and Table 60:

Table 59: 6. Treatment sequences considered in severely active RA, RTX- IR population

First-line treatment	Second-line treatment	Third-line treatment
BRC + MTX	MTX	BSC
SRL + MTX	MTX	BSC
TCZ + MTX	MTX	BSC

Table 60: 6. Severely active RA, RTX- IR population

Technologies	Total costs (£)	Total QALYs	Total LYG	Full incremental costs (£)	Full incremental QALYs	Full incremental ICER (£/QALY)
BRC + MTX	[redacted]	[redacted]	13.4	[redacted]	[redacted]	-
SRL + MTX	[redacted]	[redacted]	13.4	[redacted]	[redacted]	£217,348
TCZ IV + MTX	[redacted]	[redacted]	13.4	[redacted]	[redacted]	£114,659

ICERs for following cost-effectiveness analysis including tofacitinib are shown Table 61 and Table 62:

Table 61: 6. Treatment sequences considered in severely active RA, RTX- IR population

First-line treatment	Second-line treatment	Third-line treatment
TFC + MTX	MTX	BSC
SRL + MTX	MTX	BSC
TCZ + MTX	MTX	BSC

Table 62: 6. Severely active RA, RTX- IR population

Technologies	Total costs (£)	Total QALYs	Total LYG	Full incremental costs (£)	Full incremental QALYs	Full incremental ICER (£/QALY)
TFC + MTX	[redacted]	[redacted]	13.4	[redacted]	[redacted]	-
SRL + MTX	[redacted]	[redacted]	13.4	[redacted]	[redacted]	£194,901
TCZ IV + MTX	[redacted]	[redacted]	13.4	[redacted]	[redacted]	£129,658

The ICERs shown for both tofacitinib and baricitinib above indicate that they would (using the AbbVie model and their list prices) have been cost effective in rituximab failure patients. However neither the manufacturers of baricitinib nor tofacitinib submitted a cost effectiveness analysis for use in this population in their respective NICE appraisals. The manufacturer of sarilumab did submit such an analysis for use in this population to NICE (and was subsequently recommended for use in this population). The sarilumab manufacturer submission made similar assumptions to those made by AbbVie: Efficacy from an advanced therapy failure NMA was used to populate efficacy assumptions for rituximab failure patients. A bDMARD experienced patient study in sarilumab's case TARGET, in upadacitinib's SELECT-BEYOND was used to populate the appraised drug's efficacy estimate incorporated into the advanced therapy failure NMA in both cases.

Section C: Textual clarification and additional points

C1. Please provide the Clinical Study Report for the SELECT-SUNRISE trial

AbbVie response: This will be uploaded as a separate file on NICE Docs alongside this response.

B4. Please present a more detailed model schematic that includes the possible transitions from moderate to severe disease and from severe disease to moderate, and outline which analyses/results tables permit which of these transitions. Also:

Within the modelling of moderate RA patients, if these patients transition to severe RA but subsequently transition back to moderate RA, what is assumed in terms of their treatment sequence from the point at which they have returned to moderate RA?

Similarly, within the modelling of severe RA patients, if these patients transition to moderate RA what is assumed in terms of their treatment sequence from the point at which they transition to moderate RA?

Amended question from ERG: "Within the modelling of moderate RA patients, these patients can transition to severe RA. We would be grateful for more information about how this is modelled, particularly in the light of the model apparently being driven by the evolution of HAQ. Please describe how the model decides when a moderate patient becomes severe, and whether any patient variables in addition to the HAQ need to be tracked for this estimation. Please provide the required functional forms that are required to model estimating if and when a moderate patient becomes severe, together with full referencing to the original source data. Please provide the alternative functional forms that were also estimated (if any) together with the reasons for their rejection (as applicable) and the reasons for the selection of the final functional form. Please provide an excel spreadsheet with worked examples of the modelling of time to worsening from moderate to severe for hypothetical patient(s) sufficient to provide a clear understanding of the inputs and how they are applied within this modelling to estimate both if and when a patient transitions from moderate to severe. The ERG would also be grateful if this spreadsheet could be further augmented with worked examples in Excel of the resulting EULAR responses, given the NMA results of tables 25 and 27, and HAQ changes at each change of

treatment specifically for sequence 1 and sequence 2 for the 1a Tables 36 and 37 patient population"

AbbVie response: The model simulates patients' transitions from moderate RA to severe RA. The model does not explicitly simulate patients' transition from severe RA back to moderate RA. Figure 1 below provides a more detailed model schematic to illustrate the modelling process.

Moderate RA to severe RA transition is considered in the model: DAS28 is used to evaluate patients' disease severity in the model. The model does not track DAS28 directly. Instead, DAS28 is estimated from HAQ score, which is tracked in the model. In particular, DAS28 is estimated using the baseline DAS28 value and change in DAS28 value. Change in DAS28 is informed by the change in HAQ score, based on the relationship estimated using data from the phase 3 SELECT trials. Specifically, csDMARD-IR patients with moderately active RA (DAS28 at baseline [>3.2 and ≤ 5.1]) from the SELECT-NEXT, SELECT-COMPARE, SELECT-MONO, and SELECT-SUNRISE trials were used to inform the relationship between change in DAS28 value and change in HAQ value. Patients were excluded if they had missing DAS28 and HAQ at baseline. In addition, patients without either DAS28 or HAQ value at 3 months (or 6 months for SELECT-COMPARE only) were excluded. Observed data without imputation were used for the analysis. A linear mixed effects model was constructed to estimate the change in DAS28 from baseline at 3 or 6 months based on the change in HAQ from baseline at 3 or 6 months. A random intercept by patient was included to account for repeated measurements. The coefficient for change in DAS regressed on change in HAQ from the model was used in the cost-effectiveness model to inform DAS change by HAQ change.

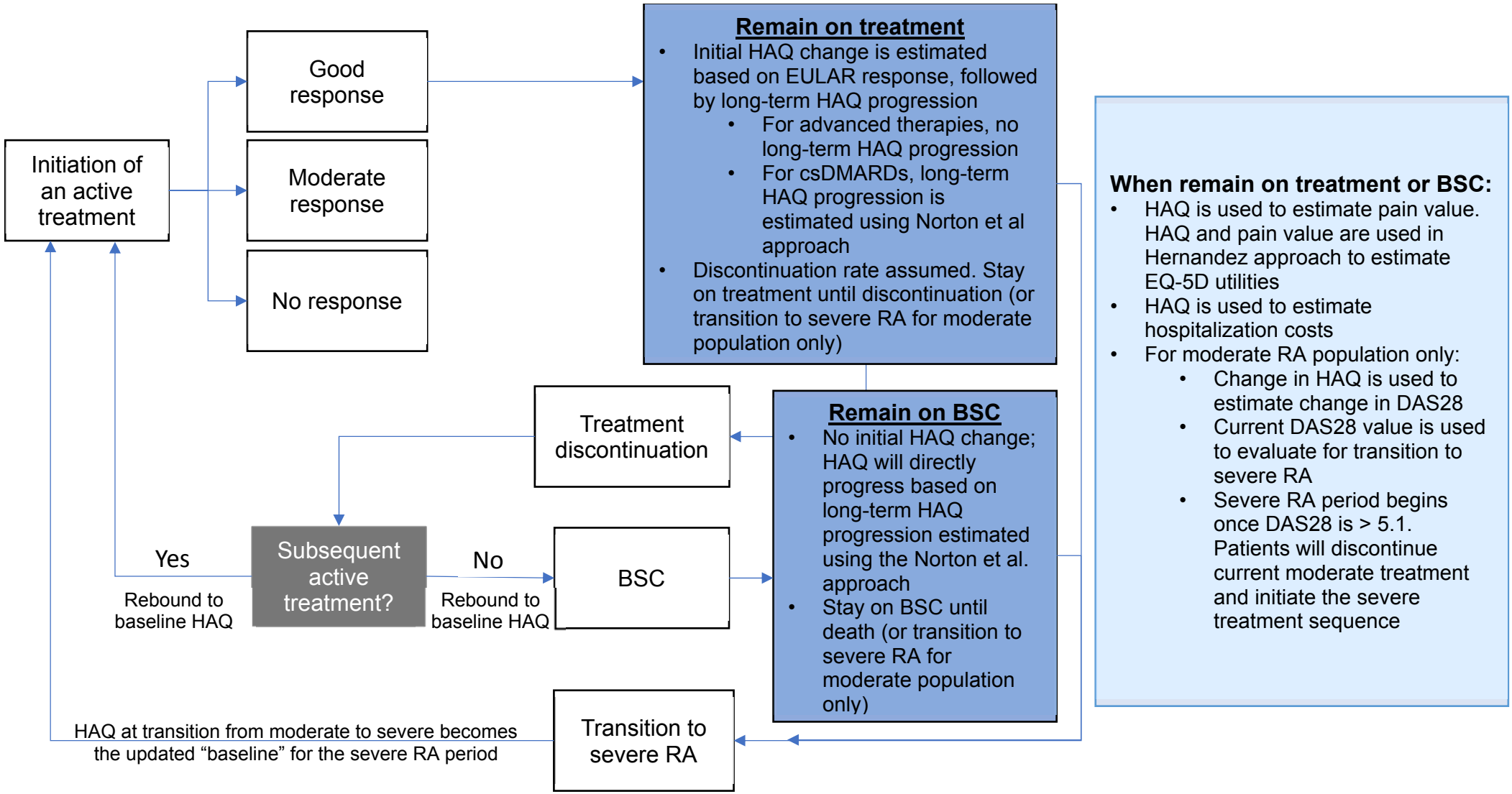
In the cost-effectiveness model, with each update of the HAQ score (referred to in response B6), the respective DAS28 value will be updated as well, which was calculated based on their baseline DAS28 and estimated change in DAS28 score (estimated from change in DAS28). The updated DAS28 value will be evaluated to see if it reaches the severe RA threshold (DAS28 >5.1). Once the DAS28 value exceeds the severe threshold, patients will initiate the severe treatment sequence, and their HAQ value at the time of transition will become the updated "baseline" HAQ

for the severe period. The schematic below outlines patients' possible transition from moderate to severe RA.

Severe RA to moderate RA transition is not considered in the model: In the model, once the patient's disease severity becomes severe, their HAQ score at the time of progression becomes the updated "baseline" HAQ score for the severe period. Patients with severe RA can experience HAQ improvement following active treatment, however, this improvement would be lost upon treatment discontinuation. At the time of discontinuation, patients' HAQ score would rebound to the "baseline" HAQ score for the severe period, which means patients would remain in the severe RA state. Patients would then continue to the next treatment in the severe RA sequence. In this sense, the model does not explicitly model the transition from severe RA to moderate RA.

Worked example illustrating HAQ progression: A worked example that illustrates the HAQ progression algorithm is documented in the *HAQ progression* worksheet in the worked examples spreadsheet. The VBA function, "haq_trajectory," that carries out the HAQ progression algorithm can be found in the fnct_haq_adjust module. Another Excel file has also been shared to further demonstrate, using hypothetical patients, how the transition from moderate RA to severe RA works and is included in the worked examples spreadsheet. This Excel file also illustrates the patients' treatment sequences and HAQ changes over time.

Figure 1: Model Schematic



The model uses a map between HAQ-DI and DAS-28 to identify the point at which patients with moderate RA (defined as DAS 28 3.2 to <5.1) progress to a point at which DAS 28 equates to a score >5.1 (severe RA is defined as >5.1). This approach was defined by the ERG in the appraisal of sarilumab and agreed by the Appraisal Committee. The model used by AbbVie is based on the model and the associated assumptions about HAQ trajectory developed by the ScHARR ERG to support the MTA TA375 (used subsequent RA drug NICE appraisals including that for sarilumab). These HAQ trajectory assumptions are that after the initial treatment impact in which HAQ-DI will improve, HAQ-DI can stay the same or progress but it does not regress (a higher HAQ-DI score corresponds to higher disease severity). There is a positive correlation between HAQ-DI and DAS 28. The model only tracks for the purpose of determining treatment initiation whether patients transition from moderate to severe RA. Patients with severe RA may as a result of the impact of treatment show an improvement in HAQ-DI which theoretically equates to a DAS 28 score corresponding to moderate RA; however this is not tracked within the model since unlike the transition from moderate to severe RA this has no purpose in determining treatment initiation.

- **Within the modelling of moderate RA patients, if these patients transition to severe RA but subsequently transition back to moderate RA, what is assumed in terms of their treatment sequence from the point at which they have returned to moderate RA?**

As stated above the model used by AbbVie is based on the model and the associated assumptions about HAQ trajectory developed by the ScHARR ERG to support the MTA TA375 (used subsequent RA drug NICE appraisals including that for sarilumab). These HAQ trajectory assumptions are that after the initial treatment impact in which HAQ-DI will decrease (improve), HAQ-DI stays the same on advanced therapies and it increases on csDMARDs (and BSC) (a higher HAQ-DI score corresponds to higher disease severity). Apart from the impact of initial treatment, HAQ-DI scores do not decrease. There is a positive correlation between HAQ-DI and DAS 28. If a patient transitions from moderate RA to severe RA he may as a result of the impact of treatment show a decrease in HAQ-DI which theoretically equates to a DAS 28 score corresponding to moderate RA; however this is not tracked within the model since it has no purpose in determining treatment initiation.

The only way that HAQ-DI can decrease (improve) (and hence the DAS 28 score become less severe) is through the initial impact of treatment.

- **Similarly, within the modelling of severe RA patients, if these patients transition to moderate RA what is assumed in terms of their treatment sequence from the point at which they transition to moderate RA?**

As stated above the model used by AbbVie is based on the model and the associated assumptions about HAQ trajectory developed by the ScHARR ERG to support the MTA TA375 (used in subsequent RA drug NICE appraisals including that for sarilumab). These HAQ trajectory assumptions are that after the initial treatment impact in which HAQ-DI will decrease (improve), HAQ-DI stays the same on advanced therapies and it increases on csDMARDs (and BSC) (a higher HAQ-DI score corresponds to higher disease severity). Apart from the impact of initial treatment, HAQ-DI scores do not decrease. There is a positive correlation between HAQ-DI and DAS 28. A patient with severe RA may as a result of the impact of treatment show a decrease in HAQ-DI which theoretically equates to a DAS 28 score corresponding to moderate RA; however this is not tracked within the model since it has no purpose in determining treatment initiation. The only way that HAQ-DI can decrease (improve) (and hence the DAS 28 score become less severe) is through the initial impact of treatment.

B18. How should the model be set up to prevent HAQ worsening for those on csDMARDs? How should the model be set up to prevent HAQ worsening for those on BSC if this differs?

AbbVie response: In the re-submitted model, the flexibility to test alternative assumptions about HAQ worsening to the AbbVie (TA375) base case HE model were added. Two dropdown menus for “HAQ progression for csDMARD” and “HAQ progression for BSC” with three options “TA375 base case progression” (this was used as the base case in the AbbVie submission) and “No progression” and “TA375 sensitivity analysis progression” have been added to the *Model settings* worksheet to provide different assumptions on HAQ worsening for csDMARDs and BSC. The third option of “TA375 sensitivity analysis progression” assumed an annual linear HAQ

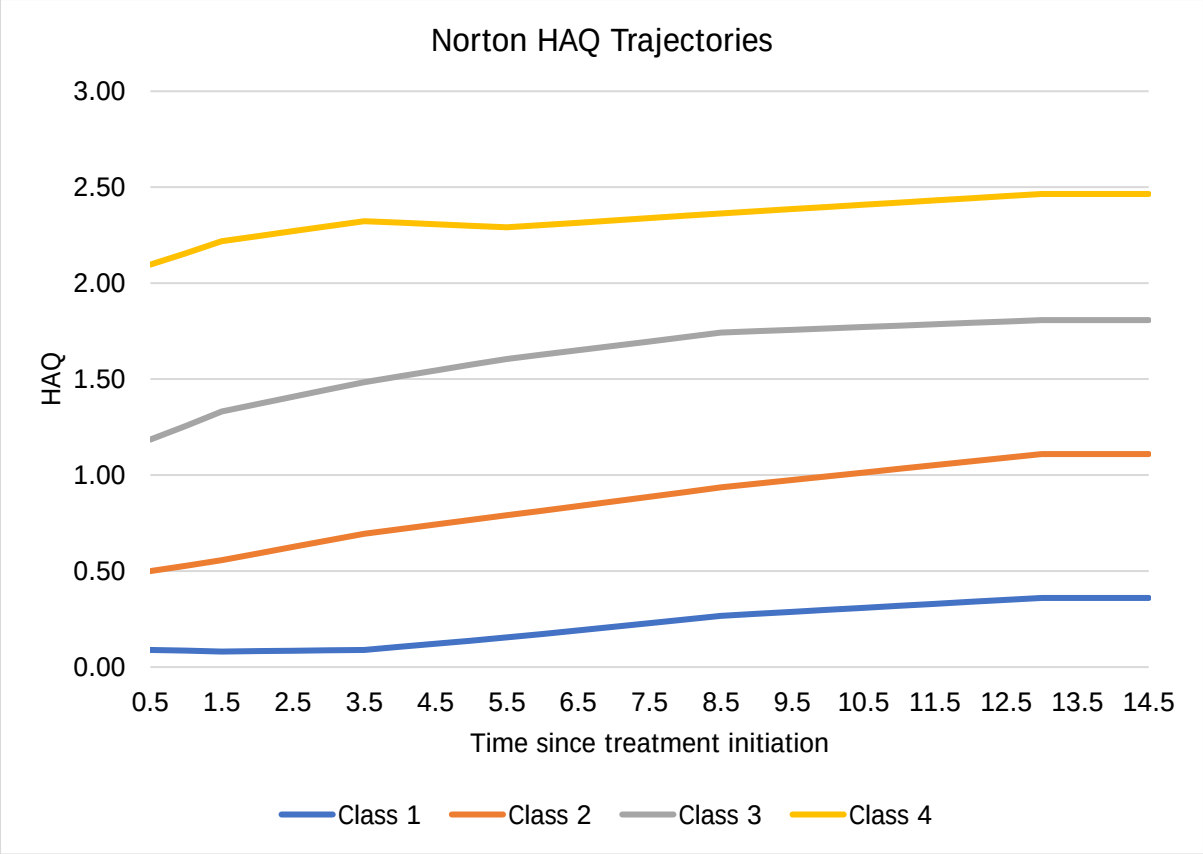
progression of 0.045 for csDMARDs and 0.06 for BSC. This was based on studies at the time of TA375 which reported similar rates which are covered in more detail below.

It is well documented that HAQ will continue to progress for patients who are on csDMARD and BSC, and this assumption was used in TA375 and all prior and subsequent RA submissions. TA375[1] also conducted an evaluation of different approaches to model HAQ progression while on csDMARD, and have suggested the Norton et al. approach[1]. Beyond Norton et al, three publications were identified by TA375[1] which reported HAQ trajectory while patients receiving csDMARD. The annual HAQ change reported in the three publications ranges from 0.05 to 0.08 (Table 170 of TA375[1] reproduced below).

Publication	**Number of patients analysed**	**cDMARDs**	**Mean follow up (years)**	**Average HAQ progression per annum**
Plant et al[2]	421	Hydroxychloroquine, sodium aurothimalate, auranofin and pencillamine	5	0.08 (from years 1 to 5)
Symmons et al[3]	466	Intensive csDMARDs	3	0.06
Munro et al[4]	440	Intramuscular gold	5	0.05 (from years 2 to 5)

Because Norton et al used data from a large, UK-based, prospective, observational data with patients followed for 10 years (n=1460) and the findings from Norton et al was validated in a separate database[5], TA375 concluded that it is a more reliable data source to predict HAQ trajectory for patients on csDMARD and BSC. The Norton et al. based HAQ progression approach were also used in baricitinib and tofacitinib RA NICE submissions. In the sarilumab RA submission, the company assumed a linear HAQ progression of 0.06 per year, whereas the ERG suggested that the non-linear HAQ progression using the Norton approach would be more appropriate. In all the situations, regardless of which approach to be used, HAQ is assumed to progress while patients receiving on csDMARD and BSC.

It should also be noted that using the Norton et al approach moderate RA and severe RA patients in the AbbVie base case HE model would reflect different rates of HAQ progression on csDMARDs or BSC. This is because each patient simulated in the model is allocated a probability of belonging to four latent classes. Each of these classes has a different HAQ trajectory as shown by the curves below. This allocation process is dependent upon a number of baseline characteristics of these patients including DAS 28 and current disease duration. The differing DAS 28 score profiles and disease duration for patients receiving BSC or csDMARD result in different latent class allocation profiles and consequently different HAQ trajectory profiles.



AbbVie would strongly advise against any assumption assuming there is no HAQ progression on BSC and csDMARD since these are not supported by clinical evidence. Furthermore, the use of Norton et al as used in TA375 and the AbbVie base case model has substantial scientific support and has been identified as a robust modelling assumption in a number of NICE Appraisals.

B23. Please present 3-month and 6-month model validation data for the change in HAQ and change in EQ-5D modelled for UPA, UPA+csDAMRD, ADA, ADA+csDAMRD alongside ≈3 month (control cross-over) and 6 month data for the SELECT trials arms: UPA, UPA+csDAMRD, control, control+csDMARD and placebo as available.

AbbVie response:

A version of the model only to be used to generate HAQ output at 6 months has been provided in response to this answer. For the HAQ at 6 months data, data was first exported for each individual's HAQ after evaluating their EULAR response during the simulation (stored in tte plot data pop X worksheets, variables started with HAQ6m followed with their first-line treatment label, e.g., HAQ6m_UPA 15mg + MTX). A calculation was made of the the average HAQ at 6 months for the simulated population (stored in tte plot data pop X worksheets, in row 10002 of each HAQ6m columns) and presented in the Model Results worksheet. For each individual, their HAQ at 6 months include the following scenarios:

- Patients who died before 6 months: baseline HAQ is exported
- No response: baseline HAQ is exported
- Moderate response: Maximum of (0, modified(baseline HAQ - 0.317))
- Good response: Maximum of (0, modified(baseline HAQ - 0.671))

Validation using moderate to severe RA output

QALY output at 6 months for moderate and severe population (set in "Model Settings" by setting drop down menu for "Switch cDMARD severe population to moderate-to-severe population" to "Yes") shown in Table 2 and Table 3 below. To show a QALY change at 6 months the model was set so that HAQ change (and associated QALY change occurred at treatment initiation. Setting HAQ change to occur at 6 months (in line with the base case analysis) would lead to no QALY change occurring due to drug

efficacy in the first six months. Treatment sequences used are summarised below (for csDMARD-=IR population – used to validate SELECT-COMPARE, SELECT-NEXT and SELECT-MONOTHERAPY output). A bDMARD-IR RTX ineligible population severe RA is used to validate SELECT-BEYOND output – this analysis is shown in a separate validation using the severe population shown below:

Table 1: cDMARD-IR setting

First-line treatment	Second-line treatment
UPA + MTX	BSC
UPA mono	BSC
ADA + MTX	BSC
MTX	BSC
csDMARD	BSC
Intensive csDMARD	BSC

Table 2: Three month trial data (change in EQ-5D-5L from baseline) compared to QALY change in HE model output at 6 months (moderate and severe population)

	SELECT-COMPARE			SELECT-NEXT		SELECT-MONOTHERAPY	
	PBO + MTX	ADA + MTX	UPA 15mg + MTX	PBO + csDMARD	UPA 15 mg + csDMARD	MTX	UPA 15 mg
3 month trial data (QALY change from baseline)	0.104	0.174	0.208	0.078	0.186	0.079	0.159
3month trial data (difference between UPA and comparators)	-0.104	-0.034		-0.108		-0.08	
6 month HE model output (difference between UPA and comparators)	-0.038*	-0.006		-0.038*/ -0.028**		-0.038*	

***csDMARD / MTX and **intensive csDMARD**

Table 3: Six month trial data (change in EQ-5D-5L from baseline) compared to QALY change in HE model output at 6 months (moderate and severe population)

	SELECT-COMPARE		
	PBO + MTX	ADA + MTX	UPA 15mg + MTX
6 month trial data (QALY change)	0.111	0.205	0.220
6month trial data (difference between UPA and comparators)	-0.109	-0.015	
6 month HE model output (difference between UPA and comparators)	-0.038*	-0.006	

***csDMARD / MTX**

The adjustment of the 6-month quality adjusted output from the model to estimate QALYs (and hence QALY differences is shown in Table 4

Table 4: Moderate and severe population

	Quality adjusted output at 6 months	LYG (at 6 mths)	Estimated full year QALY (quality adjusted output at 6 months / LYG at 6 months)	Difference in QALYs (UPA combo compared to other treatments)
UPA combo	0.301	0.498	0.604	
UPA mono	0.298	0.498	0.598	-0.006
ADA combo	0.298	0.498	0.598	-0.006
MTX / csDMARD	0.282	0.498	0.566	-0.038
intensive csDMARD	0.287	0.498	0.576	-0.028

Table 5: 3 month trial data (change in HAQ from baseline) compared to calculated change in HAQ HE model output at 6 months (moderate and severe population)

	SELECT-COMPARE			SELECT-NEXT		SELECT-MONOTHERAPY	
	PBO + MTX	ADA + MTX	UPA 15mg + MTX	PBO + csDMARD	UPA 15 mg + csDMARD	MTX	UPA 15 mg
3 month trial data	-0.281	-0.492	-0.598	-0.257	-0.606	-0.321	-0.652
HE model output (baseline HAQ)	1.520	1.520	1.520	1.520	1.520	1.520	1.520
HE model (HAQ at 6 months)	1.317	1.195	1.169	1.317/ 1.282	1.169	1.317	1.195
Change from baseline (at 6 months)- HE model	-0.203*	-0.325	-0.351	-0.203* / -0.238**	-0.351	-0.203*	-0.325

***csDMARD / MTX and **intensive csDMARD**

Table 6: 6 month trial data (change in HAQ from baseline) compared to calculated change in HAQ HE model output at 6 months (moderate and severe population)

	SELECT-COMPARE		
	PBO + MTX	ADA + MTX	UPA 15mg + MTX
6 month trial data	-0.332	-0.574	-0.692
HE model output (baseline HAQ)	1.520	1.520	1.520
HE model (HAQ at 6 months)	1.317	1.195	1.169
Change from baseline (at 6 months)- HE model	-0.203*	-0.325	-0.351

***csDMARD / MTX**

Validation using moderate RA population output

An additional validation exercise has been completed specifically for the moderate RA population. SELECT-BEYOND has been excluded from this validation exercise because it relates to a bDMARD-IR population which is not relevant to moderate RA where at present no advanced therapies are used.

QALY output at 6 months for moderate population (csDMARD-IR with transition to severe RA set to "No") is shown in Table 7 and Table 8 below. To show a QALY change at 6 months the model was set so that HAQ change (and associated QALY change occurred at treatment initiation. Setting HAQ change to occur at 6 months (in line with the base case analysis) would lead to no QALY change occurring due to drug efficacy in the first six months. Treatment sequences used are summarised below:

Table 7: Moderate RA

First-line treatment	Second-line treatment
UPA + MTX	BSC
UPA mono	BSC
MTX	BSC
csDMARD	BSC
Intensive csDMARD	BSC

Table 8: Three month trial data (change in EQ-5D-5L from baseline) compared to QALY change in HE model output at 6 months (moderate RA)

	SELECT-COMPARE		SELECT-NEXT		SELECT-MONOTHERAPY	
	PBO + MTX	UPA 15mg + MTX	PBO + csDMARD	UPA 15 mg + csDMARD	MTX	UPA 15 mg
3 month trial data (QALY change from baseline)	xxxxx	xxxxx	xxxxx	xxxxx	xxxxx	xxxxx
3month trial data (difference between UPA and comparators)	xxxxx		xxxxx		xxxxx	
6 month HE model output (difference between UPA and comparators)	-0.028*		-0.028*/ -0.022**		-0.028*	

***csDMARD / MTX and **intensive csDMARD**

Table 9: 6 month trial data (change in EQ-5D-5L from baseline) compared to QALY change in HE model output at 6 months (moderate RA)

	SELECT-COMPARE	
	PBO + MTX	**UPA 15mg + MTX**
6 month trial data (QALY change)	xxxxx	xxxxx
6month trial data (difference between UPA and comparators)	xxxxx	
6 month HE model output (difference between UPA and comparators)	-0.028*	

***csDMARD / MTX**

The adjustment of the 6-month quality adjusted output from the model to estimate QALYs (and hence QALY differences is shown below:

Table 10: Moderate RA

	Output from model (HAQ change and hence utility change set to occur at treatment initiation)			
	Quality adjusted output at 6 months	LYG (at 6 mths)	Estimated full year QALY (quality adjusted output at 6 months / LYG at 6 months)	Difference in QALYs (UPA combo compared to other treatments)
UPA combo	0.340	0.498	0.683	
UPA mono	0.337	0.498	0.677	0.006
MTX / csDMARD	0.326	0.498	0.655	0.028
intensive csDMARD	0.329	0.498	0.661	0.022

Table 11: 3 month trial data (change in HAQ from baseline) compared to calculated change in HAQ HE model output at 6 months (moderate RA)

	SELECT-COMPARE		**SELECT-NEXT**		**SELECT-MONOTHERAPY**	
	PBO + MTX	**UPA 15mg + MTX**	**PBO + csDMARD**	**UPA 15 mg + csDMARD**	**MTX**	**UPA 15 mg**
3 month trial data	xxxxx	xxxxx	xxxxx	xxxxx	xxxxx	xxxxx
HE model output (baseline HAQ)	1.114	1.114	1.114	1.114	1.114	1.114
HE model (HAQ at 6 months)	0.958	0.817	0.958*/ 0.922**	0.817	0.958*	0.841
Change from baseline (at 6 months)- HE model	-0.156*	-0.297	-0.156* / -0.192**	-0.297	-0156*	-0.273

***csDMARD / MTX and **intensive csDMARD**

Table 12: 6 month trial data (change in HAQ from baseline) compared to calculated change in HAQ HE model output at 6 months (moderate RA)

	SELECT-COMPARE	
	PBO + MTX	UPA 15mg + MTX
6 month trial data	xxxxx	xxxxx
HE model output (baseline HAQ)	1.114	1.114
HE model (HAQ at 6 months)	0.958	0.817
Change from baseline (at 6 months)- HE model	-0.156*	-0.297

***csDMARD / MTX**

Validation using severe RA population output

A third validation exercise has been completed specifically for the severe RA population.

QALY output at 6 months for severe population (csDMARD-IR with transition to severe RA set to "No") is shown in the first two output tables below. To show a QALY change at 6 months the model was set so that HAQ change (and associated QALY change occurred at treatment initiation. Setting HAQ change to occur at 6 months (in line with the base case analysis) would lead to no QALY change occurring due to drug efficacy in the first six months. Treatment sequences used are summarised below (for csDMARD-IR population – used to validate SELECT-COMPARE, SELECT-NEXT and SELECT-MONOTHERAPY output). A bDMARD-IR RTX ineligible population severe RA is used to validate SELECT-BEYOND output.

Table 13: cDMARD-IR population (severe RA)

First-line treatment	Second-line treatment
UPA + MTX	BSC
UPA mono	BSC
ADA + MTX	BSC
MTX	BSC
csDMARD	BSC
Intensive csDMARD	BSC

Table 14: bDMARD-IR RTX ineligible population (severe RA)

First-line treatment	Second-line treatment
UPA + MTX	BSC
csDMARD	BSC

Table 15: Three month trial data (change in EQ-5D-5L from baseline) compared to QALY change in HE model output at 6 months (severe RA) – csDMARD-IR population

	SELECT-COMPARE			SELECT-NEXT		SELECT-MONOTHERAPY	
	PBO + MTX	ADA + MTX	UPA 15mg + MTX	PBO + csDMARD	UPA 15 mg + csDMARD	MTX	UPA 15 mg
3 month trial data (QALY change from baseline)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3month trial data (difference between UPA and comparators)	[redacted]	[redacted]		[redacted]		[redacted]	
6 month HE model output (difference between UPA and comparators)	-0.042*	-0.008		-0.042*/ -0.032**		-0.042*	

***csDMARD / MTX and **intensive csDMARD**

Table 16: 6 month trial data (change in EQ-5D-5L from baseline) compared to QALY change in HE model output at 6 months (severe RA) – csDMARD-IR population

	SELECT-COMPARE		
	PBO + MTX	ADA + MTX	UPA 15mg + MTX
6 month trial data (QALY change)	[redacted]	[redacted]	[redacted]
6month trial data (difference between UPA and comparators)	[redacted]	[redacted]	
6 month HE model output (difference between UPA and comparators)	-0.042*	-0.008	

***csDMARD / MTX**

The adjustment of the 6-month quality adjusted output from the model to estimate QALYs (and hence QALY differences is shown below:

Table 17: Severe RA – csDMARD-IR population

	Output from model (HAQ change and hence utility change set to occur at treatment initiation)			
	Quality adjusted output at 6 months	LYG (at 6 mths)	Estimated full year QALY (quality adjusted output at 6 months / LYG at 6 months)	Difference in QALYs (UPA combo compared to other treatments)
UPA combo	0.284	0.498	0.570	
UPA mono	0.280	0.498	0.562	0.008
ADA combo	0.280	0.498	0.562	0.008
MTX / csDMARD	0.263	0.498	0.528	0.042
intensive csDMARD	0.268	0.498	0.538	0.032

Table 18: 3 month trial data (change in HAQ from baseline) compared to calculated change in HAQ HE model output at 6 months (severe RA) – csDMARD-IR population

	SELECT-COMPARE			**SELECT-NEXT**		**SELECT-MONOTHERAPY**	
	PBO + MTX	**ADA + MTX**	**UPA 15mg + MTX**	**PBO + csDMARD**	**UPA 15 mg + csDMARD**	**MTX**	**UPA 15 mg**
3 month trial data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HE model output (baseline HAQ)	1.670	1.670	1.670	1.670	1.670	1.670	1.670
HE model (HAQ at 6 months)	1.474	1.350	1.323	1.474/1.438	1.323	1.474	1.350
Change from baseline (at 6 months)- HE model	-0.196*	-0.320	-0.347	-0.196* / -0.232**	-0.347	-0.196	-0.320

***csDMARD / MTX and **intensive csDMARD**

Table 19: 6 month trial data (change in HAQ from baseline) compared to calculated change in HAQ HE model output at 6 months (severe RA) – csDMARD-IR population

	SELECT-COMPARE		
	PBO + MTX	**ADA + MTX**	**UPA 15mg + MTX**
6 month trial data	[redacted]	[redacted]	[redacted]
HE model output (baseline HAQ)	1.670	1.670	1.670
HE model (HAQ at 6 months)	1.474	1.350	1.323
Change from baseline (at 6 months)- HE model	-0.196*	-0.320	-0.347

***csDMARD / MTX**

Table 20: Three month trial data (change in EQ-5D-5L from baseline) compared to QALY change in HE model output at 6 months (severe RA) – bDMARD-IR RTX ineligible population

	SELECT-BEYOND	
	PBO + csDMARD	UPA 15 mg + csDMARD
3 month trial data (QALY change from baseline)	xxxxx	xxxxx
3month trial data (difference between UPA and comparators)	xxxxx	
6 month HE model output (difference between UPA and comparators)	-0.034*	

***csDMARD / MTX. intensive csDMARD = no efficacy data in NMA for bDMARD-IR population**

Table 21: 6 month trial data (change in EQ-5D-5L from baseline) compared to QALY change in HE model output at 6 months (severe RA) – bDMARD-IR, RTX ineligible population

	SELECT-BEYOND
	UPA 15 mg + csDMARD
6 month trial data (QALY change)	xxxxx
6month trial data (difference between UPA and comparators)	N/A
6 month HE model output (difference between UPA and comparators)	N/A

Table 22: Severe RA – bDMARD-IR RTX ineligible population

	Output from model (HAQ change and hence utility change set to occur at treatment initiation)			
	Quality adjusted output at 6 months	LYG (at 6 mths)	Estimated full year QALY (quality adjusted output at 6 months / LYG at 6 months)	Difference in QALYs (UPA combo compared to other treatments)
UPA combo	0.270	0.498	0.542	
MTX / csDMARD	0.253	0.498	0.508	0.034

Table 23: 3 month trial data (change in HAQ from baseline) compared to calculated change in HAQ HE model output at 6 months (severe RA) – bDMARD-IR RTX ineligible population

	SELECT-BEYOND	
	PBO + csDMARD	UPA 15 mg + csDMARD
3 month trial data	xxxxx	xxxxx
HE model output (baseline HAQ)	1.730	1.730
HE model (HAQ at 6 months)	1.558	1.437
Change from baseline (at 6 months)- HE model	-0.172	-0.293

***csDMARD / MTX. intensive csDMARD no efficacy data from bDMARD-IR NMA**

Table 24: 6 month trial data (change in HAQ from baseline) compared to calculated change in HAQ HE model output at 6 months (severe RA) – bDMARD-IR RTX ineligible population

	SELECT-BEYOND
	UPA 15 mg + csDMARD
6 month trial data	[redacted]
HE model output (baseline HAQ)	1.730
HE model (HAQ at 6 months)	1.437
Change from baseline (at 6 months)- HE model	-0.293

References

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2. Plant, M.J., O'Sullivan, M.M., Lewis, P.A., Camilleri, J.P., Coles, E.C., Jessop, J.D. What factors influence functional ability in patients with rheumatoid arthritis. Do they alter over time? Rheumatology 2005; 44(9):1181-1185.
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4. Munro, R., Hampson, R., McEntegart, A., Thompson, E., Modhok, R., Capell, H. Improved functional outcome in patients with early RA treated with intramuscular gold: results of a five year prospective study. Ann Rheum Dis 1998; 57:88-93.
5. Norton et al. Common trajectories of HAQ disability progression over 15-years in the Early Rheumatoid Arthritis Study and the Norfolk Arthritis Register. 2012

Question: There is no account of what changes the company has made to the original 05072019 model to arrive at the resubmitted 15082019 model. To the ERG is appears that the changes made are: revise discontinuation curve parameters in Trt discontinuation worksheet cells F8:K31, plus apply the cPAS price for upadacitinib in the Drug Cost worksheet, plus the two drop downs for modelling HAQ progression in the Model Settings worksheet.

AbbVie Response:

In the response made by AbbVie on the 13th August we made NICE aware of the following changes that were made to the 05072019 model to arrive at the 15082019 model:

- Revised treatment discontinuation functions by revising the curve parameters in the Trt discontinuation worksheet (cells F8:M31)
- Added two drop down menus for modeling HAQ progression for csDMARDs and BSC in the Model settings worksheet
- Updated the cPAS price for upadacitinib in the Drug Cost worksheet (cells Z67 and AA67)

Following receipt of the questions from NICE on the 20th, and clarification discussions with the modeler who made the modifications to the 05072019 model, please see below the additional changes that were made to the model:

- Revised treatment discontinuation functions by updating the estimation of time to discontinuation in the time_on_trt() VBA function within the fnct_trt_disc module
- Fixed an error to update the HAQ baseline score upon moderate RA patients' transition to severe RA in the transition_to_severe() VBA function within the fnct_das_adjust module
- Update made to the formula discounting life years to avoid discounting life years of year 1 during the simulation.

Question: For the revisions to the treatment discontinuations, given the model changes the ERG would be grateful if the company could cross check the gammas median time to discontinuation: 14.867 yrs for the good and 7.765 yrs for the moderate in the 05072019 model and 9.304 yrs for the good and 3.868 yrs for the moderate in the resubmitted 15082019 model.

AbbVie Response:

AbbVie confirms that the median times to treatment discontinuation based on the generalized gamma curves are the same as the estimates provided by the ERG (14.9 years for good responders and 7.8 years for moderate responders in the 05072019 model and 9.3 years for good responders and 3.9 years for moderate responders in the resubmitted 15082019 model). The median time to treatment discontinuation in the digitized TA375 curves were also estimated based on the reconstructed pseudo-

IPD (8.7 years for good responders and 4.1 years for moderate responders), which correspond reasonably well with the generalized gamma curves used in the resubmitted 15082019 model.

Question: The ERG has revised the 05072019 model to apply the revised central estimates of the gamma coefficients as taken from the resubmitted 15082019 model and to apply the updated upadacitinib PAS. The ERG has then revised the population to be the csDMARD-IR moderate patient, generated the cohort and run the model with an ICER £X per QALY resulting. Selecting the same population in the resubmitted 15082019 model, revising the Change in HAQ dropdown and the time horizon of the resubmitted 15082019 model to be the same as the originally submitted model, generating the cohort and running the model results in an ICER £Y per QALY. The ICERs are noticeably different with X being 13% worse than Y. Please provide an account of this.

AbbVie Response:

AbbVie concur that the changes made between the 050719 and the 150819 model lead to the magnitude of changes in some of the moderate csDMARD-IR ICERs identified by the ERG. These changes are explained by the changes made to the 050719 model outlined in the response outlined in this document to the questions sent by NICE on 20th August 2019.

Question: Please provide a copy of the original 05072019 amended with additional reversible drop downs such that running this model can result in the output of (1) the original 05072019 model as submitted and of (2) the resubmitted 15082019 when the drop downs are set appropriately.

AbbVie Response:

A revised 05072019 model with three additional reversible drop down menus to generate the results of both the original 05072019 and the resubmitted 15082019 models will be submitted to NICE on August 27th 2019. The three drop down menus will include: (1) update treatment discontinuation function (05072019 setting vs. 08152019 setting), (2) update baseline HAQ score upon moderate to severe transition (05072019 setting vs. 08152019 setting), and (3) update cPAS pricing for upadacitinib (05072019 annual UPA price of [redacted] vs. 08152019 annual UPA price of [redacted]).

Question: Please outline what has been changed with full cell referencing to get from the 05072019 model to the resubmitted 15082019 model, and also outline which of these changes affects the results of the modelling of the moderate RA patients and which affects the modelling of the severe RA patients.

AbbVie response:

Detailed descriptions for each change are summarised below:

Revised treatment discontinuation functions

- Revised curve parameters in the Trt discontinuation worksheet (cells F8:M31). Please refer to AbbVie's responses to the clarification question B13 for details regarding this update.

- Updated the estimation of time to discontinuation in the time_on_trt() VBA function within fnct_trt_disc module

    - The first update involved the removal of a fixed 6 months addition to the treatment duration. In the 05072019 model (time_on_trt function, line 162), an additional 6 months' time was added to the time to discontinuation estimate to ensure that patients continued using the treatment for at least 6 months. However, upon further consideration, this was deemed as unnecessary since the model only starts to apply a treatment discontinuation generalized gamma curve after 6 months using the corresponding treatment. Therefore, the 6 months addition was removed in the 15082019 model.

    - The second update involved incorporating slightly different survival functions to estimate the time to discontinuation for the generalized gamma curves, depending on the values of the shape parameter. Based on the R package (flexsurv) used to estimate treatment discontinuation parameters for the original and the resubmitted models, a random probability should be used to estimate the time to discontinuation when the shape parameter of the generalized gamma curve is negative, whereas (1 – the random probability) should be used instead with a positive shape parameter (Cox et al 2007, Jackson 2016). In the 05072019 model, a random probability was always used to estimate the time to discontinuation regardless of a positive or negative shape parameter. This was corrected in the 15082019 model in the time_on_trt() function (line 140-144).

The changes made to the treatment discontinuation inputs and function result in a shorter treatment duration for all treatments in the resubmitted 15082019 model relative to the original 05072019 model.

Added two drop down menus for modeling HAQ progression for csDMARDs and BSC in the Model Settings worksheet.

Please refer to AbbVie's responses to the clarification question B18 for details regarding the options and functionalities of the two drop down menus.

Updated the cPAS price for upadacitinib in the Drug Cost worksheet (cells Z67 and AA67)

Fixed an error in the VBA transition_to_severe() function in the fnct_das_adjust module.

For the csDMARD-IR moderate population, the model was intended to update the baseline HAQ to the HAQ score upon transitioning to severe RA (as described in the submission document B.3.2.2). However, this functionality was not incorporated correctly in the original 05072019 model. Therefore, an additional correction was made to the transition_to_severe () function within the fnct_das_adjust module (line 110) to ensure that baseline HAQ was updated to the HAQ upon transitioning from moderate RA to severe RA in the resubmitted 15082019 model.

Update made to the formula discounting life years to avoid discounting life years of year 1 during the simulation.

Update made to the formula discounting life years in the run_simulation() function, line 1027 to avoid discounting life years of year 1 during the simulation.

This update does not affect the ICERs as the discounting of QALYs are incorporated correctly in a separate function (apply_discount() function in the fnct_apply_discount module).

How the changes affect the results of the modelling of the moderate RA patients and the severe RA patients.

The aforementioned changes made to the treatment discontinuation function and the cPAS price will affect results for all populations.

The update made to the transition_to_severe() function will only affect the csDMARD-IR moderate population when transition to severe RA is considered.

The two newly added drop down menus for modeling HAQ progression of csDMARDs and BSC does not impact the simulation results when the TA375 base case HAQ progression approach is specified for both csDMARDs and BSC.

The update to the formula discounting life years in the run_simulation() function to avoid discounting life years of year 1 during the simulation is minor. This update does not affect the ICERs as the discounting of QALYs are incorporated correctly in a separate function (apply_discount() function in the fnct_apply_discount module).

References

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Upadacitinib for treating moderate to severe rheumatoid arthritis [ID1400]

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**
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 this condition? ☐ 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).	British Society for Rheumatology is a UK specialist medical society for rheumatology and musculoskeletal care professionals. Funding comes from a variety of sources including membership fees, events, biologics and biosimilars registers, journal etc.
5b. 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,	The main aim of treatment for rheumatoid arthritis is to stop progression of disease to disability, to treat painful swollen joints and to manage symptoms. Some treatments also reduce cardiovascular risk by reducing the burden of inflammation. There is no cure for rheumatoid arthritis.

or prevent progression or 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.)	A reduction in DAS 28 to below 3.2 is a good response. A moderate response is a drop in DAS 28 by at least 1.2 but not reaching below 3.2. This is the EULAR moderate and good response criteria. Other measurements of response are ACR 20, 50 and 70 showing a 20%, 50% and 70% improvement in the American College of Rheumatology Criteria. 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, physician global assessment, functional ability measure [most often Health Assessment Questionnaire (HAQ)], visual analog pain scale, and erythrocyte sedimentation rate or C-reactive protein (CRP). ACR50 and ACR70 are the same instruments with improvement levels defined as 50% and 70% respectively versus 20% for ACR20.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There is unmet need for patients with rheumatoid arthritis as although the number of drugs is increasing. Patients still can be allergic to, have side effects from, be intolerant to or have no response to the currently available treatments. Approximately 60% of patients respond to synthetic DMARDs and biologic DMARDs leaving 40% who do not respond to that specific drug.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Rheumatoid arthritis is currently initially treated with standard Disease modifying Rheumatic Drugs (DMARD) alone or in combination. These include methotrexate, sulfasalazine, leflunomide and hydroxychloroquine with or without the adjunct of steroids. If therapy with these standard DMARDs does not bring the DAS28 below 5.1 (high disease activity) then treatment with synthetic DMARDs such as Janus kinase inhibitors (currently tofacitinib and baricitinib) or biologic DMARDs such as abatacept,

	tocilizumab, sirolumab, anti TNFs such as etanercept, adalimumab, infliximab, golimumab and certolizumab. Rituximab is usually third line treatment.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE Rheumatoid arthritis pathway and technology appraisals https://pathways.nice.org.uk/pathways/rheumatoid-arthritis EULAR guidelines in treating rheumatoid arthritis 2017 https://ard.bmj.com/content/76/6/960
• 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 of care is relatively well defined with " treat to target"- this can be remission or low disease activity in terms of DAS28. The use of which DMARD to use is consistent. Combination versus monotherapy has become controversial- previously combination therapy was thought to be superior to monotherapy. The choice of DMARD, s DMARD and b DMARD is often dictated by local pathways and clinical preference.
• What impact would the technology have on the current pathway of care?	
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	It will be used in the same way as other high cost drug treatment for rheumatoid arthritis- usually after the inefficacy of two DMARDs

• How does healthcare resource use differ between the technology and current care?	This is an additional drug in the JAK inhibitor group. The healthcare resource used is the same as that used for tofacitinib and baricitinib.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care, prescribed by consultant rheumatologist
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	The facilities should already be in place as for the other JAK inhibitors already available.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	The data published regarding this drug suggests that there is a meaningful response to this technology in terms of reduction of DAS28 and improvement of ACR 20. This drug widens the range of options available to patients who may have been intolerant to, had side effects from or had inefficacy from current treatments.
• Do you expect the technology to increase length of life more than current care?	No.

• Do you expect the technology to increase health-related quality of life more than current care?	The published data suggest equivalence to current synthetic DMARDs and biologic DMARDs.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Needle phobic patients prefer tablets. There is data to suggest this drug is effective in biologic naïve patients, can be used as monotherapy (useful for those intolerant of methotrexate) and after biologic DMARDs with similar effects.
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	It appears to be the same to use as current technology with a similar level of screening required before use and monitoring during use.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The same screening requirements as per the BSR guidelines for biologic use. https://academic.oup.com/rheumatology/article/58/2/220/5076445 .TB screening, HIBV, HBV, and HCV screening. Ideally patients will have had the pneumococcal and shingles vaccine prior to use and will have yearly flu vaccines. I presume this drug will like the other JAK inhibitors only be for use after the failure of two DMARDs and if the DAS28 is above 5.1. Although to bring in line with the rest of the world this should be a DAS28 of greater than 3.2 as per EULAR guidelines and ACR guidelines.
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?	Adequately treating active rheumatoid arthritis can reduce requirement for joint replacements and improve longevity of work. Active RA is associated with losing employment, often within the first year of diagnosis.
16. Do you consider the technology to be innovative in its potential to make a	It is a JAK inhibitor similar to tofactinib and baricitinib. It improves patient choice and increases likelihood of finding the right drug for the right patient.

significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	no
• Does the use of the technology address any particular unmet need of the patient population?	Needlephobic patients, also those who need a rapid offset e.g high infection risk patients.
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?	
Sources of evidence	

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes. The populations in the trials were North American, Western and Eastern European. Arthritis Rheumatol. 2016 Dec;68(12):2867-2877. doi: 10.1002/art.39801. A Phase IIb Study of ABT-494, a Selective JAK-1 Inhibitor, in Patients With Rheumatoid Arthritis and an Inadequate Response to Anti-Tumor Necrosis Factor Therapy. Kremer JM, Emery P, Camp HS, Friedman A, Wang L, Othman AA, Khan N, Pangan AL, Jungerwirth S, Keystone EC. Lancet. 2018 Jun 23;391(10139):2503-2512. doi: 10.1016/S0140-6736(18)31115-2. Epub 2018 Jun 18. Safety and efficacy of upadacitinib in patients with rheumatoid arthritis and inadequate response to conventional synthetic disease-modifying anti-rheumatic drugs (SELECT-NEXT): a randomised, double-blind, placebo-controlled phase 3 trial. Burmester GR, Kremer JM, Van den Bosch F, Kivitz A, Bessette L5, Li Y, Zhou Y, Othman AA, Pangan AL, Camp HS. Lancet. 2018 Jun 23;391(10139):2513-2524. doi: 10.1016/S0140-6736(18)31116-4. Epub 2018 Jun 18. Safety and efficacy of upadacitinib in patients with active rheumatoid arthritis refractory to biologic disease-modifying anti-rheumatic drugs (SELECT-BEYOND): a double-blind, randomised controlled phase 3 trial. Genovese MC, Fleischmann R, Combe B, Hall S, Rubbert-Roth A, Zhang Y, Zhou Y, Mohamed MF, Meerwein S, Pangan AL. Lancet. 2019 Jun 8;393(10188):2303-2311. doi: 10.1016/S0140-6736(19)30419-2. Epub 2019 May 23. Upadacitinib as monotherapy in patients with active rheumatoid arthritis and inadequate response to methotrexate (SELECT-MONOTHERAPY): a randomised, placebo-controlled, double-blind phase 3 study.

	Smolen JS, Pangan AL, Emery P, Rigby W, Tanaka Y, Vargas JI, Zhang Y, Damjanov N, Friedman A, Othman AA, Camp HS, Cohen S.
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	The primary outcome measures used were ACR 20 response at 12 weeks and DAS28 – CRP below 3.2 at 12 weeks. Safety data was also collected. These were measured in the trials.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	These primary outcomes are commonly used in clinical trials of this kind in rheumatoid arthritis. Low disease activity and remission rates are related to reduce erosions and thus reduce longterm disability.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The adverse effects that have come to light in the trials are increased infection risk, increased herpes zoster risk, changes in cholesterol and a rise in CK not related to rhabdomyolysis. In the select -beyond trial there were 3 malignancies, one major cardiovascular event and one death in the upadacitinib arm, with none seen in the placebo arm. Select – monotherapy showed 3 major adverse

	cardiovascular events, one pulmonary embolism and one death in the upadactinib arm. In the select-next trial there was two malignancies, on major cardiovascular event and five serious infections with no deaths.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance [TA195, TA225, TA247, TA375, TA415, TA466, TA480, TA485]?	Upadacitinib versus Placebo or Adalimumab in Patients with Rheumatoid Arthritis and an Inadequate Response to Methotrexate: Results of a Phase 3, Double-Blind, Randomized Controlled Trial. Fleischmann R, Pangan AL, Song IH, Mysler E, Bessette L, Peterfy C, Durez P, Ostor AJ, Li Y, Zhou Y, Othman AA, Genovese MC8. Arthritis Rheumatol. 2019 Jul 9. doi: 10.1002/art.41032. Comparison of the efficacy and safety of tofacitinib and upadacitinib in patients with active rheumatoid arthritis: A Bayesian network meta-analysis of randomized controlled trials. Song GG, Choi SJ, Lee YH. Int J Rheum Dis. 2019 Jun 18. doi: 10.1111/1756-185X.13616.
21. How do data on real-world experience compare with the trial data?	I am not aware of real world data regarding this drug. Real world data regarding the biologic DMARDs and other synthetic DMARDs e.g from the BSR biologics register has been reassuring regarding malignancy risk but supports the cautions regarding increased infection risk.

Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment? For example, do people with rheumatoid arthritis struggle to complete clinical assessments because of their condition?	No
22b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
23a. At what positions in the treatment pathway would you consider using upadacitinib monotherapy?	After 2 conventional DMARDs. After a biologic such as anti TNF, abatacept or anti IL6.

23b. Would upadacitinib monotherapy ever be considered in people with severe rheumatoid arthritis who can tolerate methotrexate?	Possibly- as it is effective as monotherapy and the study does show that it is effective in methotrexate responders.
24a. What biosimilar products are currently available for the treatment of moderate to severe rheumatoid arthritis?	Biosimilar etanercept, infliximab and adalimumab. There are no biosimilars or generics for the JAK inhibitors.
24b. Relative to branded technologies, what is the uptake of biosimilars? Are you aware of any prescribing data to support this?	All new patients by national policy go onto a biosimilar first line. However, there are no equivalent biosimilars for this product.
Key messages	

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

- Upadacitinib is a novel JAK 1 specific inhibitor
- It is effective in treating high disease activity rheumatoid arthritis with similar ACR 20 response rates to current synthetic and biologic DMARDs
- The safety profile is similar to the other JAK inhibitors and the clinical trials have shown the possible increased risk of thromboembolic disease which were picked up in post marketing surveillance in the case of tofactininib.
- The major adverse events are infections including herpes zoster.
- It is a useful addition to the range of drugs available for the treatment of severe rheumatoid arthritis

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Upadacitinib for treating moderate to severe rheumatoid arthritis [ID1400]

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.

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	National Rheumatoid Arthritis Society (NRAS)
3. Job title or position	National Patient Champion
4a. Brief description of the organisation (including who funds it). How many members does it have?	The National Rheumatoid Arthritis Society (NRAS), is the only patient-led organisation in the UK specialising in rheumatoid arthritis (RA) and juvenile idiopathic arthritis (JIA). Due to its targeted focus on RA and JIA, NRAS provides truly expert and wide-ranging services to support, educate and campaign for people living with these complex autoimmune conditions, their families and the health professionals who treat them. Their vision is to support all with RA or JIA to live life to the full with an underpinning mission to: • support everyone living with the impact of RA or JIA at the start and every step of their journey • to inform – be their first choice for reliable information, and • empower all to have a voice and take control of their RA or JIA We are funded through a wide range of income streams including Trust and Grant giving organisations, Events, legacies, membership, donations, in memorium gifts, individual giving, etc. We receive educational grants from a number of pharmaceutical companies and this income is capped at 15% of our total income and is often less than this.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
5. How did you gather information about the experiences of patients and	**As the national organisation for people with RA, we are constantly gathering the views of people with RA through surveys, social media, feedback, focus groups,our community groups across the UK, feedback from our webinars, anecdote, research, YouGov polls, our website, our helpline, etc.**

carers to include in your submission?	
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?	Being diagnosed with an incurable, painful disease like RA can be extremely distressing as it is life-changing and as you can be diagnosed at any age post 16, it can have a major impact on your future life plans, dreams and aspirations, although being diagnosed today has significantly better potential outcomes than when I was diagnosed over 35 years ago when treatments and the way the disease was treated were quite different. RA impacts on every area of life and impacts both physical and emotional wellbeing. Health beliefs, how you come to diagnosis (how long it takes to be diagnosed), your attitude to taking medication for life, whether you work or not, have children or not, the network of support you have and how aggressive the disease is will all impact on how you come to terms with your diagnosis and cope day to day. It can be very distressing for a partner of someone with RA to witness their loved-one in severe pain and suffering the debilitating effects of fatigue and so this disease does very much impact on the whole family. As ¾ of people are diagnosed when of working age, anxiety over job-loss due to their disease is a significant factor and whilst we are making steps towards seeing work as a health outcome, we are far from a situation where rheumatology teams pay enough attention to how worried patients may be about their job. This is particularly true at time of diagnosis when they may have already had quite a lot of time off work in the process of finding out what is wrong and may already be at risk of losing their job. This disease impacts on emotional wellbeing, sexuality and relationships – all areas that health professionals find difficult to tackle. For young people who are not yet in a permanent relationship, it can

	be very hard to come to terms with the fact that they have a long term condition and we know from our own research that RA can have a huge impact, making them feel less desirable, much less confident and worried that they will not find a partner. For older people diagnosed as they approach retirement for example, dreams of being able to travel and look after grand-children can suddenly seem unachievable. Diagnosed in mid-years with young children to care for can also be incredibly challenging. Imagine not being able to pick up your baby and change its nappy. For whilst much has been done in terms of new and innovative therapies coming into rheumatology and the way in which we now treat the disease, there remains significant unmet need, and a lot of pain and distress at all stages of this disease. Even people in so called drug induced remission, may still experience significant pain and fatigue.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Care is significantly variable across the UK and whilst some patients experience excellent care and treatment, others do not. The national audit is slowly helping to drive up standards which is good news, but we have a considerable way to go to ensure that there is equity of best evidence based care for all.
8. Is there an unmet need for patients with this condition?	Yes there is. The BSR Biologics Register did a national study which has identified the frequency of bDMARD refractory disease to be at least 6% of patients who have ever received bDMARDs. The overall ***response rate*** to a second anti-***TNF*** agent in first ***TNFα*** inhibitor refractory ***patients*** seems to be 50–65%. Loss of efficacy is common after a period of time no matter what the target. The number of patients achieving drug induced remission is between 30-50% so to think that we have RA cracked is a major mistake. There remains major unmet need with this syndrome.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	The key driver of RA is inflammation which can result quite quickly in bone erosion leading ultimately to joint destruction and potential disability. The JAK inhibitors offer a completely new class of innovative therapy that can be positioned post DMARD failure or post first TNF failure. This is fantastic because it really adds to the therapeutic options available to clinicians and patients. Also the fact that this is an oral therapy means that there are no costs associated with infusion based therapies or those delivered via sub-cut route. All those costs associated with home care delivery companies also disappear. It's beneficial for patients and clinicians as it adds to the options of biologic/biosimilar therapies available Patients are very likely to prefer an oral (biologic) drug to have a regular infusion or having to inject themselves.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	I'm not aware of any.

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Patients who work and don't want to have to take time off work to attend hospital for infusions. Patients with dexterity/mobility problems and/or fear of needles will also benefit from being able to take an oral therapy.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology? For example, do people with rheumatoid arthritis struggle to complete clinical assessments because of their condition?	Not that I am aware of If you are inferring that in order to qualify for such therapies you would have to undertake a clinical assessment where some people may be disadvantaged, I don't believe this is the case as the qualifying criteria require a DAS score to be taken by a clinician and the only patient part of that is the Patient Global Assessment which is done on a 1-10 or 1-100 visual analogue scale and this would not disadvantage patients with low levels of literacy.

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:

- This is an additional option in a relatively new class of therapy and is to be welcomed
- Patients are likely to be more prepared to take an oral medicine than inject themselves or be infused
- It has the potential to save a lot of costs due to the fact that it is oral
- It can be used in different places in the current pathway, ie. post dmard failure and post TNF failure

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Upadacitinib for previously treated moderate to severe active rheumatoid arthritis [ID1400]

Thank you for agreeing to give us 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.

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 expert statement

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Professor Christopher Edwards**
2. Name of organisation	**University Hospital Southampton NHS Foundation Trust**

3. Job title or position	**Consultant Rheumatologist**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? **X** a specialist in the treatment of people with this condition? ☐ 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)	**X** 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

The aim of treatment for this condition	
7. 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 reduce inflammatory disease activity, prevent damage to joints and improve function along with reducing important patient reported outcomes such as pain. Achieving this will reduce progression to disability.
8. 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.)	Achieving ACR20, low disease activity (DAS28) and reducing joint damage.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, many patients still do not achieve a good outcome despite the presence of a number of existing therapies.
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	Well established and covered by NICE guidance and TAs
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE, EULAR, ACR and BSR all have published guidelines.
• 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.)	Yes, well defined but many patients still have unmet need. General approach is not disputed but not all patients respond.
• What impact would the technology have on the current pathway of care?	New therapy that may allow successful treatment of patients with RA.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Not currently used.

• How does healthcare resource use differ between the technology and current care?	No major change
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No new facilities or equipment needed. As with any new therapy a degree of education will be needed but the approach is similar to current therapies.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, although there are a number of therapies available for RA not all patients currently respond so addition of a new therapy gives the chance of benefit to additional patients.
• Do you expect the technology to increase length of life more than current care?	Yes, for those patients that respond that have not responded to existing therapies. Although RA is rarely acutely life-shortening it is associated with a reduced lifespan due to the negative effects of chronic inflammation and disability.

• Do you expect the technology to increase health-related quality of life more than current care?	Yes, for those patients that do not currently respond.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Yes, may be useful for patients that are needle-phobic or those who cannot take concomitant methotrexate.
The use of the technology	
14. 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	There are benefits associated with this being an oral therapy.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Similar standards should apply as those currently used for existing biological therapies and other JAK inhibitors.
16. 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?	Reduced major joint surgery such as Total Hip and Total knee replacement.
17. Do you consider the technology to be innovative in its potential to make a significant and substantial	New JAK inhibitor directed at JAK1 inhibition (existing therapies target multiple JAK). New approach may allow successful treatment of patients that do not respond to current therapy.

impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Greater targeting of JAK1 than existing therapies.
• Does the use of the technology address any particular unmet need of the patient population?	Oral therapy, may be effective for currently resistant patients and good efficacy for the patient reported outcome of pain.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Similar to current therapies.
Sources of evidence	

19. Do the clinical trials on the technology reflect current UK clinical practice?	Mainly. However, the trials also show benefit for patients with moderate disease activity. According to current related TAs only patients with severe disease can be treated with existing tsDMARDs and bDMARDs. UK is an outlier in this regard compared to many similar countries within Europe.
• If not, how could the results be extrapolated to the UK setting?	As above
• What, in your view, are the most important outcomes, and were they measured in the trials?	In UK setting DAS28, radiographic damage, function (HAQDI) and pain are most important.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Well established standard measures used
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
20. Are you aware of any relevant evidence that might	No

not be found by a systematic review of the trial evidence?	
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance?	No
22. How do data on real-world experience compare with the trial data?	NA
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	RA effects 3 women for every 1 man.

23b. Consider whether these issues are different from issues with current care and why.	Same as current care.

Key messages

24. In up to 5 bullet points, please summarise the key messages of your statement.

- Not all patients with RA respond to current therapy
- RA is a severe, damaging and life-shortening disease
- Upadacitininb fufills all well-established requirements to be accepted as a therapy for RA
- Oral therapies such as this provide advantages for patient preference, education and logistics of supply compared to bDMARDs
- JAK inhibitor use supported by international guidelines such as latest EULAR RA management recommendations (recently presented EULAR 2019)

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.

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Upadacitinib for treating moderate to severe rheumatoid arthritis [ID1400]

A Single Technology Appraisal

Produced by	Peninsula Technology Assessment Group (PenTAG) University of Exeter Medical School South Cloisters St Luke's Campus Heavitree Road Exeter EX1 2LU
Authors	**Dr Max Barnish**, Research Fellow[1] **Dr Ewen Cummins**, Health Economist[2] **Dr Helen Coelho**, Research Fellow[1] **Dr Rhona Johnston**, Computer Programmer[2] **Mr David Packman**, Research Assistant[1] **Ms Naomi Shaw**, Information Specialist[1] **Dr Richard C Haigh**, Consultant Rheumatologist[3] **Ms Louise Crathorne**, Senior Research Fellow[1] **Prof G.J. Melendez-Torres**, Professor of Clinical and Social Epidemiology[1] [1] Peninsula Technology Assessment Group (PenTAG), University of Exeter Medical School, Exeter [2] McMDC Ltd, Harrogate 3 Royal Devon and Exeter Hospital, Exeter
Correspondence to	Dr Max Barnish 3.09f South Cloisters, St Luke's Campus, Heavitree Road, Exeter, EX1 2LU; m.s.barnish@exeter.ac.uk
Date completed	10/09/2019
Source of funding	This report was commissioned by the NIHR Systematic Reviews Programme as project number 12/82/32.

Declared competing interests of the authors	Dr Richard C. Haigh declares that Pfizer (manufacturer of tofacitinib, a drug in the same class as upadacitinib) provided an educational grant to cover the registration fee to attend the British Society for Rheumatology Conference 2019. No other authors declare any competing interests.
Rider on responsibility for document	The views expressed in this report are those of the authors and not necessarily those of the NIHR SR Programme. Any errors are the responsibility of the authors. The ERG noted that the elements of the model which are programmed in visual basic should be treated as a "black box" and as such the ERG was not able to parse the programming accuracy of these elements of the electronic model (discussed with NICE July 2019). However, the ERG will cross validate model outputs with the ERG model from TA375.
This report should be referenced as follows	Barnish M, Cummins E, Coelho H, Johnston R, Packman D, Shaw N, Haigh RC, Crathorne L, Melendez-Torres GJ. Upadacitinib for treating moderate to severe rheumatoid arthritis [ID1400]: A Single Technology Appraisal. Peninsula Technology Assessment Group (PenTAG), 2019.
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Abbreviations

ABT	abatacept
ACR	American College of Rheumatology
ADA	adalimumab
AEs	adverse events
AIC	Akaike information criterion
AIMS	Arthritis Impact Measurement Scales
bDMARD	biologic disease-modifying antirheumatic drugs
BIC	Bayesian information criterion
BID	twice-daily
BIW	twice-weekly
BRC	baricitinib
BSC	best supportive care
BSRBR	British Society of Rheumatology Biologics Register
CDAI	clinical disease activity index
CMU	Commercial Medicines Unit
cPAS	comparator patient access scheme
CPK	creatine phosphokinase
CR	complete response
CrI	credible interval
CRP	C-reactive protein
CS	company submission
csDMARDs	conventional synthetic disease-modifying antirheumatic drugs
CSR	clinical study report
CT	controlled trial
CTZ	certolizumab pegol
DAS-28	disease activity score 28-joint count
DB	double blind
DIC	deviance information criterion
DMARDs	disease-modifying antirheumatic drugs
E	events
EAER	exposure adjusted event rates
EAIR	exposure adjusted incidence rates
EMA	European Medicines Agency
EOW	every other week
EPAR	European public assessment report
EQ-5D-3L	three-level EuroQol five dimension
EQ-5D-5L	five-level EuroQol five dimension
ERG	Evidence Review Group

ERG	Evidence Review Group
ESR	erythrocyte sedimentation rate
ETN	etanercept
EU	European
EULAR	European League Against Rheumatism
FACIT-F	Functional Assessment of Chronic Illness Therapy - Fatigue
FAD	final appraisal determination
FAS	full analysis set
g	gram
GOL	golimumab
HAQ-DI	health assessment questionnaire disability index
HCHS	hospital and community health services
HCQ	hydroxychloroquine
HRQoL	health-related quality of life
HTA	health technology assessment
ICER	incremental cost-effectiveness ratio
IFX	infliximab
IL-1/6	interleukin-1/6
Increm.	incremental
IQR	interquartile range
ITT	intention to treat
IV	intravenous
JAK	Janus kinase
kg	kilogram
KM	Kaplan-Meier
LDA	low disease activity
LOCF	last observation carried forward
M	median
MACE	major adverse cardiac event
MACTAR	McMaster Toronto Arthritis patient preference questionnaire
mg	milligram
mITT	modified intention to treat
MJS	morning joint stiffness
MTX	methotrexate
NA	not applicable
NG	NICE guideline
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis

NR	Not reported
NRI	non-responder imputation
OL	open-label
PAS	patient access scheme
PASLU	Patient Access Schemes Liaison Unit
PBO	placebo
PC	placebo-controlled
PG	parallel group
PICOS	population, interventions, comparators, outcomes, and study design
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSSRU	Personal Social Services Research Unit
PYs	person years
QA	quality assessment
QALYs	quality-adjusted life years
QD	once-daily
QW	once weekly
qXw	every *x* weeks
RA	rheumatoid arthritis
RCT	randomised controlled trial
RTX	rituximab
SAEs	serious adverse events
SB	single blind
SC	subcutaneous
SD	standard deviation
SDAI	simple disease activity index
SE	standard error
SF-36	36-item short form survey
SJC	swollen joint count
SJC	swollen joint count
SLR	systematic literature review
SmPC	summary of product characteristics
SOPs	standard operating procedures
SRK	sirukumab,
SRL	sarilumab
STA	single technology appraisal
SUCRA	surface under the cumulative ranking curve
TA	technology appraisal
TCZ	tocilizumab
TE	treatment emergent

TEAEs	treatment emergent adverse events
TFC	tofacitinib
TJC	tender joint count
TNF-alpha	tumour necrosis factor alpha
Trt	treatment
tsDMARDs	targeted synthetic disease-modifying antirheumatic drugs
UPA	upadacitinib
VAS	visual analogue scale
vs	versus
WPAI-RA	work productivity and activity impairment questionnaire: rheumatoid arthritis

1 Summary

1.1 Critique of the decision problem in the company submission

The National Institute for Health and Care Excellence (NICE) final scope for TA1400 defines the population of interest as adults with moderate to severe rheumatoid arthritis (RA) who have responded inadequately to one or more disease-modifying antirheumatic drugs (DMARDs). This represents the same position in the treatment pathway at which other advanced therapies are recommended in the European League Against Rheumatism (EULAR) guidelines. Unlike in prior appraisals, the company sought to position upadacitinib (UPA) as an option irrespective of methotrexate (MTX) tolerance. The Evidence Review Group (ERG) considered the population in the company submission (CS) to be appropriate and to be consistent with the NICE final scope for this appraisal.

The intervention in the decision problem is UPA, a selective oral Janus kinase (JAK)-1 inhibitor, either as monotherapy or in combination with conventional synthetic (cs) DMARDS, including MTX. The dose of UPA in the decision problem was 15 mg QD. The anticipated date of European Medicines Agency (EMA) approval for UPA in this indication is [redacted]. The ERG considered the description of the technology of interest in the CS to be appropriate. Included trials considered UPA as both monotherapy and in combination with MTX or adalimumab (ADA). Comparators in this appraisal varied depending on disease severity, the number of csDMARD failures, as well as tolerance or intolerance to MTX. While the ERG considered the comparators in the CS to be compatible with those presented in the NICE final scope, it considered that best supportive care would not be used in routine practice, while rituximab (RTX) may be used earlier in the treatment pathway.

The NICE final scope includes the following outcomes: disease activity, physical function, joint damage, pain, mortality, fatigue, radiological progression, extra-articular manifestations, adverse effects of treatment and health-related quality of life. The ERG considered the outcomes reported in the CS for UPA to be appropriate, and noted that only safety data were available for extra-articular manifestations.

The ERG agreed with the company that there were no significant equity issues in the context of this appraisal.

A patient access scheme (PAS) has been submitted to the Patient Access Schemes Liaison Unit (PASLU) for consideration. During the course of this appraisal, [redacted]

1.2 Summary of clinical effectiveness evidence submitted by the company

The company presented a systematic literature review (SLR) of randomised controlled trials (RCTs) on UPA (and comparators) for the treatment of moderate and severe RA. Four key trials were included from the SLR: SELECT-COMPARE which compared UPA 15 mg QD with ADA 40 mg every other week (eow), and with placebo (PBO) followed by UPA 15 mg QD; SELECT-NEXT which compared UPA 15 mg QD with UPA 30 mg QD and with PBO followed by UPA 15 mg or 30 mg QD; SELECT-MONOTHERAPY which compared UPA 15 mg QD with UPA 30 mg QD and with MTX; and SELECT-BEYOND which compared UPA 15 mg QD with UPA 30 mg QD and with PBO followed by UPA 15 mg or 30 mg QD. In the pivotal trials except SELECT-MONOTHERAPY, UPA was administered in combination with other csDMARDs: SELECT-COMPARE included stable background therapy of MTX while SELECT-NEXT and SELECT-BEYOND included stable background therapy of up to two csDMARDs. SELECT-MONOTHERAPY did not include any UK sites, while UK sites were included in the remaining three pivotal RCTs. In

[redacted]

An additional RCT – SELECT-SUNRISE – was not included in the company's presentation of the clinical effectiveness evidence, but was included in the network meta-analysis (NMA) and therefore informed the company's economic model. SELECT-SUNRISE was conducted in an exclusively Japanese population and was not an EMA registration trial.

ACR response was assessed in all four trials. When compared with PBO over a 12-week period (SELECT-NEXT and SELECT-BEYOND), and over a 14-week period (SELECT-MONOTHERAPY), UPA 15 mg QD demonstrated higher ACR20/50/70 and clinical remission in, despite differences between trials in concomitant treatments. The SELECT-COMPARE trial (through Week 26), a head-to-head comparison with ADA, demonstrated that the ACR20 response rate at Week 12 was significantly higher among UPA 15 mg QD treated patients compared with the 327 ADA-treated patients, at 71% versus 63% ($p<0.05$).

Clinical remission was assessed in all four trials based on DAS-28 CRP <2.6. Clinical remission with UPA 15 mg at 12-14 weeks (14 weeks in SELECT MONOTHERAPY and

12 weeks in the other three trials) was consistent across all trials (28.7%, 30.8%, 28% and 28.7% in SELECT COMPARE, SELECT NEXT, SELECT MONOTHERAPY and SELECT BEYOND respectively), despite differences between trials in concomitant treatments. Clinical remission was consistently higher with UPA 15 mg than with PBO: the clinical remission rates for PBO at 12-14 weeks (across the three PBO controlled trials) were 6.1%, 10.0% and 9.5% for SELECT COMPARE, SELECT NEXT and SELECT BEYOND respectively.

At 14 weeks, the clinical remission rate with UPA 15 mg QD monotherapy was significantly higher than that for MTX monotherapy (28% versus 8%, p<0.001). When taken in combination with MTX, UPA 15 mg QD also resulted in a significantly higher remission rate than ADA combined with MTX at both 12 weeks (UPA 15 mg 28.7% ADA 18.0%, p<0.001) and 26 weeks (UPA 15 mg 40.9% ADA 26.9%, p<0.001).

The EQ-5D-5L and the SF-36 PCS were used to assess HRQoL at 12-14 weeks in all four trials (14 weeks for SELECT MONOTHERAPY). For SELECT COMPARE, EQ-5D-5L data were also reported at 26 weeks.

In all three PC trials (SELECT COMPARE, SELECT NEXT and SELECT BEYOND), and despite differences in concomitant treatments, UPA 15mg resulted in greater improvement on the EQ-5D-5L index at 12-14 weeks (0.2 versus 0.10 respectively in all three studies, p<0.001 in all three trials). Similar results were found for the SF-36 PCS at 12 weeks: there was greater improvement with UPA 15 mg QD than with PBO (mean change from baseline 7.9 versus 3.6 respectively, p<0.001 for SELECT COMPARE, 7.6 versus 3.0 respectively, p<0.001 for SELECT NEXT; 5.8 versus 2.4, p<0.001 for SELECT BEYOND). In SELECT COMPARE there was also greater improvement on the EQ-5D-5L with UPA 15 mg QD versus PBO at 26 weeks (EQ-5D-5L 0.22 versus 0.11 respectively, p<0.001).

At 14 weeks, there was greater improvement on both the EQ-5D-5L index and the SF-36-PCS with UPA 15 mg QD monotherapy compared with MTX monotherapy (EQ-5D-5L 0.2 vs 0.1 respectively, p<0.001; SF-36 PCS 8·3 versus 4·3 respectively, p<0·001). When taken in combination with MTX, UPA 15 mg QD resulted in a similar improvement on the EQ-5D-5L index as ADA combined with MTX at both 12 weeks (UPA 15 mg 0.21 ADA 0.17) and 26 weeks (UPA 15 mg 0.22 ADA 0.20). Change from baseline in SF-36 PCS scores was also similar with UPA 15 mg and ADA at 12 weeks (7.9 versus 6.3 respectively).

The network meta-analyses (NMA) submitted by the company related to two broad populations: csDMARD-experienced populations and bDMARD-experienced populations. NMAs focused only on ACR outcomes, using a statistical model to integrate ACR20, ACR50 and ACR70 outcomes even when trials reported more than one of these. The company then used a probabilistic algorithm to match NMA findings on ACR outcomes onto EULAR response, which then informed the cost-effectiveness model. NMAs supported the effectiveness of UPA in improving the probability of ACR20, ACR50 and ACR70 in both populations. Because SELECT trial data contributed three-month time points, the company used a meta-regression method together with other trials' data from three months and from six months to 'project' the effectiveness of UPA at six months.

Thus, key findings relate to effectiveness at six months as 'projected' for UPA. In the csDMARD-experienced population, UPA 15 mg yielded a probability of ACR20 of [redacted]. UPA 15 mg in combination with csDMARDs yielded a probability of ACR20 of [redacted]. For both regimens, the probability of inferiority as compared to PBO was <0.001, and as compared to csDMARDs alone was <0.001 as well. In the bDMARD-experienced population, UPA 15 mg in combination with csDMARDs yielded a probability of ACR20 [redacted] The probability of inferiority as compared to csDMARDs alone was 0.003.

1.3 Summary of the ERG's critique of the clinical effectiveness evidence submitted

The company conducted a SLR that was appropriately aligned with the NICE final scope. The ERG considered the company's search strategies to be well-conducted and reported. Although some issues were noted, the ERG was broadly satisfied that the company identified all relevant RCTs for UPA and comparators. The ERG was broadly satisfied with the study selection and quality assessment (QA) methods for the UPA trials. The ERG noted however that there was a lack of detail on how the study selection criteria were applied, meaning that the ERG could not definitively confirm that no trials for the technology of interest were inappropriately excluded during the screening process. Moreover, the ERG considered that the SELECT-SUNRISE trial did meet the inclusion criteria for the SLR and therefore detailed clinical effectiveness evidence should have been provided for this trial, especially since it informs the NMA and economic modelling.

The ERG considered the four trials that were included as pivotal trials in the clinical evidence submission to be appropriate and fulfilled the inclusion criteria. All were RCTs and the study designs were in line with the NICE final scope and the SLR inclusion criteria. The ERG noted that UPA was used as monotherapy in one of the pivotal trials (SELECT-MONOTHERAPY), and was administered in combination with MTX and other csDMARDs in other trials. The included trials were a mixture of PBO and/or active controlled trials – active control was with ADA in SELECT-COMPARE and with MTX in SELECT-MONOTHERAPY. The ERG noted that there were no UK sites in SELECT-MONOTHERAPY and that the [redacted] The ERG considered the study populations in all four trials to be relevant to the decision problem and to exhibit a large degree of between-trial comparability, although differences in prior medication regimens were noted.

Head-to-head evidence is provided for certain comparisons, although the key clinical effectiveness comparisons that serve as inputs to the economic model are comparative data derived from an NMA, in order to take into account the totality of the available evidence across the network. The evidence presented in the CS broadly covered the range of outcomes included in the NICE final scope, although it was noted that only safety data were available for extra-articular manifestations. The ERG agreed that there was generally a low risk of bias in the four pivotal trials for the technology of interest.

The ERG found no discrepancies in trial results compared to the respective CSRs. The ERG noted that here was some variation between the studies in the primary and secondary outcomes used to assess clinical and functional efficacy and HRQoL of UPA. The ERG also noted that, for three of the trials, between-group data were reported only at 12-14 weeks. It is important to consider that the 26 week data include patients who switched treatments.

Feasibility assessment was not explicitly reported for the NMAs undertaken. This is a major omission that threatens the credibility of the NMAs presented. The ERG considered the inclusion criteria for the NMA to be largely appropriate. However, due to a lack of clarity in the reasons of exclusion, the ERG could not rule out the potential of inappropriate exclusion of trials from the NMAs. The company appraised the quality of the 61 trials included in the two NMAs (55 that were included in the NMA for the biologic (b)DMARDs experienced population and 12 that were included in the NMA for the csDMARD experienced population, noting that six trials were included in both NMAs). In order to provide a general check of accuracy of these 61 QA assessments, the ERG

randomly selected seven of these studies (≈10%). One of the studies randomly selected by the ERG was the SELECT BEYOND study; a critique of the QA for SELECT BEYOND had already been performed. For five of the remaining six selected studies, the ERG was mostly in agreement with the ratings made by the company. However, for one of these studies,[1] the ERG found errors in the QA that are likely to underestimate the quality of this study. The ERG also noted that the QA was not used to select or weight studies in the NMA, or in the economic modelling. The ERG considered, therefore, that any errors or potential errors in the QA of the remaining studies could affect transitivity of networks in NMA, but would not necessarily impact choice of studies for NMA or economic modelling.

In addition to these issues, the ERG urges caution in the interpretation of these NMAs for several reasons. First, as noted above, data for six months from SELECT relies on a 'projection' from three month data, though sensitivity analyses to these projections suggested results were reasonably robust. Second, the ERG identified potential issues in inclusion and exclusion of studies as well as data extraction that preclude certainty as to whether all studies and all data from studies were appropriately included. Third, while the statistical methods and assumptions used were standard and appropriate, the ERG was unable to replicate the company's NMA due to an issue with the code provided and with the time allotted could not reconstruct the NMA in alternate software. Fourth, the ERG noted remaining ambiguities as to how reference arm probabilities were pooled to estimate the 'absolute' probabilities of response for each treatment in each network. Fifth, the ERG considered that interpretation of NMA findings was complicated by the need for strong conceptual assumptions relating to exchangeability of effect at different points in the treatment pathway and different disease severities; that is, moderate and severe RA were not considered separately, and treatment effects are assumed to be equivalent, for example, after one csDMARD and after two or more csDMARDs, or after one bDMARD and after two or more bDMARDs. This also means that data used to inform comparisons where no head-to-head data exist include people who are potentially not 'at risk' of receiving these treatments.

1.4 Summary of cost-effectiveness evidence submitted by the company

Note that all results in this document include the UPA PAS but do not include the other advanced DMARDs' PAS or the confidential prices of the biosimilars. The prices for biosimilars of ADA and ETN have a particularly large effect upon some results, as presented in the cPAS appendix.

The company performed a literature review to identify economic evaluations of interventions used to treat people with moderate or severe RA. No prior economic evaluations of UPA in the specified population were identified. The company also presented an SLR of utilities and healthcare resource utilisation and costs, and used identified studies to inform model parameters.

The company develops a de novo individual patient discrete event simulation model programmed in visual basic, with an Excel front end acting as a database store of values. Each model run simulates 10,000 patients and shows reasonable convergence. The structure and inputs to it mirror much of that of TA375. The main differences are that the company:

- Models the progression from moderate RA to severe RA, this relying upon a HAQ to DAS-28 mapping derived from the SELECT trials.
- Derives an alternative HAQ to pain mapping function from the SELECT trials and applies this to estimate quality of life values using the same HAQ and pain to EQ-5D quality of life function as TA375.

The company presents validation data that shows the company model closely replicates the results of the TA375 model provided that the progression from moderate RA to severe RA is not applied and that the TA375 HAQ to pain mapping function is applied.

Patients receive either first line UPA monotherapy or first-line UPA in combination with MTX. Among moderate RA patients the first-line treatment in the comparator arm is either BSC, MTX or intensified csDMARDs depending upon the position sought. Among severe RA patients the full range of advanced DMARDs are considered as possible alternative first-line treatments, as monotherapy or with MTX depending upon the position sought.

EULAR response rates are taken from the company csDMARD-IR NMA and bDMARD-IR NMA. BSC is assumed to have a 0% EULAR response rate.

Patients who achieve a EULAR response remain on treatment and their HAQ score is reduced. Patients who do not achieve a EULAR response have that line of treatment withdrawn and their HAQ rebounds to the baseline value. They may then try a subsequent line of treatment and if they achieve a EULAR response to that line of treatment their HAQ score is reduced.

Those remaining on bDMARDs are assumed to have a constant HAQ, which is the same assumption as made in TA375. Those not on bDMARDs see their HAQ worsen over time, based upon the same function as used in TA375.

Those who achieve a EULAR response do not remain on that line of treatment forever. Treatment discontinuation curves are derived from TA375, differentiated by whether patients have moderate RA or severe RA.

Patients progress through the various line of treatment and eventually reach BSC or palliative care.

As noted above, quality of life values are calculated from a HAQ and pain score mapping function to EQ-5D values. This is the same function that was used in TA375. The difference is that the company derives a HAQ to pain score mapping function from the SELECT trial data whereas that of TA375 was based upon the large NDB dataset.

In addition to the direct drug costs the TA375 administration and monitoring costs are applied, uplifted to 2018 prices using the HCHS index. The TA375 HAQ to inpatient costs are also used, though the company adopts a quadratic fit to the TA375 costs rather than applying the TA375 costs directly.

The company models the following 10 population subgroups, with the resulting cost effectiveness estimates.

- 1a: Moderate RA, MTX intolerant, RTX tolerant, failed one csDMARD. UPA monotherapy compared to intensified csDMARDs has a cost effectiveness of £16,554 per QALY.
- 1b: Moderate RA, MTX tolerant, RTX tolerant, failed one csDMARD. UPA monotherapy compared to intensified csDMARDs has a cost effectiveness of £22,659 per QALY. UPA with MTX compared to intensified csDMARDs has a cost effectiveness of £21,631 per QALY.
- 2a: Moderate RA, MTX intolerant, RTX tolerant, failed ≥2 csDMARD. UPA monotherapy compared to BSC has a cost effectiveness of £8,885 per QALY.
- 2b: Moderate RA, MTX tolerant, RTX tolerant, failed ≥2 csDMARD. UPA monotherapy compared to MTX has a cost effectiveness of £13,568 per QALY. UPA with MTX compared to MTX has a cost effectiveness of £13,434 per QALY.

- 3a: Severe RA, MTX intolerant, RTX tolerant, failed ≥2 csDMARD. UPA monotherapy dominates almost all bDMARDs. Tocilizumab (TCZ) results in slightly higher patient gains but its cost effectiveness is poor at around £500k per QALY.

- 3b: Severe RA, MTX tolerant, RTX tolerant, failed ≥2 csDMARD. UPA monotherapy dominates or is very cost effective compared to bDMARDs. UPA with MTX dominates all bDMARDs with the exception of certoluzumab pegol which confers slightly greater patient benefits but has a poor cost effectiveness of around £800k per QALY.

- 4a: Severe RA, MTX intolerant, RTX tolerant, failed one bDMARD. UPA monotherapy is estimated to be quite a lot cheaper and marginally better than bDMARDs, so formally dominates them.

- 4b: Severe RA, MTX tolerant, RTX intolerant, failed one bDMARD. UPA monotherapy dominates or is very cost effective compared to bDMARDs. UPA with MTX dominates all bDMARDs with the exception of intravenous TCZ which confers slightly greater patient benefits but has a poor cost effectiveness of over £2mn per QALY.

- 5: Severe RA, MTX tolerant, RTX tolerant, failed one bDMARD. RTX dominates both UPA monotherapy and UPA with MTX.

- 6: Severe RA, MTX tolerant, RTX tolerant, failed RTX. Compared to UPA monotherapy both sarilumab (SRL) with MTX and intravenous TCZ with MTX yield slight benefits but at considerable additional cost and a cost effectiveness of £988k per QALY and £298k per QALY respectively. UPA with MTX dominates sarilumab with MTX. Compared to UPA with MTX intravenous TCZ with MTX yields slight benefits but at considerable additional cost and a cost effectiveness of £420k per QALY.

1.5 Summary of the ERG's critique of the cost-effectiveness evidence submitted

The key difference from the TA375 modelling is that moderate RA patients can progress to be severe RA patients. This requires that the relationship between the HAQ and the DAS-28 be specified. The company estimates this from the three-month and six-month data of the SELECT trials. This is then used to extrapolate over the 45-year time horizon of the model. It may be questionable to use six-month data when the HAQ and the DAS-

28 are generally improving to extrapolate over 45 years when the HAQ is generally modelled as worsening. There is also a question about a disappearing company intercept term and whether it should be applied in the modelling. The application of the intercept term generally worsens the cost-effectiveness estimates.

The ERG corrected some bDMARDs drug and administration costs.

The ERG preferred the HAQ to inpatient costs mapping of TA375 but this had little effect upon results.

The ERG preferred the HAQ to pain mapping of TA375, in part due to the size of the database it stems from and in part due to the visual fit to the SELECT trials' quality of life data. This worsens the cost-effectiveness estimates by a reasonable margin, but in itself is unlikely to change the overall conclusions.

The ERG thinks that the csDMARD-IR NMA results should be applied to patients who are bDMARD naïve and that the bDMARD-IR NMA results should be applied to patients who are bDMARD experienced. In the modelling of moderate RA patients this implies that for those progressing to severe RA the clinical effectiveness of first-line ADA for treatment of severe RA in the UPA arm should be drawn from the bDMARD-IR NMA while in the comparator arm it should be drawn from the csDMARD-IR NMA. The response rates of the bDMARD-IR NMA are typically worse than those of the csDMARD-IR NMA. But due to a lack of evidence, company assumptions mean that the response rates for ADA monotherapy in the csDMARD-IR NMA are a little worse than in the bDMARD-IR NMA. Given this, the ERG thinks that the cost-effectiveness estimates for MTX-tolerant moderate RA patients are likely to be more reliable than the cost effectiveness estimates for MTX intolerant moderate RA patients.

For moderate RA patients the company models treatment sequences where after UPA it is possible to intensify csDMARDs. ERG modelling suggests that among moderate RA patients it is more cost effective to intensify csDMARDs prior to using UPA and to use UPA among those failing to response to intensified csDMARDs; i.e. try the cheap treatment first and use the expensive treatment if this does not work.

A key difference between the company and the ERG is that the company thinks that when UPA is compared with BSC, BSC should be assumed to have 0% EULAR response rates. The ERG notes that in all SELECT trials there were significant EULAR response rates in the control arms. Whether the response rates in the control arms were due to natural recovery or to a pure trial or PBO effect is not known. The ERG thinks that

BSC should be assumed to have the EULAR response rates of PBO in the company NMA or of the control arms in the SELECT trials. If the company approach is accepted UPA is estimated to be cost effective for moderate RA patients at conventional willingness to pay thresholds. If the ERG approach is accepted UPA is estimated to be not cost effective for moderate RA patients at conventional willingness to pay thresholds.

It should be noted that the company NMA results for PBO and intensified csDMARDs may be subject to more uncertainty than those for advanced DMARDs. But applying the head to head results of the SELECT trials generally results in qualitatively similar cost effectiveness estimates for the modelling of moderate RA patients.

A key question if UPA is approved among moderate RA patients is whether, as a last in line therapy, if a patient fails to achieve a moderate EULAR response but shows some DAS-28 improvement they would have UPA withdrawn. The ERG thinks that if those trialling UPA who receive some benefit but do not achieve a EULAR response will tend to remain on UPA the cost effectiveness of UPA for moderate RA patients will be considerably worse that the estimates presented in this document. A related question is the possible ease of manipulating DAS-28 scores, given the significance of the patient reported general health visual analogue score to its calculation.

A difference between the ERG modelling and both the company modelling and the modelling of TA375 is that the ERG does not include a final line of MTX monotherapy. The ERG thinks that it is not appropriate to model patients who have failed on other lines of therapy such as intensified csDMARDs, who by implication have already previously failed on MTX monotherapy, as having a response to a last line of MTX monotherapy. But the modelling that includes this somewhat worsens the cost-effectiveness estimates. The ERG thinks that it is likely that those who do not respond to their final line of treatment will receive some ongoing treatment and that this will have some effect, if not a EULAR response. If this was included in the modelling the ERG thinks that this would worsen the cost-effectiveness estimates.

The ERG revisions to the company modelling of severe RA patients do not particularly affect the cost-effectiveness estimates and the results that should be drawn from them.

UPA is estimated to be cost effective among those who have failed to respond to RTX. It should be noted that these patients will have had at least two previous advanced DMARDs. The bDMARD-IR NMA estimates may be less reliable for these patients. It can also be noted that less than 20% of SELECT-BEYOND patients were RTX experienced.

The main differences of opinion between the ERG modelling and the company modelling are:

- The treatment sequences. Is it sensible to model EULAR responses to a last line treatment with MTX monotherapy when by definition these patients will have previously failed on MTX monotherapy?
- The treatment sequences. Is it sensible or likely to be cost effective to try UPA before trying intensified csDMARDs?
- Should natural recovery and the PBO effect be included in the comparator arm, given that they will be present in the UPA arm?
- Is the HAQ to pain mapping of TA375 more reliable than the company estimates from the SELECT trials?
- Are the ERG revised drug costs more accurate?

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

- The company's SLR was well aligned with the NICE scope for this appraisal.
- The company's literature searches were generally appropriate and well-reported.
- The ERG was broadly satisfied with the study selection criteria and QA methods for the UPA trials.
- The four included trials all appeared relevant and appropriate, and were largely considered to be at low risk of bias.
- The study populations in all four trials were relevant to the decision problem and exhibited a large degree of between-trial comparability.
- The NMA inclusion criteria were largely appropriate.

1.6.2 Weaknesses

- The ERG noted however that there was a lack of detail on how the study selection criteria were applied.
- The ERG considered that the SELECT-SUNRISE trial fulfilled the SLR inclusion crtieria and should have been presented in the clinical effectiveness evidence, not solely in the NMA and economic model sections.

- One of the four included trials did not include any UK sites, while the proportion in the other three trials was [redacted].
- Between-trial differences in prior medication regimens were noted.
- Feasibility assessment was not explicitly reported for the NMAs undertaken. This is a major omission that threatens the credibility of the NMAs presented.
- NMA data for six months relies on a 'projection' from three-month data.
- The ERG identified a range of potential issues in inclusion and exclusion of studies as well as data extraction that preclude certainty as to whether all studies and all data from studies were appropriately included.
- The ERG was unable to replicate the company's NMA due to an issue with the code provided.
- The ERG noted remaining ambiguities as to how reference arm probabilities were pooled to estimate the 'absolute' probabilities of response for each treatment in each network.
- The ERG considered that interpretation of NMA findings was complicated by the need for strong conceptual assumptions relating to exchangeability of effect at different points in the treatment pathway and different disease severities; that is, moderate and severe RA were not considered separately, and treatment effects are assumed to be equivalent, for example, after one csDMARD and after two or more csDMARD, or after one bDMARD and after two or more bDMARDs. This also means that data used to inform comparisons where no head-to-head data exist include people who are potentially not 'at risk' of receiving these treatments.

1.6.3 Areas of uncertainty

Remaining areas of uncertainty include:

- What should be assumed for those who are without a response and are at end of line? These patients are assumed to receive palliative care with no benefit. Moderate RA patients may tend to be treated with whatever combination of csDMARDs worked best for them, even if a EULAR response was not achieved. The ERG thinks that including this would worsen the cost effectiveness estimates.
- If UPA is trialled as last in line among moderate RA patients would those who got some benefit from it but did not achieve a EULAR response tend to remain on it?

The ERG thinks that if they would this would considerably worsen the cost-effectiveness estimates.

- Is it reasonable to extrapolate the company HAQ to DAS relationship based upon six-month improvements in the SELECT trials to 45 years when the HAQ is generally modelled as worsening? The ERG thinks that if this relationship breaks down over time this could worsen the cost-effectiveness estimates, though whether this is more of a modelling issue than a real world concern is debateable.

- Are EULAR response rates the same at different lines of treatment? The response rates in the bDMARD-IR NMA are typically worse than those of the csDMARD-IR NMA. The ERG thinks that this does not particularly affect the modelling of moderate RA patients, but it might mean that progressing to severe RA is more serious and so more to be avoided. What effect this would have upon the cost-effectiveness estimates is difficult to speculate upon, in part due to the bDMARD-IR NMA applying from first-line therapy for severe RA in the UPA arm but only applying from second-line therapy for severe RA in the comparator arm.

- Are the clinical effectiveness estimates applicable to those who have failed RTX? The ERG noted that these patients would have failed at least two lines of advanced DMARDs and that only a small proportion of SELECT-BEYOND patients were RTX experienced.

- While more of a clinical issue there may also be concerns about the reliability of the NMAs' clinical effectiveness estimates for PBO and intensified csDMARDs. The ERG explored this by applying the head-to-head results of the SELECT trials.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG modelling of moderate RA patients differs from the company in four main ways.

- Having modelled a comparison of (1) intensification of csDMARDs after trialling UPA with (2) intensification of csDMARDs before trialling UPA and found (1) to be not cost effective, the main ERG modelling does not consider intensification of csDMARDs after UPA.

- Where UPA is compared with BSC, the ERG applies the PBO response rates of the company csDMARD-IR NMA or the SELECT trials' head-to-head results for UPA compared to the control arm.
- The ERG applies the TA375 HAQ to pain mapping.
- The ERG corrects some comparator drug and administration costs.

The ERG typically estimates that among moderate RA patients UPA is not cost effective, with cost-effectiveness estimates exceeding £30k per QALY and often exceeding £50k per QALY.

If the treatment sequences for those transitioning from moderate RA to severe RA are differentiated by arm as seems reasonable this tends to worsen the cost effectiveness estimates.

Applying the company HAQ to pain mapping function typically improves the cost effectiveness estimates but does not qualitatively change the main thrust of the results.

The exception to this is if it is assumed that (1) there was no natural recovery in the SELECT trials' comparator arms and (2) any PBO effect in the SELECT trials should not be applied. This causes the ERG to estimate UPA to be cost effective compared to BSC among moderate RA patients.

The ERG costs-effectiveness estimates among severe RA patients are qualitatively similar to the company estimates.

2 Background

2.1 Critique of company's description of underlying health problem

The health condition and treatment pathways is provided in the CS (pages 18-29).

Rheumatoid arthritis (RA) is an inflammatory autoimmune disease that typically affects the synovial tissue of the small joints of the hands and feet but can affect any synovial joint, causing swelling, stiffness, pain and progressive joint destruction. Extra-articular manifestations of RA can include the lungs, heart and eyes.

The incidence of RA has been estimated to be 40 per 100,000 person years.[2] Globally, the prevalence of RA has been estimated to be between 0.5% and 1% of the population, with a higher prevalence in women and the elderly.[3] RA risk can be attributed to a combination of environmental and genetic factors, the latter predicting around 50% of the risk.[4]

Disease activity is the key clinical indicator and prognostic marker in RA and is classified using the disease activity score 28-joint count (DAS-28) scoring system,[5] a composite measure based upon the number of joints impacted by disease and biomarkers of inflammation. It also usually includes a patient reported outcome for global health assessment based on a 100 mm visual analogue scale (VAS) scored from 0 to 100. A DAS-28 score between 3.2 and 5.1 indicates moderate RA, while a score over 5.1 indicates severe RA. A score less than 2.6 indicates disease remission.[6] Forty-three percent of RA patients have been estimated to have moderate RA according to DAS-28, 27% severe RA and 31% mild RA.[7]

ERG comment:

The ERG considered the company's description of the disease area to be appropriate and broadly representative of the literature.

2.2 Critique of company's overview of current service provision

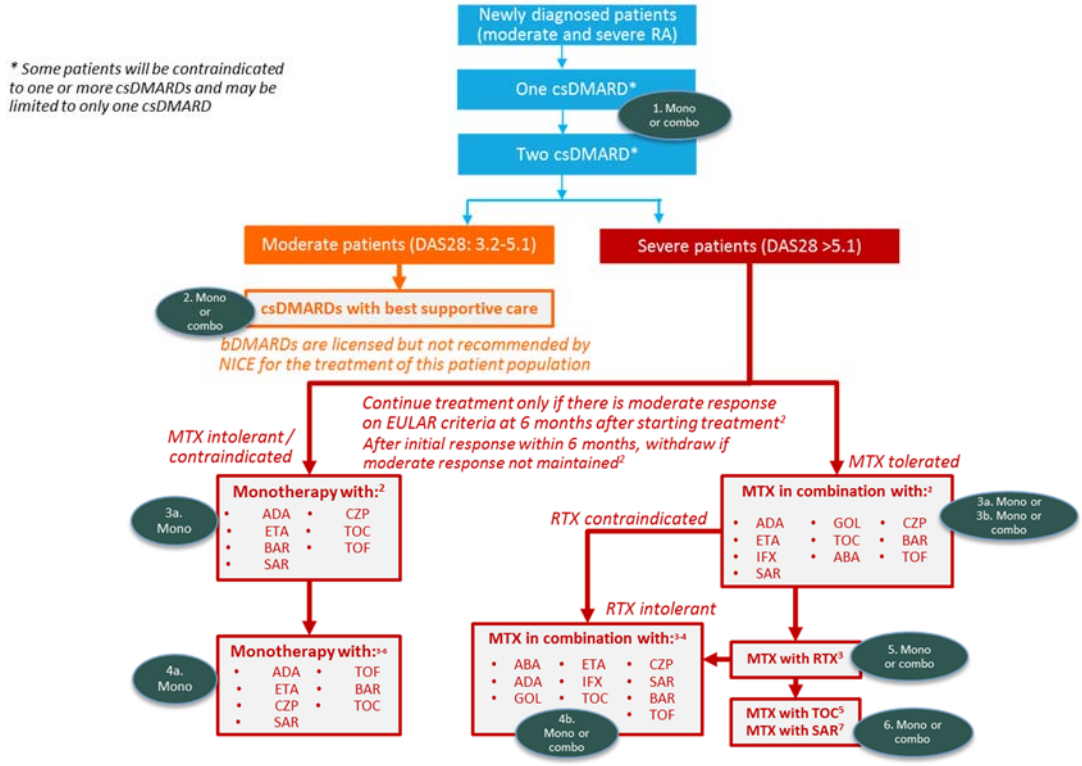
The CS states that the treatment pathway is based on NICE Clinical Guideline (CG) 100[8] as depicted in Figure 1.

NICE CG100 recommends that first-line treatment for newly diagnosed RA should be with csDMARD monotherapy with oral MTX, leflunomide or sulfasalazine. If patients are intolerant or do not respond to the first csDMARD, additional csDMARDs (oral MTX, leflunomide, sulfasalazine or hydroxychloroquine [HCQ]) should be offered in combination in a step-up strategy when the treatment target (remission or low disease

activity) has not been achieved despite dose escalation. In the NICE CG100 treatment pathway, 'advanced therapies' – bDMARDs (including interleukin-6 [IL-6] inhibitors) – are introduced only for patients with severe RA. NICE TAs 375, 466, 480 and 485 recommend bDMARDs (ADA, etanercept [ETN], infliximab [IFX], certolizumab pegol [CTZ], golimumab [GOL], tocilizumab [TCZ], abatacept [ABT] and sarilumab [SRL]) or other targeted synthetic (ts) DMARDs (baricitinib [BRC] and tofacitinib [TFC]) each in combination with MTX (if not intolerant/contraindicated) for severe RA only.

EULAR guidelines[9], in contrast, introduce advanced therapies at an earlier stage in the treatment pathway. EULAR guidelines recommend that advanced therapies such as a bDMARD or tsDMARD should be considered if the treatment target is not met with the first csDMARD strategy and poor prognostic factors are present. This distinction is relevant to the company's proposed positioning of udadacitinib as critiqued in Section 3 of this report. The company considered that: "In the UK the lack of flexibility allowed to clinicians to tailor the use of advanced therapy to the needs of patients may result in poorer long-term outcomes" (CS, p.27).[10]

Figure 1. Positioning of UPA within the existing NICE pathway



Abbreviations: csDMARDs, conventionsl synthetic disease modifying antirheumatic drugs; NICE, National Institute for Health and Care Excellence; UPA, upadacitinib

Source: CS, p.29, Figure 2.

The company estimated that there would be [redacted] moderate RA and [redacted] candidates for advanced therapies one year after launch, rising to [redacted] and [redacted] respectively after five years (Company budget impact assessment, p.8, Tables 3 and 5). The ERG noted, however, that these figures related to all advanced therapies and were not specific to UPA. Not all eligible patients commence UPA due to the existence of a range of treatment options in the corresponding position in the treatment pathway. The company estimated a market share for UPA of [redacted] one year after launch in severe RA rising to [redacted] after five years (Company budget impact assessment, p.14, Table 19). It is projected that this would put UPA in [redacted] place in terms of market share [redacted] For moderate RA, the estimated market share was [redacted] after one year rising to [redacted] after five years (Company budget impact assessment, p.15, Table 21).

ERG comment:

The ERG considered the company's description of current service provision to be appropriate and relevant to the appraisal. The treatment pathway was considered to be reasonably representative of standard NHS treatment for moderate and severe RA in England and Wales, and to be in line with NICE CG100. It was considered that BSC would rarely be used, instead being largely a historical treatment. It was considered that RTX may in routine clinical practice be used earlier in the treatment pathway than shown. It was also considered that the diagram may make a sharper delineation between how moderate and severe RA are treated than would be observed in routine clinical practice where a more pragmatic approach following the 'treat to target' principle (i.e. where treatments are chosen and combined to reach patient-defined treatment goals), and patient preference may also play an important role. No service provision beyond the current levels of monitoring and assessment would be necessitated by the introduction of UPA into the current treatment pathway. The ERG noted that there were considerable simplifications in the assumptions underpinning the budget impact projections for moderate RA.

3 Critique of company's definition of decision problem

3.1 Population

The population corresponds to the full proposed marketing authorisation for UPA. This is for the treatment of moderate to severe active RA in adult patients who have responded inadequately to, or who are intolerant to one or more csDMARDs, i.e the position in the treatment pathway at which advanced therapies are recommended in the EULAR guidelines. The ERG agreed with the company that the population presented in the CS is consistent with the final scope for this appraisal.[11] The ERG noted that the CS categorised the populations and associated comparators by tolerance or intolerance to MTX. Previous NICE TAs have only recommended advanced therapies for severe RA in patients who are intolerant to MTX or for whom it is contraindicated, or when patients have not responded to prior csDMARDs. The company sought to position UPA as an option as a monotherapy regardless of MTX tolerance. Additionally, on the advice of an advisory board,[12] the company considered a population of severe active RA that has not responded adequately to both MTX and RTX.

ERG comment:

The ERG considered the population in the CS to be appropriate. The trials were largely similar in their demographic and clinical profiles, although they did differ in terms of permitted prior medication regimens.

3.2 Intervention

The intervention in the scope and decision problem is UPA (brand name unknown), an oral JAK-1 inhibitor, either as monotherapy or in combination with other csDMARDS, including MTX. The dose of UPA in the decision problem is 15 mg QD. The draft summary of product characteristics (SmPC) and European public assessment report (EPAR) were provided in Appendix C of the CS. Note that UPA does not currently have EU marketing authorisation. In the CS, the company stated that it submitted an application in December 2018, with European approval expected in [redacted]. The CS did state that the planned launch for UPA in the UK is [redacted] and that a submission to the Scottish Medicines Consortium was also planned.

ERG comment:

The ERG considered the description of the technology of interest in the CS to be accurate. The scope for this appraisal and the trials included in the CS consider UPA both as monotherapy and in combination with other csDMARDS, including MTX. This

dual positioning is a factor that needs to be taken into consideration in this appraisal. In all trials, the dose of UPA corresponds to the dose in the decision problem.

3.3 Comparators

UPA is compared to a range of comparators in the CS, categorised by disease activity (moderate or severe RA according to DAS-28) and tolerance or intolerance to MTX, in addition to a specific sub-population of severe active RA that has not responded adequately to both MTX and RTX. The comparators in the company decision problem in each position in the treatment pathway are shown in Table 1.

Table 1. Comparators by position in treatment pathway

1 and 2: For moderate active RA that has not responded adequately to therapy with csDMARDs (comparators will vary dependent upon MTX tolerance/contraindication and one or two csDMARD failure):

- Combination therapy with csDMARDs (including MTX and at least one other DMARD, such as sulfasalazine and leflunomide).
- csDMARD monotherapy with dose escalation.
- BSC (only where csDMARDs are not appropriate due to intolerance).

3a & 3b: For severe active RA that has not responded adequately to therapy with csDMARDs only and who tolerate MTX and it is not contraindicated:

- Advanced therapies in combination with MTX (ADA, ETN, IFX, CTZ, GOL, TCZ, ABT, BRC, TFC or SRL).

3a: For severe active RA that has not responded adequately to therapy with csDMARDs only and who do not tolerate MTX, or it is contraindicated:

- ADA, ETN, CTZ, TCZ, BRC, TFC or SRL (each as monotherapy)

4a: For severe active RA that has not responded adequately to therapy with advanced therapies and when RTX is contraindicated or withdrawn due to adverse events and who do not tolerate MTX, or it is contraindicated:

- ADA, ETN, CTZ, TCZ, TFC, BRC, or SRL (each as monotherapy)

4b: For severe active RA that has not responded adequately to therapy with advanced therapies and when RTX is contraindicated or withdrawn due to AEs and who tolerate MTX and it is not contraindicated:

- ADA, ETN, IFX, ABT, TCZ, CTZ, GOL, BRC, TFC, or SRL, each in combination with MTX

5: For severe active RA that has not responded adequately to therapy with advanced therapies either in combination with MTX or as monotherapy and who tolerate MTX and RTX and it is not contraindicated:

- RTX in combination with MTX

6: For severe active RA that has not responded adequately to therapy with RTX and MTX:

- TCZ, SRL in combination with MTX

Abbreviations: ABT, abatacept; ADA, adalimumab; AEs, adverse events; BRC, baricitinib; BSC, best supportive care; CTZ, certolizumab pegol; csDMARDs, conventional synthetic disease modifying antirheumatic drugs; ETN, etanercept; GOL, golimumab; IFX, infliximab; MTX, methotrexate; RA, rheumatoid arthritis; RTX, rituximab; SRL, sarilumab; TCZ, tocilizumab; TFC, tofacitinib

Source: CS, pp.13-14, Table 1.

The CS categorises the population additionally by tolerance or intolerance to MTX, in addition to presenting a sub-population for people who have not responded to both MTX

and RTX. This presents the population in greater granularity than the NICE scope, but is not incompatible with it, and is principally relevant to UPA as a monotherapy rather than in combination with MTX.

ERG comment:

The ERG considered the comparators in the CS to be compatible with those presented in the NICE scope. The ERG considered that BSC would not be used in routine practice, while RTX may be used earlier in the pathway. Therefore, while the positioning of comparators in the pathway may align with clinical guidelines, it may not align completely with routine clinical practice.

3.4 Outcomes

The outcomes reported in the decision problem, described in the CS, and used in the economic evaluation, match those in the NICE scope subject to one proviso. The outcomes in the NICE scope are: disease activity, physical function, joint damage, pain, mortality, fatigue, radiological progression, extra-articular manifestations of disease, adverse effects (AEs) of treatment, and health-related quality of life (HRQoL). It is reported in the CS (pages 14-15, Table 1) that: "extra-articular manifestations of disease were not captured as a specific outcome in the SELECT clinical trial programme. However, the relevant related outcomes are reported in the safety analysis in Section B.2".

ERG comment:

The ERG considered the outcomes reported in the CS for UPA to be appropriate. The ERG noted that only safety data and not clinical effectiveness data were available for extra-articular manifestations, which is a limitation in terms of capturing the full clinical impact of RA. Nevertheless, disease activity is the key measure.

3.5 Other relevant factors

The company stated that there were no significant equity issues in the context of this appraisal. A PAS has been submitted to the PASLU for consideration.

ERG comment:

The ERG agreed with the company that there were unlikely to be significant equity issues in the context of this appraisal.

[redacted]

[redacted], which has been taken into account in the work of the ERG,
[redacted]

4 Clinical effectiveness

4.1 Critique of the methods of review(s)

4.1.1 Searches

Searches to identify RCTs relevant to UPA (and comparators) in patients with RA were completed by the company in December 2017, and updated in April 2019. The clinical effectiveness searches are reported in Appendix D of the CS.

The following bibliographic databases were searched: Ovid Embase, MEDLINE, and EBM Reviews (incorporating the Cochrane Library databases). The search strategy uses a combination of indexing (e.g. MeSH in MEDLINE) and free text (i.e. title and abstract) terms, and searches were not limited by language. Additional searches were conducted for trials in conference proceedings, on health technology assessment (HTA) websites and on ClinicalTrials.gov.

The clinical effectiveness searches use a combination of terms for the population (RA), intervention (UPA), comparators (ADA, ETN, IFX, GOL, CTZ, TFC, baracitinib, filgotinib, peficitinib, RTX, ABT, TCZ, SRL, and anakinra) and study design (RCTs). These were combined appropriately using Boolean logic.

The population component of the search used the exploded subject heading for rheumatoid arthritis and free text term for 'rheumatoid arthritis'. The searches did not include alternative synonyms for rheumatoid arthritis as utilized in search strategies for the NICE guideline,[8] such as inflammatory arthritis, polyarthritis and rheumarthritis. However, the ERG considered that their inclusion in the search strategy was unlikely to yield additional relevant trials.

Searches for all biosimilars and brand names for comparators have not been included in the search strategies. Subject headings were used for generic drug names, but the following free-text search terms for the comparators were not used in search strategies:

- For IFX: Inflectra, Renflexis, Zessly, Revellex, Ixifi, Flixabi, Flammegis, Infimab
- For ETN: Erelzi, Lifmior, TuNEX (ENIA11), Brenzys, Intacept, Etacept, Davictrol
- For ADA: Amjevita, Amgevita, Cyltezo, Halimatoz, Hefiya, Hyrimoz, Hulio, abp 501, abp501, Imraldi, Solymbic, Exemptia, Adfrar
- For TCZ: LusiNEX, atlizumab, R1569
- For TFC: tasocitinib
- For sirukumab (SRK): Plivensia

- For RTX: Tuxella, Rituzena, Ritemvia, Blitzima, Truxima, Riximyo, Rixathon, Reditux; Zytix, AcellBia, Maball, MabTas, Rituxirel

Furthermore, search terms for drug categories such as tumour necrosis factor (TNF)-alpha, bDMARDs, and JAK inhibitors were not included in the search strategies. As a result, the searches may have failed to identify all relevant trials for comparators.

The company has not cited a validated filter for RCTs, and this is not one the ERG recognised. However, the company used a variety of terms for RCTs. The company also completed a search in all databases combining search terms for UPA, with RA terms (with no study design filter) in order to identify observational studies for UPA only.

We undertook a search using additional drug terms for biosimilars and brand names, with a validated filter for identifying RCTs[13] (search date: 6th August 2019), and we did not retrieve any further trials. Details of the ERG's additional literature search are available in Section 4.5.1.

The ERG noted several other issues with the searches. The Embase search excluded abstract report publication types, and as a result may have missed conference abstracts indexed with this term. Update searches completed in April 2019 did not include all relevant date fields, and update searches may have failed to identify all new records added to the database since the original search. For example, in Ovid MEDLINE, *.dt.* (Create Date) and *.ez.* (Entrez Date, i.e. the date the citation was added to PubMed),[14] and in Ovid Embase, *.em.* (Entry Week) and *.dc.* (Date Created)[15] could also be applied for a comprehensive update search.

The Ovid MEDLINE update search includes an error in the .ed. date limit. The .ed. field refers to Entry Date, or the date that processing of a record is completed by PubMed. The CS search was limited in error up until January 2019 (instead of April 2019). This search may have failed to identify any new trials added to MEDLINE between January and April 2019.

The supplementary searches of conference proceedings, HTA websites and ClinicalTrials.gov are not well reported in Appendix D of the CS. In a response to a clarification question, the company confirmed that searches were completed for ongoing trials in ClinicalTrials.gov using the term 'rheumatoid arthritis'. This is an appropriate approach to identify ongoing trials for all comparators.

ERG comment:

Overall the bibliographic database searches for clinical effectiveness were well-conducted and reported. The ERG noted several issues outlined above. The ERG

conducted additional searches (Section 4.5.1) and are now broadly satisfied that the search strategy utilized by company identified all relevant RCTs for UPA and comparators.

4.1.2 Inclusion criteria

The inclusion and exclusion criteria for the SLR were provided in the CS (Table 1, Appendix D.1.4), which is reproduced below (Table 2). These criteria were designed to match the population, interventions, comparators, outcomes, and study design (PICOS) in the NICE final scope and the ERG agreed that the inclusion criteria and the NICE scope were broadly in agreement.

Table 2: Eligibility criteria for clinical review

#	Inclusion criteria	Exclusion criteria	Justification
Population	Adult patients (≥18 years of age) meeting the ACR Classification criteria for RA, and an inadequate response to csDMARDs or bDMARDs	Patients with any other disease	In line with NICE potential scope
Interventions	UPA 15 mg or 30 mg QD in monotherapy or in combination	-	In line with NICE potential scope
Comparators	JAK-inhibitors: • TFC (Xeljanz®) • BRC (Olumiant®) • Filgotinib • Peficitinib bDMARDs TNF-α inhibitors: • ADA (Humira®) • ETN (Enbrel®) • IFX (Remicade®) • GOL (Simponi®) • CTZ (Cimzia®) Anti-B-cell therapy • RTX (Rituxan®) Co-stimulatory inhibitor molecules: • ABTOrencia®) Anti IL-6 therapy • TCZ (Actemra®) • SRL Anti IL-1 therapy: • Anakinra (Kineret®) Additional interventions: • Filgotinib and peficitinib	Any intervention other than the included list	In line with NICE potential scope

#	Inclusion criteria	Exclusion criteria	Justification
	Biosimilars to any of the interventions listed above		
Outcomes	Clinical study SLR (final list of outcomes of interest to be agreed in conjunction with Abbvie) **Efficacy** • ACR 20/50/70 response rate to treatment (defined as a 20%/50%/70% improvement in TJC and SJC and the same level of improvement in three of the five following variables: patient and physician global assessments, pain, HAQ-DI, and acute phase reactants). • HAQ-DI (change from baseline) • EULAR response ('good', 'moderate', 'good/moderate', 'no response'; may also be reported as DAS-28 response) • DAS-28 score (change from baseline, assessed using ESR or CRP) • DAS-28 remission (defined based on DAS-28 score) • CDAI score • Patient assessment of functional ability (HAQ-DI, AIMS, MACTAR). • Radiographic progression (as measured by a valid scoring system e.g. Larsen/Sharp/modified Sharp score). • Patient's assessment of pain (VAS or Likert scale). • Patient/physician assessment of disease activity (VAS or Likert scale) • Morning stiffness, number of flares • Fatigue (FACIT-F; Worse Tiredness Score) • Disease activity (SDAI) • Physical function (MJS) • RA-related mortality	Outcome(s) not listed	In line with NICE potential reference case

#	Inclusion criteria	Exclusion criteria	Justification
	• Extra-articular manifestations of the disease (captured under safety reporting) **Safety** • Incidence of AEs, including allergic reactions, infections, and thromboembolic events • Incidence of SAEs, including MACE • Treatment withdrawal (and reason for withdrawal, e.g. lack of efficacy, AEs, SAEs) **HRQoL:** • As **measured** by SF-36 or other instruments • EQ-5D-5L and 3L • WPAI-RA		
Study design	RCTs, with no restriction on phase or study design (long term extensions will be included if randomisation is maintained) Observational studies, to include prospective cohort studies, case-control studies, registries for UPA only	Any other study design	In line with NICE potential reference case
Language restrictions	English language publications and English language abstracts of foreign language publications	Foreign language publications without an English abstract	-
Date of publication	No restriction	-	-
Countries/global reach	No restriction	-	-

Abbreviations: ABT, abatacept; ACR, American College of Rheumatology; ADA, adalimumab; AEs, adverse events; AIMS, Arthritis Impact Measurement Scales ; bDMARDs, biologic disease modifying antirheumatic drugs; BRC, baricitinib; BSC, best supportive care; CDAI, Clinical disease activity index; CRP, C-reactive protein; CTZ, certolizumab pegol; csDMARDs, conventional synthetic disease modifying antirheumatic drugs; DAS-28, disease activity score 28-joint count; EQ-5D-3L, three-level EuroQol five dimension; EQ-5D-5L, five-level EuroQol five dimension; ESR, erythrocyte sedimentation rate; ETN, etanercept; EULAR, European League Against Rheumatism; FACIT-F, Functional Assessment of Chronic Illness Therapy – Fatigue; GOL, golimumab; HAQ-DI, Health assessment questionnaire disability index; HRQoL, health-related quality of life; IFX, infliximab; IL-1/6, interleukin 1/6; JAK, Janus kinase; MACE, major adverse cardiac event; MACTAR, McMaster Toronto Arthritis patient preference questionnaire; MJS, morning joint stiffness; MTX, methotrexate; NICE, National Institute for Health and Care Excellence; QD, once daily; RA, rheumatoid arthritis; RCTs, randomised controlled trials; RTX, rituximab; SAEs, serious adverse events; SDAI, simple disease activity index; SF-36, 36-item short form survey; SJC, swollen joint count; SLR, systematic literature review; SRL, sarilumab; TCZ, tocilizumab; TFC, tofacitinib; TJC, tender joint count; TNF-alpha, tumour necrosis factor alpha; WPAI-RA, Work Productivity and Activity Impairment Questionnaire: Rheumatoid arthritis

Source: Reproduced from Table 1, CS Appendix D.1.4, page 42

The company stated that the included comparators were those currently used to treat moderate-to-severe RA. Investigational and off-label therapies were initially searched for and included in the SLR even if not finally included in analyses due to lack of relevance to the submission (refer to Table 4, D.1.10, Appendix D of the CS for details on studies included in the SLR but excluded from the NMA in the CS). The ERG additionally noted that, in addition to the comparators listed in Table 2, csDMARDs, BSC, and PBO were eligible comparators in the decision problem (refer to Section 2.1 for further detail).

The ERG also noted that in Table 2, UPA was included as an intervention at 15 mg and 30 mg QD dosages. This is consistent with the NICE final scope, even though the company's decision problem focuses on the 15 mg QD dosage. The ERG considered that it was appropriate to include both dosages as interventions in the SLR.

4.1.3 Critique of screening and data extraction processes

The company provide limited information about screening and data extraction processes. Appendix D.1.7 of the CS stated that screening was conducted by two reviewers according to pre-defined inclusion/exclusion criteria (refer to Section 4.1.2) with discrepancies resolved by a third person. This is in line with usual practice, although the ERG noted that it was not clearly specified whether double-independent screening occurred at both stages of the screening process (title and abstract screening; full text screening).

Appendix D.1.7 of the CS reported that data were extracted into a template by one reviewer and checked by a second reviewer (with inconsistencies resolved through discussion). This is consistent with usual practice. No additional details about the data extraction template were provided, so the ERG could not further comment on the data extraction processes.

4.1.4 Quality assessment

QA for the four pivotal RCTs (SELECT-COMPARE, SELECT-MONOTHERAPY, SELECT-NEXT and SELECT-BEYOND) were provided in Appendix D of the CS (refer to Section D.1.17, Table 30) together with the QA for all studies included in the network meta-analyses (see Section 4.3.4.1 for a critique of the QA of these studies). The QA was performed using the checklist provided in the NICE single technology appraisal (STA) user guide,[16] and therefore based upon guidance from the Centre for Reviews and Dissemination (University of York).[17]

ERG comment:

The ERG considered the company QA to have been conducted using appropriate methods. In accordance with usual practice, the QA conducted by the company was primarily concerned with internal validity. ERG comments on the external validity of the trials are provided in Section 4.2 of this report.

4.1.5 Evidence synthesis

The CS did not present a meta-analysis of UPA trials. The company stated that: "whilst a meta-analysis of RCTs was theoretically feasible, the fact that a comprehensive network meta-analysis of all relevant comparators was conducted and allowed for more precise estimates of treatment effects to be calculated meant that this approach was favoured instead of a meta-analysis of these RCT studies" (CS, p.86).

ERG comment:

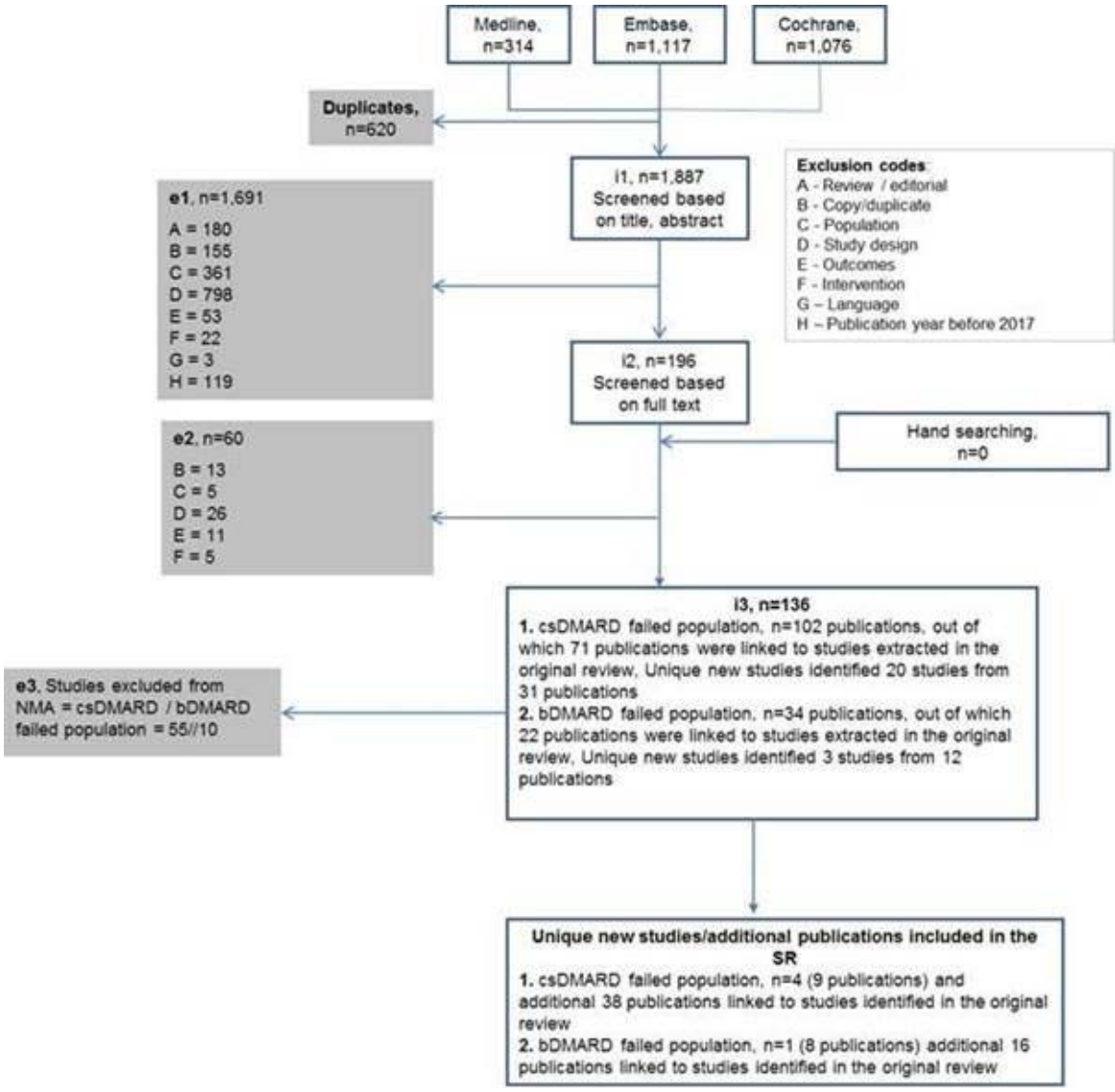
The ERG noted that it is recommended to also provide pairwise meta-analyses in addition to NMAs.[18] However, the ERG considered the presentation of pairwise meta-analyses not to be essential in this appraisal given the characteristics of the network structure with a wide range of comparisons and relatively few trials contributing to each potential pairwise comparison. The ERG was therefore broadly satisfied with the company's decision to only present the NMA results, since the ERG considered these to be the most relevant clinical effectiveness results in the decision-making context of this appraisal. The ERG critique of the NMA is presented in Section 4.4.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

4.2.1 Excluded studies

As discussed in Section 4.1.1, the company conducted a SLR to identify potentially relevant trials. The clinical effectiveness PRISMA flow diagram is provided in the CS (Appendix D, Figure 1, p.57). A PRISMA flow diagram from the company's updated search was provided in the company's response to the ERG clarification questions, and is reproduced below as Figure 2.

Figure 2. PRISMA flow diagram for updated clinical effectiveness searches



Abbreviations: bDMARDs, biologic disease modifying antirheumatic drugs; csDMARDs, conventional synthetic disease modifying antirheumatic drugs; NMA, network meta-analysis; SR, systematic review

Source: Company clarification response pt. 1, A4.

A table of studies excluded from the SLR is provided in the CS (Appendix D, Table 2, pp. 58-100) for the original search and CS Appendix D (Table 3, pp.100-106) for the updated search. Only broad classifications of the reasons for exclusion are provided, listed as 'Outcomes', 'Copy/duplicate', 'Study design', 'Intervention', 'Population' and 'Review/editorial'. These reasons are potentially consistent with the inclusion and exclusion criteria for the SLR. However, with the exception of 'Copy/duplicate' and 'Review/editorial', the information in the CS lacked sufficient detail in order to allow the ERG to critique whether or not any studies for the technology of interest may have been inappropriately excluded during the screening process. The ERG also noted that the

reason for exclusion for two studies in Table 2 was stated as '0', which may be a typographical error by the company, as there was no indication provided what this code represents.

4.2.2 Included studies

The CS presents four pivotal clinical effectiveness studies for the technology of interest UPA: SELECT-COMPARE,[19,20] SELECT-NEXT,[21,22] SELECT-MONOTHERAPY[23,24] and SELECT-BEYOND. [25,26] All are RCTs, were used to support the application for marketing authorisation and are used in the economic model. A summary profile of these four trials was provided in the CS as Table 3, p.36, and is reproduced below as Table 3.

Table 3. Overview of pivotal clinical effectiveness studies

Study	SELECT-COMPARE	SELECT-NEXT	SELECT-MONOTHERAPY	SELECT-BEYOND
Study Design	Phase III multicentre randomised, double-blind, parallel-group, PBO-controlled and active comparator-controlled trial	Phase III multicentre, randomised, double-blind, parallel-group, PBO-controlled trial	Phase III multicentre, randomised, double-blind, parallel-group, controlled trial	Phase III multicentre, randomised, double-blind, parallel-group, PBO-controlled period
Population	Subjects with moderately to severely active RA who are on a stable background of MTX and who have an inadequate response to MTX	Subjects with moderately to severely active RA who are on a stable dose of csDMARDs and had an inadequate response to csDMARDs	Subjects with moderately to severely active RA despite stable doses of MTX (inadequate response to MTX)	Subjects with moderately to severely active RA who are on a stable dose of csDMARDs and had an inadequate response to or intolerance to at least 1 bDMARD.
Intervention	UPA 15 mg orally QD (N=651) from Day 1 to Week 48 (Period 1) and thereafter up to 5 years (Period 2)	UPA 15 mg (N=221) and 30 mg (N=219) orally QD (N=200) from Day 1 to Week 12 (Period 1) and thereafter up to 5 years (Period 2)	UPA 15 mg (N=217) and 30 mg (N=215) orally QD (N=200) from Day 1 to Week 14 (Period 1) and thereafter up to Week 226 (Period 2)	UPA 15 mg (N=164) and 30 mg orally QD (N=165) from Day 1 to Week 24 (Period 1) and thereafter up to Week 216 (Period 2)
Comparators	PBO (N=651) either orally QD or SC eow according to the matching drug (UPA or ADA) from Day 1 to Week 26, followed by UPA 15 mg QD from Week 26 to Week 48 (Period 1) and thereafter up to 5 years (Period 2) ADA 40 mg SC eow (N=327) from Day 1 to Week 48 (Period 1) and thereafter up to 5 years (Period 2)	PBO (N=221) from Day 1 to Week 12, followed by UPA 15 mg or 30 mg orally QD (in two different randomised groups) at Week 12 and thereafter up to 5 years	MTX (N=216) once weekly from Day 1 to Week 14 (Period 1), followed by UPA 15 mg or 30 mg orally QD at Week 14 and thereafter up to Week 226 (Period 2)	PBO (N=169) from Day 1 to Week 12, followed by UPA 15 mg or 30 mg orally QD (in two different randomised groups) at Week 12 to Week 24 (Period 1) and thereafter up to Week 216 (Period 2)
Permitted and disallowed concomitant medication	• Subjects should continue their stable background MTX therapy up to Week 24. • Subjects taking MTX should take a dietary supplement of oral folic acid throughout study participation.	• Subjects should continue their stable background csDMARD therapy up to Week 24. • Subjects taking MTX should take a dietary supplement of oral folic acid throughout study participation.	• Subjects taking MTX should take a dietary supplement of oral folic acid throughout study participation. • Subjects should continue their stable doses of NSAIDs, acetaminophen/paracetamol, or inhaled corticosteroids.	• Subjects should continue their stable background csDMARD therapy up to Week 24. • Subjects taking MTX should take a dietary supplement of oral folic acid throughout study participation.

Study	SELECT-COMPARE	SELECT-NEXT	SELECT-MONOTHERAPY	SELECT-BEYOND
	• Subjects should continue their stable doses of NSAIDs, acetaminophen/paracetamol, or inhaled corticosteroids. • Prior exposure to JAK inhibitors is not allowed. • Oral corticosteroids are not allowed during the first 24 weeks of the study. • All biologic therapies are prohibited during the study (i.e., Periods 1 and 2). • Systemic use of known strong CYP3A inhibitors or strong CYP3A inducers is excluded from the Screening Visit through the end of the study (i.e., end of Period 2). • High potency opiates are not permitted during the study (i.e., Periods 1 and 2). • Investigational drugs are also prohibited during the study. • Live vaccines are not allowed within 4 weeks prior to the first dose of study drug and during the study (i.e., Periods 1 and 2). • Oral traditional Chinese medicine is not permitted during the study.	• Subjects should continue their stable doses of NSAIDs, acetaminophen/paracetamol, or inhaled corticosteroids. • Prior exposure to JAK inhibitors is not allowed. • Oral corticosteroids are not allowed during the first 24 weeks of the study. • All biologic therapies are prohibited during the study (i.e., Periods 1 and 2). • Systemic use of known strong CYP3A inhibitors or strong CYP3A inducers is excluded from the Screening Visit through the end of the study (i.e., end of Period 2). • High potency opiates are not permitted during the study (i.e., Periods 1 and 2). • Investigational drugs are also prohibited during the study. Live vaccines are not allowed within 4 weeks prior to the first dose of study drug and during the study (i.e., Periods 1 and 2). • Oral traditional Chinese medicine is not permitted during the study.	• Prior exposure to JAK inhibitors is not allowed. • Oral corticosteroids are not allowed during the first 24 weeks of the study. • Subjects must have discontinued all csDMARDs (other than MTX) prior to the first dose of study drug as specified in the washout procedures. • All biologic therapies are prohibited during the study (i.e., Periods 1 and 2). • Systemic use of known strong CYP3A inhibitors or strong CYP3A inducers is excluded from the Screening Visit through the end of the study (i.e., end of Period 2). • High potency opiates are not permitted during the study (i.e., Periods 1 and 2). • Investigational drugs are also prohibited during the study. • Live vaccines are not allowed within 4 weeks prior to the first dose of study drug and during the study (i.e., Periods 1 and 2). • Oral traditional Chinese medicine is not permitted during the study.	• Subjects should continue their stable doses of NSAIDs, acetaminophen/paracetamol, or inhaled corticosteroids. • Prior exposure to JAK inhibitors is not allowed. • Oral corticosteroids are not allowed during the first 24 weeks of the study. • All biologic therapies are prohibited during the study (i.e., Periods 1 and 2). • Systemic use of known strong CYP3A inhibitors or strong CYP3A inducers is excluded from the Screening Visit through the end of the study (i.e., end of Period 2). • High potency opiates are not permitted during the study (i.e., Periods 1 and 2). • Investigational drugs are also prohibited during the study. Live vaccines are not allowed within 4 weeks prior to the first dose of study drug and during the study (i.e., Periods 1 and 2). • Oral traditional Chinese medicine is not permitted during the study.

Study	SELECT-COMPARE	SELECT-NEXT	SELECT-MONOTHERAPY	SELECT-BEYOND
Does trial support MAA?	Yes	Yes	Yes	Yes
Is trial used in model	Yes	Yes	Yes	Yes
Reported outcomes specified in the decision problem	• Disease activity • Physical function • Joint damage, pain • Fatigue • Radiological progression • AEs of treatment • HRQoL	• Disease activity • Physical function • Joint damage, pain • Fatigue • AEs of treatment • HRQoL	• Disease activity • Physical function • Joint damage, pain • AEs of treatment • HRQoL	• Disease activity • Physical function • Joint damage, pain • AEs of treatment • HRQoL

Abbreviations: ADA, adalimumab; bDMARD, biological disease modifying anti-rheumatic drug; csDMARDs , conventional synthetic disease modifying anti-rheumatic drug; eow, every other week; MAA, marketing authorization application; MTX, methotrexate; PBO, placebo; QD, once daily; RA, rheumatoid arthritis; SC, subcutaneous; UPA, upadacitinib

Source: CS, Table 3, p.36.

A fifth UPA trial also features in the CS. This is the SELECT SUNRISE trial.[27,28] This was also a Phase III RCT. The company explained that the: "data [for that trial] are not presented in this section [clinical effectiveness evidence]" because the trial was "comprised entirely of Japanese patients [and] this was not an EMA registration trial" (CS, p.35). The ERG considered that the exclusively Japanese population of SELECT SUNRISE may be a limitation of the trial in terms of relevance to the UK decision-making context. Nevertheless, the ERG considered that this trial did meet the SLR inclusion criteria and should not have been excluded from the presentation of clinical effectiveness evidence. It should be noted that the SELECT SUNRISE trial was included in the company's base case NMA, although a scenario analysis was presented excluding this trial. Indeed, the company stated: "Please note, data from SELECT-SUNRISE were available and included in the NMAs as it met the NMA selection criteria." (CS, p.36). Therefore, this trial does inform the company base case economic model, and as such the ERG considered that its clinical effectiveness should therefore have been profiled in detail in the CS. The ERG's critique of study design, population characteristics, intervention characteristics, outcome assessment and QA in the following sections were conducted on the four pivotal RCTs as defined by the company and profiled in detail in the clinical effectiveness section of the CS.

Comparator trials and their assessment for potential inclusion in the NMA are critiqued in Section 4.3.

4.2.2.1 Study design

The methodology of the four pivotal trials is summarised by the company in CS (refer to Table 4, pp.43-48), and reproduced below as Table 4.

Table 4. Comparative summary of trial methodology

Study	SELECT-COMPARE	SELECT-NEXT	SELECT-MONOTHERAPY	SELECT-BEYOND
Location where the data was collected	286 study sites located in 41 countries (Argentina, Australia, Belarus, Belgium, Bosnia and Herzegovina, Brazil, Bulgaria, Canada, Chile, Colombia, Croatia, Czech Republic, Estonia, France, Germany, Greece, Hong Kong, Hungary, Israel, Italy, Kazakhstan, Republic Of Korea, Latvia, Lithuania, Malaysia, Mexico, New Zealand, Poland, Portugal, Puerto Rico, Romania, Russian Federation, Serbia, Slovakia, South Africa, Spain, Taiwan [Province Of China], Turkey, Ukraine, United Kingdom, United States)	150 study sites located in 35 countries (Argentina, Australia, Austria, Belgium, Bosnia and Herzegovina, Bulgaria, Canada, Croatia, Czech Republic, Estonia, Finland, France, Germany, Greece, Hong Kong, Hungary, Ireland, Kazakhstan, Korea, Latvia, Lithuania, Mexico, New Zealand, Poland, Portugal, Romania, Russian Federation, Slovakia, South Africa, Spain, Switzerland, Taiwan, Ukraine, United Kingdom, United States)	138 study sites located in 24 countries (Argentina, Austria, Belgium, Bulgaria, Chile, Czech Republic, Estonia, Greece, Hungary, Israel, Italy, Japan, Mexico, Poland, Portugal, Puerto Rico, Romania, Russian Federation, Serbia, South Africa, Spain, Turkey, Ukraine, United States)	152 sites in 26 countries (Australia, Austria, Belgium, Canada, Czech Republic, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Israel, Korea, Latvia, New Zealand, Poland, Portugal, Puerto Rico, Russian Federation, Slovakia, Spain, Sweden, Turkey, United Kingdom, United States)
Trial Design	Phase III multicenter study that includes two periods. Period 1 is a 48-week randomised, double-blind, parallel-group, PC and active comparator-controlled period designed to compare the safety and efficacy of UPA 15 mg QD versus PBO, and versus ADA, for the treatment of signs and symptoms of subjects with moderately to severely active RA who were on a stable dose of MTX and had an inadequate response to MTX. Period 1 was also designed to compare the efficacy of UPA 15 mg QD versus PBO for the prevention of structural progression. Period 2 is a long-term extension to evaluate the safety, tolerability, and efficacy of UPA 15 mg QD in subjects with RA who had completed Period 1.	Phase III multicenter study that includes two periods. Period 1 was a 12-week, randomised, double-blind, parallel-group, PC period designed to compare the safety and efficacy of UPA 30 mg QD and 15 mg QD versus PBO for the treatment of signs and symptoms of subjects with moderately to severely active RA who were on a stable dose of csDMARDs and had an inadequate response to csDMARDs. Period 2 is a blinded long-term extension period to evaluate the long-term safety, tolerability, and efficacy of UPA 30 mg QD and 15 mg QD in subjects with RA who had completed Period 1.	Phase III multicenter study that includes two periods. Period 1 was a 14-week, randomised, double-blind, parallel-group, controlled treatment period designed to compare the safety and efficacy of UPA 30 mg QD alone and 15 mg QD alone versus continuing MTX alone for the treatment of signs and symptoms of RA in subjects with moderately to severely active RA despite stable doses of MTX (inadequate response to MTX). Period 2 is a blinded, long-term extension period to evaluate the long-term safety, tolerability, and efficacy of UPA 30 mg QD and 15 mg QD in subjects with RA who have completed Period 1.	Phase III multicenter study that included two periods. Period 1 was a 24-week, randomised, double-blind, parallel-group, PC period designed to compare the safety and efficacy of UPA 30 mg QD and 15 mg QD versus PBO for the treatment of signs and symptoms of subjects with moderately to severely active RA who were on a stable dose of csDMARDs and had an inadequate response to or intolerance to at least 1 bDMARD. Period 2 is a blinded long-term extension period to evaluate the long-term safety, tolerability, and efficacy of UPA 30 mg QD and 15 mg QD in subjects with RA who had completed Period 1.

Study	SELECT-COMPARE	SELECT-NEXT	SELECT-MONOTHERAPY	SELECT-BEYOND
Eligibility criteria for participants	• •Adult male or female, at least 18 years old. • Diagnosis of RA for ≥3 months, fulfilling the 2010 ACR/EULAR classification criteria for RA • Subjects must have been on oral or parenteral MTX therapy ≥3 months and on a stable prescription of 15 to 25 mg/week (or ≥10 mg/week in subjects intolerant of MTX at doses ≥15 mg/week) for ≥4 weeks prior to the first dose of study drug. In addition, all subjects should take a dietary supplement of folic acid or folinic acid throughout the study participation. • Participants are required to have: o at least 6 swollen joints and at least 6 tender joints at the screening and baseline visits as judged by joint counts o hsCRP ≥ 5 mg/L (central lab, ULN 2.87 mg/L) at screening visit • Patients are also required to have: o ≥3 bone erosions on x-ray; or o ≥1 bone erosion and a positive rheumatoid factor; or o ≥ 1 bone erosion and a positive ACPA • Patients were required to discontinue all csDMARDs, with the exception of MTX	• Adult male or female, at least 18 years old • Diagnosis of RA for ≥3 months who also fulfil the 2010 ACR/EULAR classification criteria for RA • Subjects have been receiving csDMARD therapy ≥3 months and on a stable dose for ≥4 weeks prior to the first dose of study drug • Subjects must have failed at least one of the following: MTX, sulfasalazine, or leflunomide • Subject meets both of the following disease activity criteria: o ≥6 swollen joints (based on 66 joint counts) and ≥ 6 tender joints (based on 68 joint counts) at Screening and baseline Visits; and o hsCRP ≥ 3 mg/L (central lab) at Screening Visit • Subjects with prior exposure to at most one bDMARD may be enrolled if exposure ≤3 months OR if discontinued due to intolerability (up to 20% of study population)	• Adult male or female, at least 18 years old • Diagnosis of RA for ≥3 months who also fulfil the 2010 ACR/ EULAR classification criteria for RA • Subjects must have been on oral or parenteral MTX therapy ≥3 months and on a stable dose (15 to 25 mg/week; or ≥10 mg/week in subjects who are intolerant of MTX at doses ≥15 mg/week after complete titration) for ≥4 weeks prior to first dose of study drug • Must have discontinued all csDMARDs (other than MTX) ≥4 weeks prior to first dose of study drug • Subject has ≥6 swollen joints (based on 66 joint counts) and ≥6 tender joints (based on 68 joint counts) at Screening and baseline Visits; and hsCRP ≥3 mg/L (central lab) at Screening Visit	• •Adult male or female, at least 18 years old • Diagnosis of RA for ≥3 months who also fulfil the 2010 ACR/EULAR classification criteria for RA • Subjects have been treated for ≥3 months prior to the screening visit with ≥1 bDMARD therapy, but continue to exhibit active RA or had to discontinue due to intolerability or toxicity, irrespective of treatment duration. • Subjects have been receiving csDMARD therapy ≥3 months and on a stable dose for ≥4 weeks prior to the first dose of study drug • Subject meets both of the following minimum disease activity criteria: o ≥6 swollen joints (based on 66 joint counts) and ≥ 6 tender joints (based on 68 joint counts) at Screening and baseline Visits o hsCRP ≥3 mg/L (central lab) at Screening Visit
Trial drugs	**Group 1:** UPA 15 mg QD (N = 600)	**Group 1:** UPA 30 mg QD (N = 200) (Period 1) → UPA 30 mg QD (Period 2)	**Group 1:** UPA 30 mg QD (N = 200) (Period 1) → UPA 30 mg QD (Period 2)	**Group 1:** UPA 30 mg QD (N = 150) (Day 1 to Week 12) → UPA 30 mg QD (Week 12 and thereafter)

Study	SELECT-COMPARE	SELECT-NEXT	SELECT-MONOTHERAPY	SELECT-BEYOND
	Group 2: PBO (N = 600) **Group 3:** ADA (40 mg eow) (N = 300)	**Group 2:** UPA 15 mg QD (N = 200) (Period 1) → UPA 15 mg QD (Period 2) **Group 3:** PBO (N = 100) (Period 1) → UPA 30 mg QD (Period 2) **Group 4:** PBO (N = 100) (Period 1) → UPA 15 mg QD (Period 2)	**Group 2:** UPA 15 mg QD (N = 200) (Period 1) → UPA 15 mg QD (Period 2) **Group 3:** MTX (N = 100) (Period 1) → UPA 30 mg QD (Period 2) **Group 4:** MTX (N = 100) (Period 1) → UPA 15 mg QD (Period 2)	**Group 2:** UPA 15 mg QD (N = 150) (Day 1 to Week 12) → UPA 15 mg QD (Week 12 and thereafter) **Group 3:** PBO (N = 75) (Day 1 to Week 12) → UPA 30 mg QD (Week 12 and thereafter) **Group 4:** PBO (N = 75) (Day 1 to Week 12) → UPA 15 mg QD (Week 12 and thereafter)
Permitted and disallowed concomitant medication	• Subjects should continue their stable background MTX therapy up to Week 24. • Subjects taking MTX should take a dietary supplement of oral folic acid throughout study participation. • Subjects should continue their stable doses of NSAIDs, acetaminophen/paracetamol, or inhaled corticosteroids. • Prior exposure to JAK inhibitors is not allowed. • Oral corticosteroids are not allowed during the first 24 weeks of the study. • All biologic therapies are prohibited during the study (i.e., Periods 1 and 2). • Systemic use of known strong CYP3A inhibitors or strong CYP3A inducers is excluded from the Screening Visit through the end of the study (i.e., end of Period 2). • High potency opiates are not permitted during the study (i.e., Periods 1 and 2).	• Subjects should continue their stable background csDMARD therapy up to Week 24. • Subjects taking MTX should take a dietary supplement of oral folic acid throughout study participation. • Subjects should continue their stable doses of NSAIDs, acetaminophen/paracetamol, or inhaled corticosteroids. • Prior exposure to JAK inhibitors is not allowed. • Oral corticosteroids are not allowed during the first 24 weeks of the study. • All biologic therapies are prohibited during the study (i.e., Periods 1 and 2). • Systemic use of known strong CYP3A inhibitors or strong CYP3A inducers is excluded from the Screening Visit through the end of the study (i.e., end of Period 2). • High potency opiates are not permitted during the study (i.e., Periods 1 and 2).	• Subjects taking MTX should take a dietary supplement of oral folic acid throughout study participation. • Subjects should continue their stable doses of NSAIDs, acetaminophen/paracetamol, or inhaled corticosteroids. • Prior exposure to JAK inhibitors is not allowed. • Oral corticosteroids are not allowed during the first 24 weeks of the study. • Subjects must have discontinued all csDMARDs (other than MTX) prior to the first dose of study drug as specified in the washout procedures. • All biologic therapies are prohibited during the study (i.e., Periods 1 and 2). • Systemic use of known strong CYP3A inhibitors or strong CYP3A inducers is excluded from the Screening Visit through the end of the study (i.e., end of Period 2).	• Subjects should continue their stable background csDMARD therapy up to Week 24. • Subjects taking MTX should take a dietary supplement of oral folic acid throughout study participation. • Subjects should continue their stable doses of NSAIDs, acetaminophen/paracetamol, or inhaled corticosteroids. • Prior exposure to JAK inhibitors is not allowed. • Oral corticosteroids are not allowed during the first 24 weeks of the study. • All biologic therapies are prohibited during the study (i.e., Periods 1 and 2). • Systemic use of known strong CYP3A inhibitors or strong CYP3A inducers is excluded from the Screening Visit through the end of the study (i.e., end of Period 2). • High potency opiates are not permitted during the study (i.e., Periods 1 and 2).

Study	SELECT-COMPARE	SELECT-NEXT	SELECT-MONOTHERAPY	SELECT-BEYOND
	• Investigational drugs are also prohibited during the study. • Live vaccines are not allowed within 4 weeks prior to the first dose of study drug and during the study (i.e., Periods 1 and 2). • Oral traditional Chinese medicine is not permitted during the study.	• Investigational drugs are also prohibited during the study. Live vaccines are not allowed within 4 weeks prior to the first dose of study drug and during the study (i.e., Periods 1 and 2). • Oral traditional Chinese medicine is not permitted during the study.	• High potency opiates are not permitted during the study (i.e., Periods 1 and 2). • Investigational drugs are also prohibited during the study. • Live vaccines are not allowed within 4 weeks prior to the first dose of study drug and during the study (i.e., Periods 1 and 2). • Oral traditional Chinese medicine is not permitted during the study.	• Investigational drugs are also prohibited during the study. Live vaccines are not allowed within 4 weeks prior to the first dose of study drug and during the study (i.e., Periods 1 and 2). • Oral traditional Chinese medicine is not permitted during the study.
Primary outcome	• Proportion of patients achieving ACR20 response • Proportion achieving clinical remission (defined by a DAS-28 score based on CRP <2.6)	• Proportion of patients achieving an ACR20 response • Proportion achieving LDA (defined by a DAS-28 score based on CRP ≤3.2)	• Proportion of patients achieving an ACR20 response • Proportion achieving LDA (defined by a DAS-28 score based on CRP ≤3.2)	• Proportion of patients achieving an ACR20 response • Proportion achieving LDA (defined by a DAS-28 score based on CRP ≤3.2)
Major secondary outcomes	• Change in HAQ-DI score • Change in HAQ-DI score (superiority versus ADA) • Proportion of patients achieving LDA based on CDAI • Proportion of patients with no radiographic progression at week 26 • Change in morning stiffness severity • Change in DAS-28 CRP • Change in SF-36 PCS from baseline • Change in FACIT-F from baseline • Change in mTSS at Week 26 • ACR50 response rates (superiority and non-inferiority versus ADA) • ACR50 response rates • ACR70 response rates	• Change in DAS-28 CRP • Proportion of patients achieving ACR50/70 response • Change in the HAQDI score from baseline • Change in SF-36 PCS from baseline • Proportion of patients achieving clinical remission (DAS-28 CRP <2.6) • Change in FACIT-F from baseline • Change in RA-WIS score at baseline • Proportion of changes in morning stiffness severity	• Decrease in DAS-28 CRP from baseline • Proportion of patients achieving an ACR50/70 response • Change in HAQ-DI score from baseline • Change in SF-36 PCS from baseline • Proportion of patients achieving clinical remission (DAS-28 CRP <2.6) • Proportion of changes in morning stiffness severity	• Change in DAS-28 CRP • Changes in the HAQ-DI score from baseline • Proportion of patients achieving ACR20/50/70 response • Change in SF-36 PCS score from baseline • ACR20 response rate at Week 1

Study	SELECT-COMPARE	SELECT-NEXT	SELECT-MONOTHERAPY	SELECT-BEYOND
	• Proportion of patients achieving LDA (defined by a DAS-28 score based on CRP ≤3.2) (non-inferiority versus ADA) • Proportion of patients achieving LDA (defined by a DAS-28 score based on CRP ≤3.2) • Change from baseline in patients assessment of pain (superiority of UPA versus ADA) • Change in RA-WIS score at baseline			
Pre-planned subgroups (primary efficacy endpoints)	• Age (<40, 40 to 64, ≥65 years) • Sex (male or female) • Weight (<60 kg or ≥60 kg); • BMI (<25 or ≥25) • Race (white, non-white), • Geographic region (North America, South/Central America, Western Europe, Eastern Europe, Asia, other) • RA disease duration (<5 or ≥5 years) • Baseline RF status (positive or negative) • Baseline anti-CCP antibody status (positive or negative) • Baseline RF and anti-CCP (at least one negative or double positive) • Baseline RF and anti-CCP (at least one positive or double negative) • Baseline DAS-28 (hsCRP) (≤5.1 or >5.1); and • Prior bDMARD use (yes or no).	• Age (<40, 40 to 64, ≥65 years) • Sex (male or female) • Weight (<60 kg or ≥60 kg) • BMI (<25 or ≥25) • Race (white, non-white), geographic region (North America, Western Europe, Eastern Europe, other) • Duration of RA diagnosis (<5 or ≥5 years) • Baseline RF status (positive or negative) • Baseline anti-CCP antibody status (positive or negative) • Baseline both RF positive and anti-CCP positive (yes or no) • Baseline both RF negative and anti-CCP negative (yes or no) • Baseline DAS-28 (CRP) (≤5.1 or >5.1); and • Prior bDMARD use (yes or no)	• Age (<40, 40 to 64, ≥65 years) • Sex (male or female) • Weight (<60 kg or ≥60 kg) • BMI (<25 or ≥25) • Race (white, non-white), • Geographic region (North America, South/Central America, Western Europe, Eastern Europe, Asia, other) • RA disease duration (<5 or ≥5 years) • Baseline RF status (positive or negative • Baseline anti-CCP antibody status (positive or negative) • Baseline RF and anti-CCP (at least one negative or double positive) • Baseline RF and anti-CCP (at least one positive or double negative) • Baseline DAS-28 (hsCRP) (≤5.1 or >5.1)	• Age (<40, 40 to 64, ≥65 years) • Sex (male or female) • Weight (<60 kg or ≥60 kg) • BMI (<25 or ≥25) • Race (white, non-white), • Geographic region (North America, South/Central America, Western Europe, Eastern Europe, other • Duration of RA diagnosis (<10 or ≥10 years) • Baseline RF status (positive or negative) • Baseline anti-CCP antibody status (positive or negative) • Baseline RF and anti-CCP (at least one negative or double positive) • Baseline RF and anti-CCP (at least one positive or double negative) • Baseline DAS-28 (hsCRP) (≤5.1 or >5.1) • Prior failed bDMARD; and failed anti-IL6 due to lack of efficacy

Abbreviations: ACR, American College of Rheumatology; ACR20/50/70, American College of Rheumatology 20%, 50%, 70% response; bDMARD, biologic disease-modifying anti-rheumatic drug; BMI, body mass index; CCP, cyclic citrullinated peptide; CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; csDMARDs, conventional synthetic disease-modifying anti-

rheumatic drug(s); DAS-28, disease activity score 28-joint count; eow, every other week; FACIT-F, Functional Assessment of Chronic Illness Therapy — Fatigue; HAQ-DI, Health Assessment Questionnaire — Disability Index; hsCRP, high-sensitivity C-reactive protein; JAK, Janus kinase; LDA, low disease activity; mTSS, modified Total Sharp Score; MTX, methotrexate; NSAIDs, non-steroidal anti-inflammatory drugs; PCS, physical component summary; QD, once daily; RA, rheumatoid arthritis; RF, rheumatoid factor; SF-36, Short Form-36; ULN, upper limit of normal; WIS, Work Instability Scale

Source: CS, Table 4, pp. 43-48

The ERG considered the study design of the trials included in the CS to be appropriate for the SLR inclusion criteria. The trials evaluated the clinical effectiveness of UPA versus either PBO or an active comparator – ADA or MTX. Head-to-head evidence is provided for certain comparisons, although the key clinical effectiveness comparisons that serve as inputs to the economic model are derived from NMAs (see Section 4.4), in order to take into account the totality of the available evidence across the network.

All four studies were conducted across a large number of sites located in a wide range of sites globally. SELECT-COMPARE was conducted in 286 sites across 41 countries, SELECT-NEXT on 150 sites across 35 countries, SELECT-MONOTHERAPY on 138 sites across 24 countries, and SELECT-BEYOND on 152 sites across 26 countries. It was noted that in the figures for SELECT-COMPARE and SELECT-NEXT, Taiwan and Hong Kong were counted as separate countries. One of the trials – SELECT-MONOTHERAPY did not include any UK sites, while the other three pivotal trials did include centres in the UK. However,

[redacted]

All four trials included two periods, the first of which was the main trial period and the second was a long-term extension period to assess longer term efficacy, safety and tolerability. ERG noted differences in the duration of the main trial period between the trials: 12 weeks (SELECT-NEXT), 14 weeks (SELECT-MONOTHERAPY), 24 weeks (SELECT-BEYOND), and 48 weeks (SELECT-COMPARE).

The planned sample size and power calculation for each of the pivotal trials is presented in CS Appendix D, Table 39, pp.258-259, and reproduced below as Table 5.

Table 5. Hypothesis and associated statistical analysis for each trial

Trial number (acronym)	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
SELECT COMPARE	Comparisons of the primary endpoint were made between the UPA 15 mg QD group and the PBO group using the Cochran-Mantel-Haenszel test adjusting for stratification factor of prior bDMARD use	The planned total sample size of 1,500 for this study (with a 2:2:1 randomization ratio) provided at least 90% power for a 22% difference in ACR20 response rate (assuming a PBO ACR20 response rate of 37%) at 2-sided significance level of 0.05 and accounting for a 10% dropout rate. It also provided at least 90% power for a 19.3% difference in CR response rate (assuming a PBO CR response rate of 6.2%)	Data Management was done by BI according to BI SOPs and Statistical Evaluation was done by AbbVie according to BI SOPs.
SELECT NEXT	Comparison of the primary endpoint was made between each UPA dose group and the combined PBO groups using the Cochran-Mantel-Haenszel test adjusted for main stratification factors.	The planned total sample size of 600 for this study provided at least 90% power for a 21% difference in ACR20 response rate (assuming a PBO ACR20 response rate of 37%), as well as at least 90% power for a 22% difference in LDA response rate (based on DAS-28 [CRP] [assuming a PBO LDA response rate of 15%]), at 2-sided significance level of 0.025 and accounting for a 10% dropout rate.	Data Management was done by BI according to BI SOPs and Statistical Evaluation was done by AbbVie according to BI SOPs.
SELECT MONOTHERAPY	Comparisons of the primary endpoint were made between each UPA dose and the combined MTX group using the Cochran-Mantel-Haenszel test adjusting for stratification factor of geographic region.	The planned total sample size of 600 for this study provided at least 90% power to detect a 21% difference in ACR20 response rate (assuming an ACR20 response rate of 37% in the continuing MTX group), as well as at least 90% power to detect a 22% difference in LDA response rate based on DAS-28 (CRP) criteria (assuming an LDA response rate of 15% in the continuing MTX group), at 2-sided α = 0.025 and accounting for 10% dropout rate.	Data Management was done by BI according to BI SOPs and Statistical Evaluation was done by AbbVie according to BI SOPs.

Trial number (acronym)	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
SELECT BEYOND	Comparison of the primary endpoint was made between each UPA dose group and the combined PBO groups using the Cochran-Mantel-Haenszel test adjusted for main stratification factors.	The planned total sample size of 450 for this study provided at least 90% power for a 20% difference in ACR20 response rate (assuming a PBO ACR20 response rate of 27%), as well as at least 90% power for a 17% difference in LDA response rate (based on DAS-28 [CRP] [assuming a PBO LDA response rate of 12%]), at a 2-sided significance level of 0.025 and accounting for a 10% dropout rate.	Data Management was done by BI according to BI SOPs and Statistical Evaluation was done by AbbVie according to BI SOPs.

Abbreviations: ACR20, American College of Rheumatology 20%; bDMARD, biologic disease modifying anti-rheumatic drugs; CRP, C-reactive protein; CR, complete response; DAS-28, disease activity score 28-joint count; LDA, low disease activity; MTX, methotrexate; SOPs, standard operating procedures

Source: CS Appendix D, Table 39, pp.258-259.

SELECT-BEYOND was planned to be the smallest of the four trials, with a total planned sample size of 450, both SELECT-NEXT and SELECT-BEYOND had a planned total sample size of 600, while SELECT-COMPARE was planned as the largest trial with a planned sample size of 1,500. A dropout rate of 10% was assumed for each trial. In each trial, the planned sample size offered 90% power to detect the intended outcome. SELECT-COMPARE was powered on a 22% difference in ACR 20 response and a 19.3% difference in CR response. SELECT-NEXT was powered on a 21% difference in ACR 20 response and a 22% difference in LDA response. SELECT-MONOTHERAPY was powered on a 21% difference in ACR 20 response and a 22% difference in LDA response. SELECT-BEYOND was powered on a 20% difference in ACR 20 response and a 17% difference in low disease activity (LDA) response. The ERG noted these differences in the measures and thresholds upon which the power calculation was based between trials.

4.2.2.2 Population characteristics

Inclusion and exclusion criteria for the four pivotal trials were presented above in Table 3.

All four trials included both male and female participants, and were conducted in an exclusively adult population. All four trials required participants to have been diagnosed with RA for at least three months. In all trials, participants had to fulfil the 2010 ACR/EULAR criteria for RA.[29] In all trials, participants were required to have at least six swollen joints and at least six tender joints. The ERG noted the high level of consistency between trials in terms of permitted clinical characteristics.

However, the ERG noted differences in terms of prior medication regimens as detailed in Table 3. In all trials, participants were required to have been on prior therapy for at least three months before trial enrolment. In SELECT-COMPARE, this prior therapy was required to be MTX. In SELECT-NEXT, participants were required to have had inadequate response to at least one of MTX, sulfasalazine or leflunomide. In SELECT-MONOTHERAPY, prior MTX therapy was required. In SELECT-BEYOND, experience with at least one bDMARD was required along with continued active RA or discontinuation of the bDMARD due to intolerability or toxicity. In addition, in SELECT-COMPARE, participants had to discontinue prior csDMARD therapy upon trial enrolment, with the exception of MTX, and were additionally required to take a dietary supplement of folic acid or folinic acid throughout trial participation. In SELECT-MONOTHERAPY, participants were required to have discontinued all prior DMARDs except MTX at least four weeks prior to the first dose of trial medication. The ERG considered that it was important to consider these differences in prior medication status at baseline and that this may introduce between trial heterogeneity.

Baseline characteristics for each pivotal trial were initially provided in the CS, but were provided with more detail in response to a clarification response from the ERG. Baseline characteristics for the total trial populations for each of the four pivotal trials are provided below as Table 6.

Baseline characteristics for participants with moderate RA and severe RA are provided in Table 7 and Table 8, respectively.

Table 6. Baseline characteristics of trial populations

Study	SELECT-COMPARE			SELECT-NEXT		SELECT-MONOTHERAPY		SELECT-BEYOND	
Treatment	**PBO (N=651)**	**ADA (N=327)**	**UPA (N=651)**	**PBO (N=221)**	**UPA 15 mg (N=221)**	**MTX (N=216)**	**UPA 15 mg QD(N=217)**	**PBO (N=169)**	**UPA 15 mg (N=164)**
Sex, n (%)									
Male	139 (21.4)	68 (20.8)	130 (20.0)	55 (24.9)	39 (17.6)	37 (17.1)	43 (19.8)	26 (15.4)	27 (16.5)
Female	512 (78.6)	259 (79.2)	521 (80.0)	166 (75.1)	182 (82.4)	179 (82.9)	174 (80.2)	143 (84.6)	137 (83.5)
Age (years) Mean (SD)	53.590 (12.2395)	53.737 (11.7028)	54.189 (12.0795)	55.991 (12.2229)	55.339 (11.4700)	55.315 (11.1185)	54.516 (12.1982)	57.645 (11.3946)	56.317 (11.3407)
Race, n (%)									
White	561 (86.2)	292 (89.3)	576 (88.5)	187 (84.6)	188 (85.1)	176 (81.5)	173 (79.7)	143 (84.6)	142 (86.6)
Black or African American	38 (5.84)	17 (5.20)	33 (5.07)	10 (4.53)	13 (5.88)	11 (5.09)	15 (6.91)	21 (12.4)	17 (10.4)
American Indian/Alaska Native	2 (0.307)	1 (0.306)	1 (0.154)	1 (0.452)	0	3 (1.39)	4 (1.84)	0	3 (1.83)
Native Hawaiian or other Pacific Islander	1(0.154)	0	0	0	0	NR	NR	0	0
Asian	39 (5.99)	15 (4.59)	31 (4.76)	19 (8.60)	19 (8.60)	24 (11.1)	24 (11.1)	5 (2.96)	2 (1.22)
Multiple	10 (1.54)	2 (0.612)	10 (1.54)	4 (1.81)	1 (0.452)	2 (0.93)	1 (0.461)	0	0
Ethnicity (Hispanic or Latino), n (%)	206 (31.6)	106 (32.4)	215 (33.0)	27 (12.2)	23 (10.4)	50 (23.1)	52 (24.0)	24 (14.2)	34 (20.7)
BMI (kg/m^2), Mean (SD)	28.675 (6.2040)	28.563 (6.5292)	29.188 (7.0045)	29.565 (6.5967)	29.721 (7.5600)	29.125 (6.9999)	28.202 (6.3166)	29.685 (7.3611)	31.168 (7.3019)
Duration of RA diagnosis (years) – continuous, Mean (SD)	8.274 (7.9966)	8.340 (8.4141)	8.101 (7.7277)	7.183 (7.4550)	7.254 (7.8880)	5.814 (6.6344)	7.458 (8.8794)	14.495 (9.2209)	12.376 (9.3827)
RF positive – categorical, n (%)	517 (79.4)	265 (81.0)	521 (80.0)	164 (74.2)	163 (73.8)	151 (69.9)	155 (71.4)	113 (66.9)	119 (73.0)
Anti-CCP positive – categorical, n (%)	529 (81.5)	264 (80.7)	525 (80.6)	167 (75.9)	174 (79.1)	153 (70.8)	159 (73.3)	117 (69.2)	119 (72.6)
RF and anti-CCP positive, n (%)	475 (73.2)	241 (73.7)	480 (73.7)	150 (67.9)	153 (69.5)	135 (62.5)	142 (65.4)	102 (60.4)	107 (65.6)
DAS-28 (CRP) – continuous, Mean (SD)	5.833 (0.9400)	5.867 (0.9556)	5.777 (0.9708)	5.557 (0.8381)	5.653 (0.9709)	5.592 (1.0445)	5.618 (0.9233)	5.829 (1.0014)	5.869 (0.9473)

Study	SELECT-COMPARE			SELECT-NEXT		SELECT-MONOTHERAPY		SELECT-BEYOND	
Treatment	**PBO (N=651)**	**ADA (N=327)**	**UPA (N=651)**	**PBO (N=221)**	**UPA 15 mg (N=221)**	**MTX (N=216)**	**UPA 15 mg QD(N=217)**	**PBO (N=169)**	**UPA 15 mg (N=164)**
CDAI – continuous, Mean (SD)	40.028 (12.7322)	39.800 (13.1799)	39.704 (12.9204)	37.764 (11.8121)	38.268 (11.8638)	37.755 (14.3901)	37.986 (13.1208)	40.966 (13.2972)	41.654 (13.2776)
TJC68, Mean (SD)	25.989 (14.3009)	26.373 (15.1555)	26.435 (15.1497)	24.697 (14.9610)	25.158 (13.7952)	25.227 (15.9852)	24.465 (15.0987)	28.491 (15.2749)	27.762 (16.3061)
SJC66, Mean (SD)	16.206 (8.9711)	16.294 (9.1922)	16.571 (10.3089)	15.367 (9.2381)	15.955 (10.0439)	16.912 (11.5242)	16.415 (10.9423)	16.320 (9.5826)	17.037 (10.7509)
HAQ-DI Mean (SD)	1.609 (0.6082)	1.647 (0.5897)	1.633 (0.6352)	1.425 (0.6343)	1.478 (0.6076)	1.466 (0.6581)	1.471 (0.6603)	1.564 (0.6035)	1.669 (0.6428)
CRP (mg/L), Mean (SD)	17.974 (21.5172)	19.809 (21.5103)	17.896 (22.4855)	12.578 (13.9597)	16.622 (19.1698)	14.526 (17.3302)	13.952 (16.4865)	16.298 (21.1013)	16.246 (18.6238)
Baseline mTSS, Mean (SD)	35.892 (51.6590)	34.534 (47.0621)	34.031 (50.0755)	NR	NR	NR	NR	NR	NR
Baseline joint erosion score Mean (SD)	16.958 (27.4302)	15.414 (23.0983)	16.512 (26.4161)	NR	NR	NR	NR	NR	NR
Baseline JSN score, Mean (SD)	18.948 (26.1216)	19.170 (25.8428)	17.482 (25.0995)	NR	NR	NR	NR	NR	NR
Morning stiffness duration (minutes), Mean (SD)	142.444 (169.7796)	146.083 (184.9339)	141.538 (187.6118)	138.861 (213.9702)	152.406 (241.9026)	153.033 (221.7151)	144.203 (215.0519)	138.426 (178.5935)	140.415 (189.7186)
EUROQOL 5D Index score, Mean (SD)	0.548 (0.2689)	0.540 (0.2741)	0.546 (0.2687)	0.623 (0.2339)	0.603 (0.2454)	0.598 (0.2550)	0.587 (0.2507)	0.573 (0.2571)	0.521 (0.2712)
MTX dose at Baseline (mg), Mean (SD)	16.840 (3.8197)	17.097 (3.7618)	17.019 (4.1669)	NR	NR	16.719 (4.4102)	16.798 (4.2139)	NR	NR
Oral corticosteroid dosing at Baseline, n (%)	392 (60.2)	202 (61.8)	388 (59.6)	NR	NR	115 (53.2)	114 (52.5)	NR	NR
Oral corticosteroid dose (mg), Mean (SD)	6.266 (2.4082)	6.499 (2.4383)	6.226 (2.2715)	NR	NR	6.165 (2.5604)	6.103 (2.5232)	NR	NR
Prior biologic DMARD use, n (%)	63 (9.7)	34 (10.4)	54 (8.3)	29 (13.1)	27 (12.2)	NR	NR	169 (100)	164 (100)

Study	SELECT-COMPARE			SELECT-NEXT		SELECT-MONOTHERAPY		SELECT-BEYOND	
Treatment	**PBO (N=651)**	**ADA (N=327)**	**UPA (N=651)**	**PBO (N=221)**	**UPA 15 mg (N=221)**	**MTX (N=216)**	**UPA 15 mg QD(N=217)**	**PBO (N=169)**	**UPA 15 mg (N=164)**
Concomitant csDMARD at baseline, n (%)									
MTX alone	NR	NR	NR	141 (64.1)	122 (55.5)	NR	NR	122 (72.6)	118 (73.3)
MTX and other csDMARD	NR	NR	NR	49 (22.3)	47 (21.4)	NR	NR	17 (10.1)	19 (11.8)
csDMARD other than MTX	NR	NR	NR	30 (13.6)	51 (23.2)	NR	NR	29 (17.3)	24 (14.9)
Missing	NR	NR	NR	1	1	NR	NR	NR	NR
Oral steroid dosing at baseline, n (%)	NR	NR	NR	106 (48.0)	96 (43.4)	NR	NR	NR	NR
Oral steroid dose (mg), Mean (SD)	NR	NR	NR	6.349 (2.5504)	6.000 (2.3606)	6.165 (2.5604)	6.103 (2.5232)	6.257 (2.4245)	5.660 (2.3658)
MTX dose (mg), Mean (SD)	NR	NR	NR	16.263 (4.8913)	17.041 (4.8750)	16.719 (4.4102)	16.798 (4.2139)	NR	NR
Prior failed bDMARDs, n (%)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Stratum 1:1 MOA and ≤2 prior bDMARDs	NR	NR	NR	NR	NR	NR	NR	117 (69.2)	116 (70.7)
Stratum 2:>1 MOA and/or >2 prior bDMARDs	NR	NR	NR	NR	NR	NR	NR	52 (30.8)	48 (29.3)
Failed at least 1 anti-TNF, n (%)	NR	NR	NR	NR	NR	NR	NR	152 (89.9)	146 (89.0)
≤5.1 DAS-28CRP at baseline (%)	130 (20.0)	71 (21.9)	149 (23.0)	33 (14.9)	20 (9.3)	73 (33.8)	72 (33.3)	38 (22.9)	39 (23.9)
>5.1 DAS-28CRP at baseline(%)	519 (80.0)	253 (79.1)	498 (77.0)	188 (85.1)	195 (90.7)	143 (66.2)	144 (66.7)	128 (77.1)	124 (76.1)

Abbreviations: ADA: Adalimumab; bDMARD: biological Disease Modifying Anti-Rheumatic Drugs; BMI: Body Mass Index; CDAI: Crohn's Disease Activity Index; CRP: C-Reactive Protein; DAS-28: Disease Activity Score version 28; csDMARD: conventional synthetic Disease Modifying Anti-Rheumatic Drugs; DMARD: Disease Modifying Anti-Rheumatic Drugs; HAQ-DI: Health Assessment Questionnaire Disability Index; JSN: Joint Space Narrowing; mTSS: modified Total Sharp Score; MOA: Mechanism of Action; MTX: Methotrexate; PBO: Placebo; RA: Rheumatoid Arthritis; RF: Rheumatoid Factor; SD: Standard deviation; SJC66: Swollen joint count based on 66 joints; TJC68: Tender joint count based on 68 joints; TNF: Tumor Necrosis Factor; UPA: Upadacitinib;

Source: Company clarification response A5.

Table 7. Baseline characteristics of moderate trial population

Study	SELECT-COMPARE			SELECT-NEXT		SELECT-MONOTHERAPY		SELECT-BEYOND	
Treatment	**PBO (N=126)**	**ADA (N=70)**	**UPA (N=145)**	**PBO (N=69)**	**UPA 15 mg (N=64)**	**MTX (N=72)**	**UPA 15 mg QD (N=72)**	**PBO (N=38)**	**UPA 15 mg (N=39)**
Sex, n (%)									
Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age (years) Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race, n (%)									
White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
American Indian/Alaska Native	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Native Hawaiian or other Pacific Islander	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Multiple	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ethnicity (Hispanic or Latino), n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI (kg/m^2), Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Duration of RA diagnosis (years) – continuous, Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RF positive– categorical, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-CCP positive – categorical, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Study	SELECT-COMPARE			SELECT-NEXT		SELECT-MONOTHERAPY		SELECT-BEYOND	
Treatment	**PBO (N=126)**	**ADA (N=70)**	**UPA (N=145)**	**PBO (N=69)**	**UPA 15 mg (N=64)**	**MTX (N=72)**	**UPA 15 mg QD (N=72)**	**PBO (N=38)**	**UPA 15 mg (N=39)**
RF and anti-CCP positive, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DAS-28 (CRP) – continuous, Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CDAI – continuous, Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TJC68, Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SJC66, Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HAQ-DI Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRP (mg/L), Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline mTSS, Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline joint erosion score Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline JSN score, Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Morning stiffness duration (minutes), Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EUROQOL 5D Index score, Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SF-36 Physical component summary	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Functional assessment of chronic illness therapy-fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue scale	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Study	SELECT-COMPARE			SELECT-NEXT		SELECT-MONOTHERAPY		SELECT-BEYOND	
Treatment	**PBO (N=126)**	**ADA (N=70)**	**UPA (N=145)**	**PBO (N=69)**	**UPA 15 mg (N=64)**	**MTX (N=72)**	**UPA 15 mg QD (N=72)**	**PBO (N=38)**	**UPA 15 mg (N=39)**
MTX dose at Baseline (mg), Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oral corticosteroid dosing at Baseline, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oral corticosteroid dose (mg), Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior biologic DMARD use, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Concomitant csDMARD at baseline, n (%)									
MTX alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MTX and other csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
csDMARD other than MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oral steroid dosing at baseline, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oral steroid dose (mg), Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MTX dose (mg), Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior failed bDMARDs, n (%)									
Stratum 1:1 MOA and ≤ 2 prior bDMARDs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Study	SELECT-COMPARE			SELECT-NEXT		SELECT-MONOTHERAPY		SELECT-BEYOND	
Treatment	**PBO (N=126)**	**ADA (N=70)**	**UPA (N=145)**	**PBO (N=69)**	**UPA 15 mg (N=64)**	**MTX (N=72)**	**UPA 15 mg QD (N=72)**	**PBO (N=38)**	**UPA 15 mg (N=39)**
Stratum 2:> 1 MOA and/or > 2 prior bDMARDs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Failed at least 1 anti-TNF, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA: Adalimumab; bDMARD: biological Disease Modifying Anti-Rheumatic Drugs; BMI: Body Mass Index; CDAI: Crohn's Disease Activity Index; CRP: C-Reactive Protein; DAS-28: Disease Activity Score version 28; csDMARD: conventional synthetic Disease Modifying Anti-Rheumatic Drugs; DMARD: Disease Modifying Anti-Rheumatic Drugs; HAQ-DI: Health Assessment Questionnaire Disability Index; JSN: Joint Space Narrowing; mTSS: modified Total Sharp Score; MOA: Mechanism of Action; MTX: Methotrexate; PBO: Placebo; RA: Rheumatoid Arthritis; RF: Rheumatoid Factor; SD: Standard deviation; SJC66: Swollen joint count based on 66 joints; TJC68: Tender joint count based on 68 joints; TNF: Tumor Necrosis Factor; UPA: Upadacitinib;

Source: Company clarification response A5.

Table 8. Baseline characteristics of severe trial population

Study	SELECT-COMPARE			SELECT-NEXT		SELECT-MONOTHERAPY		SELECT-BEYOND	
Treatment	PBO (N=519)	ADA (N=253)	UPA 15 mg (N=498)	PBO (N=152)	UPA 15 mg (N=151)	MTX (N=143)	UPA 15 mg QD (N=144)	PBO (N=128)	UPA 15 mg (N=124)
Sex, n (%)									
Male	[redacted]								
Female	[redacted]								
Age (years) Mean (SD)	[redacted]								
Race, n (%)									
White	[redacted]								
Black or African American	[redacted]								
American Indian/Alaska Native	[redacted]								
Native Hawaiian or other Pacific Islander	[redacted]								
Asian	[redacted]								
Multiple	[redacted]								
Ethnicity (Hispanic or Latino), n (%)	[redacted]								
BMI (kg/m^2), Mean (SD)	[redacted]								
Duration of RA diagnosis (years) – continuous, Mean (SD)	[redacted]								
RF – categorical, n (%)	[redacted]								
Anti-CCP – categorical, n (%)	[redacted]								
RF and anti-CCP, n (%)	[redacted]								
DAS-28 (CRP) – continuous, Mean (SD)	[redacted]								
CDAI – continuous, Mean (SD)	[redacted]								

Study	SELECT-COMPARE			SELECT-NEXT		SELECT-MONOTHERAPY		SELECT-BEYOND	
Treatment	PBO (N=519)	ADA (N=253)	UPA 15 mg (N=498)	PBO (N=152)	UPA 15 mg (N=151)	MTX (N=143)	UPA 15 mg QD (N=144)	PBO (N=128)	UPA 15 mg (N=124)
TJC68, Mean (SD)									
SJC66, Mean (SD)									
HAQ-DI Mean (SD)									
CRP (mg/L), Mean (SD)									
Baseline mTSS, Mean (SD)									
Baseline joint erosion score Mean (SD)									
Baseline JSN score, Mean (SD)									
Morning stiffness duration (minutes), Mean (SD)									
EUROQOL 5D Index score, Mean (SD)									
SF-36 PCS									
Fatigue Scale									
MTX dose at Baseline (mg), Mean (SD)									
Oral corticosteroid dosing at Baseline, n (%)									
Oral corticosteroid dose (mg), Mean (SD)									
Prior biologic DMARD use, n (%)									
Concomitant csDMARD at baseline, n (%)									
MTX alone									

Study	SELECT-COMPARE			SELECT-NEXT		SELECT-MONOTHERAPY		SELECT-BEYOND	
Treatment	PBO (N=519)	ADA (N=253)	UPA 15 mg (N=498)	PBO (N=152)	UPA 15 mg (N=151)	MTX (N=143)	UPA 15 mg QD (N=144)	PBO (N=128)	UPA 15 mg (N=124)
MTX and other csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
csDMARD other than MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oral steroid dosing at baseline, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oral steroid dose (mg), Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MTX dose (mg), Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior failed bDMARDs, n (%)									
Stratum 1:1 MOA and ≤ 2 prior bDMARDs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Others	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Failed at least 1 anti-TNF, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA: Adalimumab; bDMARD: biological Disease Modifying Anti-Rheumatic Drugs; BMI: Body Mass Index; CDAI: Crohn's Disease Activity Index; CRP: C-Reactive Protein; DAS-28: Disease Activity Score version 28; csDMARD: conventional synthetic Disease Modifying Anti-Rheumatic Drugs; DMARD: Disease Modifying Anti-Rheumatic Drugs; HAQ-DI: Health Assessment Questionnaire Disability Index; JSN: Joint Space Narrowing; mTSS: modified Total Sharp Score; MOA: Mechanism of Action; MTX: Methotrexate; PBO: Placebo; RA: Rheumatoid Arthritis; RF: Rheumatoid Factor; SD: Standard deviation; SJC66: Swollen joint count based on 66 joints; TJC68: Tender joint count based on 68 joints; TNF: Tumor Necrosis Factor; UPA: Upadacitinib

Source: Company clarification response A5.

The ERG considered the trials to show a consistent gender profile with around 80% of participants being female, which was considered to be representative of clinical practice. The gender profile was comparable between the moderate and severe trial populations. The trials all had a largely middle-aged population that was comparable between the moderate and several trial populations. An average age in the 50s was considered to be representative of clinical practice. The trials all recruited a predominantly white population, with the percentage of white participants only falling below 80% on one trial – SELECT-MONOTHERAPY. The trials may over-represent white patients compared to a typical NHS clinical practice setting in England and Wales. The arm-level mean BMI figures for the total trial population (28.2 to 31.2) were all higher than the national average for adults in England from the 2017 Health Survey for England (27.7).[30] The severe RA trial populations demonstrated a higher BMI profile than moderate RA populations, potentially reflecting greater activity limitations.

Indicators of clinical status were consistently poorer in the severe RA populations than the moderate RA populations. The ERG considered DAS28 to be the key clinical indicator.

[redacted] Disease duration varied across trials and was longest in SELECT-BEYOND, indicating a population with more established disease. Mean DAS scores were not, however, notably different in this trial. Indicators of inflammation, tender and swollen joints, and quality of life were comparable across trials. The ERG considered the four pivotal trials to be generally comparable in terms of their population characteristics.

4.2.2.3 Intervention characteristics

Intervention characteristics of the four pivotal trials were presented above in Table 4.

In all four trials, participants could be randomised to receive oral UPA 15 mg QD. As outlined in the CS (p.11), this dose of UPA, either as monotherapy or in combination therapy, is the technology under appraisal in this submission. In SELECT-COMPARE, there were 600 patients randomised to UPA 15 mg QD. There were two further arms in the trial: PBO (n=600) and ADA 40 mg eow (n=300). In SELECT-NEXT, there were 200 participants who received UPA 15 mg QD from trial onset. There were three further arms in the trial: UPA 30 mg QD (n=200), PBO in period one going onto UPA 30 mg QD in period two (n=100) and PBO in period one going onto UPA 15 mg QD in period two (n=100). In SELECT-MONOTHERAPY, there were 200 participants who received quizartinib 15 mg QD from trial onset. There were three further arms in the trial: UPA 30 mg QD (n=200), MTX in period one going onto UPA 15 mg QD in period two (n=100)

and MTX in period one going onto UPA 30 mg QD in period two (n=100). In SELECT-BEYOND, there were 150 participants who received UPA 15mg QD from trial onset. There were a further three arms in the trial: UPA 30 mg QD from trial onset, PBO initially going onto UPA 15 mg QD at 12 weeks and PBO initially going onto UPA 30 mg QD at 12 weeks.

The NICE final scope [11] for this appraisal permitted UPA to be given either as monotherapy or in combination with other conventional dMARDS, including MTX. However, Table 4 in the CS (pp. 43-48) only mentions UPA and its relevant dosing quantity and dosing schedule for UPA arms, and does not state that IN three of the trials, UPA is co-administered with MTX. However, Table 63b in the CS (p.159), profiling the clinical effectiveness inputs to the economic model, clarifies that SELECT-MONOTHERAPY is a source of data regarding UPA given as monotherapy, whereas SELECT-COMPARE, SELECT-NEXT and SELECT-BEYOND provide information on UPA administered in combination with MTX.

4.2.2.4 Outcome assessment

The outcomes evaluated in the included trials are summarised above in Table 3, and methods of statistical analysis used to analyse the trial data are reported above in Table 5.

All four pivotal trials included as a primary outcome the proportion of participants achieving ACR20 response. In all but SELECT-COMPARE, the proportion achieving LDA defined by DAS-28 score of less than or equal to 3.2 was also a primary outcome, while in SELECT-COMPARE the other primary outcome is the proportion achieving clinical remission defined by DAS-28 score of less than 2.6.

EULAR response was not available consistently across trials and is not listed as a primary outcome or major secondary outcome in any of the four pivotal trials. Therefore, the primary clinical response measure in the economic model EULAR response was mapped from ACR20 response (CS, Table 63b, pp.159-60) which was available for all pivotal trials.

Change in health assessment questionnaire disability index (HAQ-DI) from baseline as a measure of physical function was included as a major secondary outcome in all four pivotal trials. HAQ scores were used in the economic model to map to utilities (CS, Table 63b, pp.159-60).

HRQoL measures were not listed among the primary or major secondary outcomes in Table 4. The CS stated that EQ-5D-5L data were collected in the UPA Phase III trials; however, these were not used in the base case economic model (Section 5.2.2), but solely for validation purposes, in order to align modelling with previous TAs of interventions in RA such as TA375[31] and TA480[32] (CS, B.3.4.1, p.147).

4.2.3 Quality assessment

The findings of the QA as conducted by the company are presented in Table 9. QA was provided for all pivotal trials. The company's QA concluded that there was a low risk of bias in all four pivotal UPA trials. Additional columns have been added to Table 9 to summarise the ERG's commentary on the company's QA (summary additional comments from the ERG are also provided in the last row of the table).

Table 9. QA for the four pivotal trials

Study Name	SELECT-COMPARE		SELECT-MONOTHERAPY		SELECT-NEXT		SELECT-BEYOND	
	Company	ERG	Company	ERG	Company	ERG	Company	ERG
Was randomisation adequate?	Unclear Randomisation method NR	Yes: IRT	Unclear Randomisation method NR	Yes: IRT	Yes: IVRS	Yes: IVRS	Yes: IVRS	Yes: IVRS
Was allocation adequately concealed?	Unclear Allocation method NR	Yes: IRT	Unclear Allocation method NR	Yes: IRT	Yes: IVRS	Yes: IVRS	Yes: IVRS	Yes: IVRS
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes: Double blind	Yes: Double blind	Yes: Double blind	Yes: Double blind	Yes: Double blind	Yes: Double blind	Yes: Double blind	Yes: Double blind
Were there unexpected imbalances in dropouts between groups?	Unclear	No	Unclear	No	No	No	Yes[c]	Yes[c,d]
Were any outcomes measured but not reported?	Unclear	Unclear	Unclear	Unclear	No	No	Unclear	Unclear
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes: mITT; Unclear	Yes, mITT; Yes, NRI/LOCF/linear extrapolation	Yes, ITT; Unclear	Yes, ITT; Yes: NRI/MI	Yes: ITT; Unclear	Yes: ITT; [redacted][b]	Yes: FAS; NRI	Yes: FAS; NRI
Additional ERG comments:	There is now an additional publication for this study,[33] which accounts for updates to the company ratings. [redacted]	The company's QA ratings did not appear to include information available in Smolen 2019[34] [redacted]	[redacted]	[redacted]				

Abbreviations: NR = not reported; NR I= non-responder imputation; ITT = intention-to-treat analysis; mITT = modified intention- to-treat analysis; IRT = interactive response technology; LOCF = last observation carried forward; M I= multiple imputation; QA = quality assessment.

Notes: [a] Company ratings were taken from Appendix Section D.1.17, Table 30; [b] [redacted]; [c] In the first 12 weeks, the proportion of patients who discontinued the study drug because of adverse events was higher in UPA 30 mg group; [d] The proportion of patients discontinuing due to lack of efficacy was higher in the PBO group

ERG comment:

The ERG noted that for two of the four pivotal trials (SELECT-COMPARE and SELECT-MONOTHERAPY) the information given in the main body of the CS did not entirely match with the QA ratings provided in Appendix D of the CS (refer to Section B.2.5 and Section D.1.17, Tables 30 and 31). Based on the latest available data (including a newly published study for SELECT-COMPARE),[33] the ERG has found the information provided in Section B.2.5 of the CS, rather than the tabulated data in Appendix D to be correct. In order to clarify the inaccuracies in the QA data table provided in the CS (Appendix Section D.1.17, Table 30), which are likely due to omitting the most recent publications for these studies.[33,34] Table 9 provides a summary of the company's QA ratings for the four pivotal trials, alongside ratings and comments made by the ERG.

The ERG agreed that there was generally a low risk of bias in the four pivotal trials in the CS: all trials used appropriate computerised randomisation and allocation using interactive response technology, there were no apparent baseline imbalances, patients and study investigators were blinded [redacted], analyses were conducted on intention to treat (ITT), full analysis set (FAS) or modified intention to treat (mITT) samples, and appropriate methods were used to account for missing data (Table 9). The ERG highlights an imbalance in discontinuations in SELECT-BEYOND, whereby patients in UPA 30 mg group were more likely to discontinue the study drug because of adverse events than those in the UPA 15 mg and PBO groups (8%, 2% and 4% respectively), and those in the PBO group were more likely to discontinue due to lack of efficacy than those in the UPA 30 mg and 15 mg groups (6%, 1%, 0% respectively). The ERG noted that whilst these differences are important to consider, they are unlikely to result in substantial bias, and that primary efficacy analyses were conducted on the FAS with appropriate methods used to account for missing data.

4.2.4 Clinical effectiveness of the technology of interest

The trials identified included a population of RA patients with moderate-to-severe disease with inadequate response to csDMARDs, bDMARDs (SELECT-NEXT and SELECT-BEYOND, respectively), and MTX (SELECT-MONOTHERAPY AND SELECT-COMPARE). Section B.2.6.1 of the CS provided the results from all four of the pivotal trials (SELECT COMPARE, SELECT NEXT, SELECT MONOTHERAPY and SELECT BEYOND). The ERG has checked the results reported in the CS against the respective CSRs.[20,22,24,26] The following sub-sections provide a summary of the available evidence.

4.2.4.1 SELECT-COMPARE

SELECT-COMPARE, compared UPA 15 mg (+ MTX) with ADA (+ MTX) and PBO (+ MTX) at 12 and 26 weeks. A summary of clinical effectiveness results was provided in the CS (Section B.2.6.1, p.57); refer to Table 10 (below).

Table 10. Summary of clinical effectiveness results for SELECT-COMPARE

Endpoints	Week 12			Week 26		
	PBO (+MTX) (N=651)	ADA (+MTX) (N=327)	UPA 15 mg (+MTX) (N=651)	PBO (+MTX) (N=651)	ADA (+MTX) (N=327)	UPA 15 mg (+MTX) (N=651)
ACR20 response	36.4	63***	70.5***#	35.6	57.2**	67.4***
ACR50 response	14.9	29.1***	45.2***##	20.9	41.9***	53.9***
ACR70 response	4.9	13.5***	24.9***##	9.5	22.9***	34.7***
Clinical remission based on DAS28 (CRP)	6.1	18.0***	28.7***##	9.2	26.9***	40.9***
DAS28 (CRP) CFB	–1.1	–2.0***	–2.5***	–1.2	–2.3***	–2.8***
EQ-5D-5L CFB	0.1	0.2*	0.2***	0.1	0.2*	0.2***
FACIT-F CFB	4.8	7.4*	9.0***	5.48	8.24*	9.68***
HAQ-DI CFB	–0.3	–0.5**	–0.6***	–0.3	–0.6**	–0.7***
LDA CDAI	16.3	30**	40.4***	22.1	38.2	52.7***
LDA DAS28(CRP)	13.8	28.7***	45.0***##	18.0	38.5***	54.7***
LDA DAS28(CRP) - Non -Inferiority	13.8	28.7	45.0	NA	NA	NA
Morning stiffness duration (minutes) change	–48.6	-82.7	–92.6***	-53.88	-91.36	-100.25***
mTSS CFB	NA	NA	NA	0.9	0.1	0.2***
Patient's global assessment of pain change	-15.5	–25.3***	–31.8***	NA	NA	NA
Proportion of subjects with no radiographic progression	NA	NA	NA	76	86.8	83.5
RA-WIS score CFB	-2.0	-4.5	-5.2	NA	NA	NA
SF-36 PCS CFB	3.6	6.3**	7.9***	NA	NA	NA

Abbreviations: ACR20/50/70 = American College of Rheumatology 20%, 50%, 70% response; CDAI = Clinical Disease Activity Index; CFB = Change From Baseline; CRP = C-reactive protein; DAS28 = Disease Activity Score 28; FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue; HAQ-DI = Health Assessment Questionnaire – Disability Index; LDA = low disease activity; PBO, placebo; PCS = physical component summary; QD = once daily; SF-36 = Short Form-36; UPA, upadacitinib

Notes: ***, **, * Statistically significant at 0.001, 0.01, and 0.05 level, respectively UPA vs placebo;
#, ## Statistically significant at 0.05, and 0.001 level respectively for UPA vs ADA

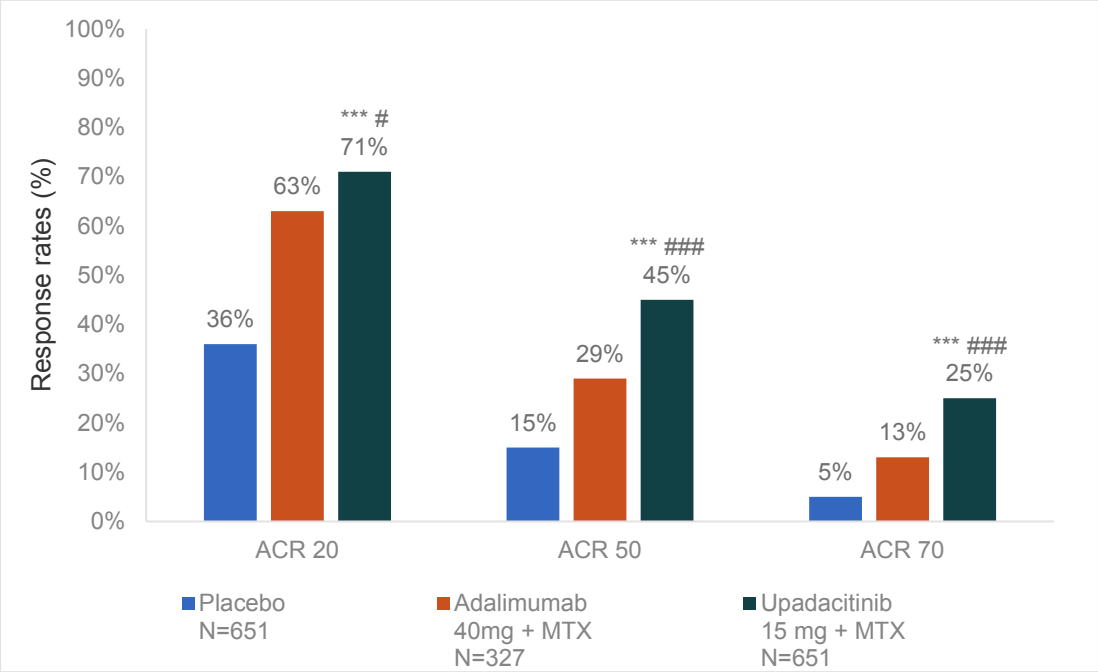
Reproduced from CS, Section B.2.6.1, Table 7, page 57

The primary endpoints were ACR20 response and the proportion of patients achieving clinical remission (DAS-28 CRP <2.6) at Week 12. Key secondary endpoints included

clinical remission at 26 weeks, ACR 50 and 70, LDA (based on DAS-28 (CRP) ≤ 3.2), patient's assessment of pain, HAQ-DI and EQ-5D-5L.

The UPA 15 mg group achieved the highest **ACR20 response** (UPA 15 mg 70.5%, ADA 63.0%, PBO 36.4%; refer to Figure 3, reproduced from the CS) and this was also the case at 26 weeks (refer to Table 10).

Figure 3. ACR response rates at Week 12 in SELECT-COMPARE



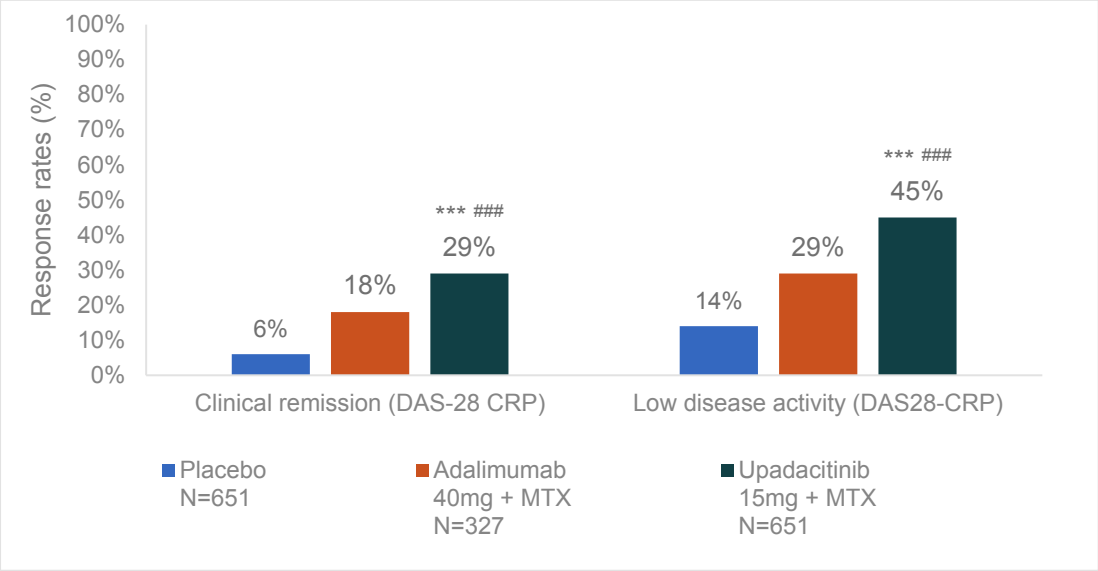
Abbreviations: ACR20/50/70, American College of Rheumatology 20%, 50%, 70% response; ADA, adalimumab; MTX, methotrexate; PBO, placebo; UPA, upadacitinib

† Primary endpoints included ACR20 and clinical remission based on DAS28 (CRP) for UPA vs. PBO (superiority). Ranked secondary endpoints included ACR50 versus ADA (both non-inferiority and superiority) and LDA versus ADA (non-inferiority) and vs. PBO (superiority). All other comparisons were not adjusted for multiplicity. Not all ranked secondary endpoints shown.

*** Denotes statistical significance at the 0.001 level for comparison versus PBO; # Denotes statistical significance at the 0.05 level for comparison versus ADA; ### Denotes statistical significance at the 0.001 level for comparison versus ADA

Reproduced from CS, Section B.2.6.1.1, Figure 7, page 59

Figure 4. Clinical remission and LDA at Week 12 in SELECT-COMPARE



Abbreviations: DAS-28, Disease Activity Score 28; MTX, methotrexate

Notes: † Primary endpoints included ACR20 and clinical remission based on DAS28 (CRP) for UPA versus placebo (superiority). Ranked secondary endpoints included ACR50 versus ADA (both non-inferiority and superiority) and LDA versus ADA (non-inferiority) and versus placebo (superiority). All other comparisons were not adjusted for multiplicity. Not all ranked secondary endpoints shown; *** Denotes statistical significance at the 0.001 level for comparison versus placebo. ### Denotes statistical significance at the 0.001 level for comparison versus ADA; a Clinical remission was based on DAS28[CRP] less than 2.6; b LDA was defined by a clinical response DAS28 CRP less than or equal to 3.2

Reproduced from CS, Section B.2.6.1.1, Figure 8, page 59

UPA 15 mg also resulted in the highest **clinical remission** rate (based on DAS-28 CRP <2.6; UPA 15 mg 28.7% ADA 18.0%, PBO 6.1%; refer to Figure 4, reproduced from the CS) at 12 weeks. With regards to clinical remission at 26 weeks, UPA 15 mg resulted in the highest remission rate (UPA 15 mg 40.9% ADA 26.9%, PBO 9.2%). Additionally, UPA 15 mg outperformed ADA and PBO with regards ACR 50 and ACR 70 at 12 weeks (refer to Figure 3), LDA (based on **DAS28 (CRP) ≤3.2**) at 12 weeks (UPA 15 mg 45.0%, ADA 28.7%, PBO 13.8%; refer to Figure 4), and LDA (based on DAS28 (CRP) ≤3.2) at 26 weeks (UPA 15 mg 54.7%, ADA 38.5%, PBO 18.0%).

Physical function was measured at 12 weeks using the HAQ-DI, with UPA 15 mg performing better than the comparators (UPA 15 mg -0.6, ADA -0.5, PBO -0.3; and the ERG noted that this was also the case at 26 weeks, refer to Table 10). With regards to reduction in pain at 12 weeks (VAS based Patient's Assessment of Pain), UPA 15 mg significantly outperformed PBO (UPA group -31.8, PBO group -15.5) and showed greater improvement than for ADA (-25.3).

HRQoL was assessed using the EQ-5D-5L index at both 12 and 26 weeks and the SF-36 PCS CFB at 12 weeks. UPA 15mg resulted in greater improvement on these HRQoL

indexes (EQ-5D-5L at 12 weeks, UPA 15 mg 0.21, ADA 0.17, PBO 0.10; EQ-5D-5L at 26 weeks UPA 15 mg 0.22, ADA 0.20 and PBO 0.11; SF-36 PCS CFB at 12 weeks UPA 15 mg 7.9, ADA 6.3, PBO 3.6).

4.2.4.2 SELECT-NEXT

SELECT-NEXT compared efficacy of UPA 15 mg QD versus PBO for the treatment of signs and symptoms of subjects with moderately to severely active RA who were on a stable dose of csDMARDs and had an inadequate response to csDMARDs at 12 weeks.

[redacted] A summary of clinical effectiveness results was provided in the CS (Section B.2.6.2, p.62); refer also to Table 11 (below).

Table 11. Summary of clinical effectiveness results for SELECT-NEXT

Endpoints	Week 12	
	PBO (+csDMARDs) (N=221)	UPA 15 mg (+ csDMARDs) (N=221)
ACR20 response	35.7	63.8***
ACR50 response	14.9	38.0***
ACR70 response	5.9	20.8***
Clinical remission based on DAS28 (CRP)	10.0	30.8***
DAS28 (CRP) CFB	–1.0	–2.2***
EQ-5D-5L CFB	0.1	0.2***
FACIT-F CFB	3.0	7.9***
HAQ-DI CFB	–0.3	–0.6***
LDA CDAI	19.0	40.3***
LDA DAS28(CRP)	17.2	48.4***
Morning stiffness duration (minutes) change	–34.3	–85.3***
RA-WIS CFB	–1.6	–4.3
SF-36 PCS CFB	3.0	7.6***

Abbreviations: ACR20/50/70, American College of Rheumatology 20%, 50%, 70% response; CDAI, Clinical Disease Activity Index; CFB, Change From Baseline; CRP, C-reactive protein; DAS28, Disease Activity Score 28; FACIT-F, Functional Assessment of Chronic Illness Therapy – Fatigue; HAQ-DI, Health Assessment Questionnaire – Disability Index; LDA, low disease activity; PBO, placebo; PCS, physical component summary; QD, once daily; SF-36, Short Form-36; UPA, upadacitinib

Notes: *** Statistically significant at 0.001 level

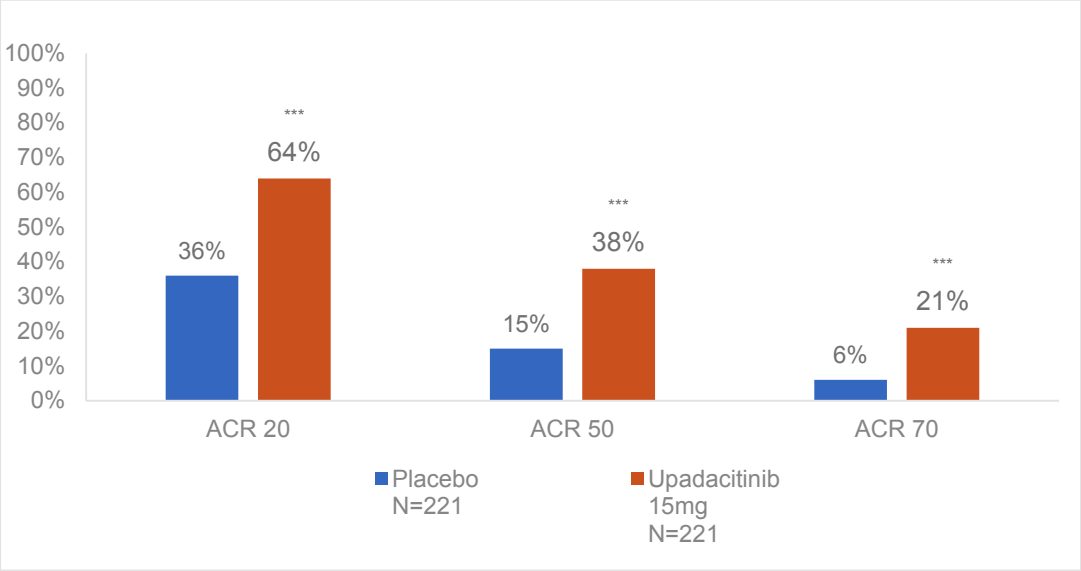
Reproduced from CS, Section B.2.6.2, p.62

At Week 12, **ACR-20** was achieved by 63.8% in the UPA 15 mg group compared with 35.7% in the placebo group (p<0.001). These data are shown alongside ACR-50 and

ACR-70 results in Figure 5 (reproduced from the CS).

[redacted]

Figure 5. ACR response rates at Week 12 in SELECT-NEXT



Abbreviations: ACR20/50/70, American College of Rheumatology 20%, 50%, 70% response

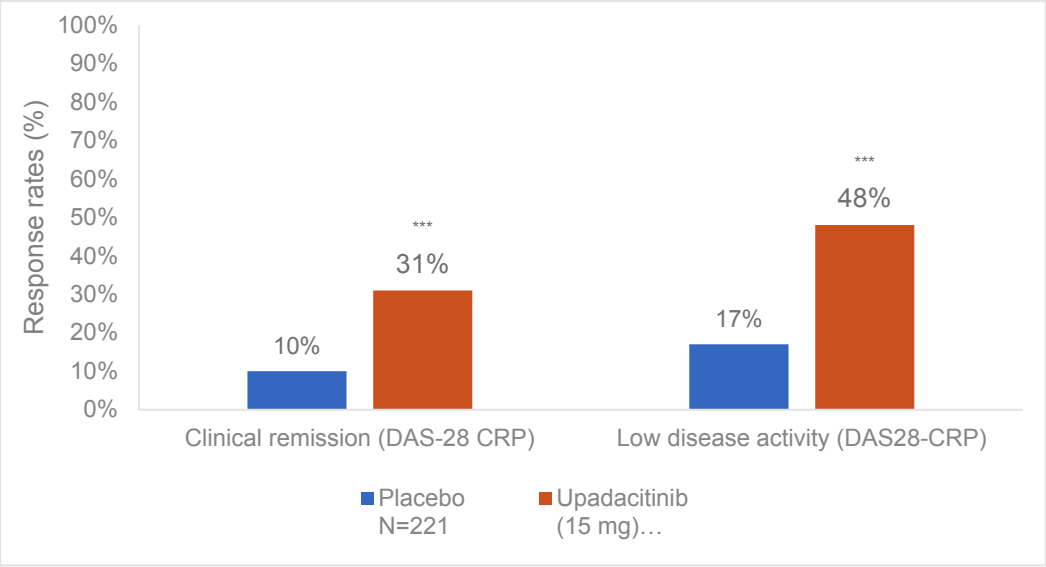
Notes: Responses for ACR20, ACR50, and ACR70 over 12 weeks, with non-responder imputation; ***Denotes statistical significance at the p<0.001 for comparison versus placebo.

Reproduced from CS, Section B.2.6.2.1, Figure 9, page 63

Similarly, there was a significant between-group difference in the proportion of patients who achieved low disease activity **(DAS-28 - CRP ≤3.2)** at 12 weeks: 47.9% of those receiving UPA 15mg compared with 17.2% of those receiving PBO, p<0.001; refer to Figure 6, reproduced from the CS).

[redacted]. Similar results were found for CDAI data: UPA 15 mg outperformed PBO (40.3% versus 19.0% respectively, p<0.001; [redacted]).

Figure 6. Clinical remission and LDA at Week 12 in SELECT-NEXT[†,a,b]



Abbreviations: DAS28, Disease Activity Score 28

Notes: [†] Patients achieving DAS28(CRP) of ≤3·2 or DAS28(CRP) <2·6 with non-responder imputation; ***Denotes statistical significance p<0.001 versus PBO for both doses; [a] Clinical remission was based on DAS28-CRP less than 2.6; [b] LDA was defined by a clinical response DAS28 CRP less than or equal to 3.2

Reproduced from CS, Section B.2.6.2.1, Figure 10, page 64

A greater proportion of patients in the UPA 15 mg group achieved **clinical remission** (based on DAS28 (CRP) < 2.6)**,** compared with PBO (30.8% versus 10.0% respectively, p<0.001, refer to Figure 6). [redacted].

Improvements from baseline in **physical function** on the basis of HAQ-DI were observed with UPA 15 mg versus PBO at Week 12: least square mean (LSM) change from baseline in HAQ-DI of −0·61 for UPA 15 mg versus −0·26 for PBO (p<0·05), [redacted].

HRQoL was assessed using the EQ-5D-5L and SF-36 PCS (refer to Table 11). At week 12, there was an improvement from baseline in mean current health status as measured by the EQ-5D-5L index with UPA 15 mg QD compared with PBO (0.2 versus 0.1, p<0.001; [redacted]). Similarly, on the SF-36 PCS, there were significant improvements for the UPA 15mg group compared with PBO (mean change from baseline 7.6 versus 3.0 respectively, p<0.001; [redacted]).

Other key secondary outcomes highlighted in the submission included VAS Pain, FACIT-F, and duration and severity of morning joint stiffness (VAS Pain mean change from baseline -29.92 versus -10.26 respectively, p<0.05; FACIT-F mean change from baseline 7.9 versus 3.0 respectively, p≤0.001; duration of morning stiffness, mean change from baseline -85.3 minutes versus -34.3 minutes respectively, p<0.001).

[redacted]

For the outcomes related to physical function, HRQoL, fatigue, pain and stiffness, similar patterns of results were found for scores ≥ minimum clinically important differences and ≥ normative values (refer to Table 12).

Table 12. Least squared mean (LSM) changes from baseline and percentage of responders for MCID and for normative values at Week 12 after UPA initiation

PRO	Change from baseline		% responders			
	LSM		Reporting scores ≥MCID, n (%)		Reporting scores ≥normative values, n (%)	
	PBO N=221	UPA 15 mg N=221	PBO N=221	UPA 15 mg N=221	PBO N=221	UPA 15 mg N=221
HAQ-DI	-0.26	-0.61*	109 (49.3)	156 (72.2)*	30 (13.6)	56 (25.9)*
Tag	-10.36	-29.67*	94 (42.5)	153 (70.5)*	32 (14.5)	78 (35.9)*
Pain VAS	-10.26	-29.92*	97 (43.9)	158 (72.8)*	-	-
FACIT-F	2.96	7.91*	91 (41.2)	138 (63.9)*	35.8 (15.8)	60 (27.8)*
Duration morning stiffness[a]	-34.27	-85.28*	29 (13.4)	57 (26.3)*,[b]	-	-
Severity morning stiffness[b]	-1.38	-2.88*	130 (60.2)	165 (76.0)*,[b]	-	-
SF-36 PCS	3.03	7.58*	106 (48.0)	152 (69.4)*	18 (8.1)	39 (17.8)*
SF-36 MCS	2.58	4.69*	91 (41.2)	120 (54.8)*	102 (46.2)	114 (52.1)

Abbreviations: HAQ-DI, Health Assessment Questionnaire, Disability Index; LSM, least squares mean; MCID, minimum clinically important differences; MCS, Mental component summary; PCS, physical component summary; PtGA, Patient's Global Assessment of Disease Activity PRO, patient reported outcomes; QD, once daily; SF-36, Short Form-36; VAS, Visual Analogue Scale

Reproduced from CS, Section B.2.6.2, p.66

4.2.4.3 SELECT-BEYOND

SELECT-BEYOND compared the efficacy of UPA 15 mg QD versus PBO for the treatment of signs and symptoms of subjects with moderately to severely active RA who were on a stable dose of csDMARDs and had an inadequate response to or intolerance

to at least one prior bDMARD at 12 and 24 weeks. A summary of clinical effectiveness results was provided in the CS (Section B.2.6.4, p.71); refer also to Table 13 (below).

Table 13. Summary of clinical effectiveness results for SELECT-BEYOND

Endpoints	Week 12		Week 24
	PBO (+ csDMARDs)	UPA 15 mg (+ csDMARDs)	UPA 15 mg (+ csDMARDs)
	n = 169	n = 164	n = 164
ACR20 response	28.4	64.6***	61.6
ACR20 response at Week 1	10.7	27.4***	NA
ACR50 response	11.8	34.1***	42.7
ACR70 response	6.5	11.6*	22.0
Clinical remission (DAS28- CRP ≤2.6)	9.5	28.7***	32.3
CDAI CFB	-13.3	-24.4***	-27.5
DAS-28 (CRP) CFB	-1.0	-2.3***	-2.6
EQ-5D-5L CFB	0.1	0.2**	0.52
HAQ-DI change from baseline	-0.2	-0.4***	-0.4
LDA based on DAS-28 (CRP) ≤ 3.2	14.2	43.3***	52.4
SDAI CFB	-13.5	-25.6***	-28.4
SF-36 PCS CFB	2.4	5.8***	5.7

Abbreviations: ACR20/50/70, American College of Rheumatology 20%, 50%, 70% response; CDAI, Clinical Disease Activity Index; CFB, Change From Baseline; CRP, C-reactive protein; DAS28, Disease Activity Score 28; FACIT-F, Functional Assessment of Chronic Illness Therapy – Fatigue; HAQ-DI, Health Assessment Questionnaire – Disability Index; LDA, low disease activity; PCS, physical component summary; QD, once daily; SF-36, Short Form-36

Notes: *** Statistically significant at 0.001 level

Reproduced from CS, Section B.2.6.4, p.71

At Week 12, **ACR20** was achieved by 106 (65%; 95% CI 57–72) of 164 patients receiving UPA 15 mg QD compared with 48 (28%; 22–35) of 169 patients receiving PBO (p<0·0001). At Week 24, ACR20 response was achieved in 61.6% of patients treated with UPA 15 mg QD + csDMARDs from study entry. LDA (**DAS-28 (CRP)) of 3·2 or less** was achieved by 71 (43%; 95% CI 36–51) of 164 patients receiving UPA 15 mg QD versus 24 (14%; 9–20) of 169 patients receiving PBO (p<0·0001). Comparisons to PBO + csDMARDs cannot be made at Week 24, since all PBO patients received either UPA 15 mg QD + csDMARDs or UPA 30 mg QD + csDMARDs from Week 12.

4.2.4.4 SELECT-MONOTHERAPY

SELECT-MONOTHERAPY compared the efficacy of UPA 15 mg QD monotherapy versus continuing MTX monotherapy at 14 weeks for the treatment of signs and symptoms of RA in subjects with moderately to severely active RA despite stable doses

of MTX (inadequate response to MTX). A summary of clinical effectiveness results was provided in the CS (Section B.2.6.2, p.62); refer also to Table 14 (below).

Table 14. Summary of clinical effectiveness results for SELECT-MONOTHERAPY

Endpoints	Week 14	
	cMTX (N=216)	UPA 15 mg QD (N=217)
ACR20 response	41.2	67.7***
ACR50 response	15.3	41.9***
ACR70 response	2.8	22.6***
Clinical remission based on DAS-28 (CRP)	8.3	28.1***
DAS28 (CRP) CFB	–1.20	–2.29***
EQ-5D-5L CFB	0.1	0.2***
HAQ-DI CFB	–0.32	–0.65***
LDA DAS28(CRP)	19.4	44.7***
Morning stiffness duration (minutes) change	–53.03	–94.56**
SF-36 PCS CFB	4.32	8.28***

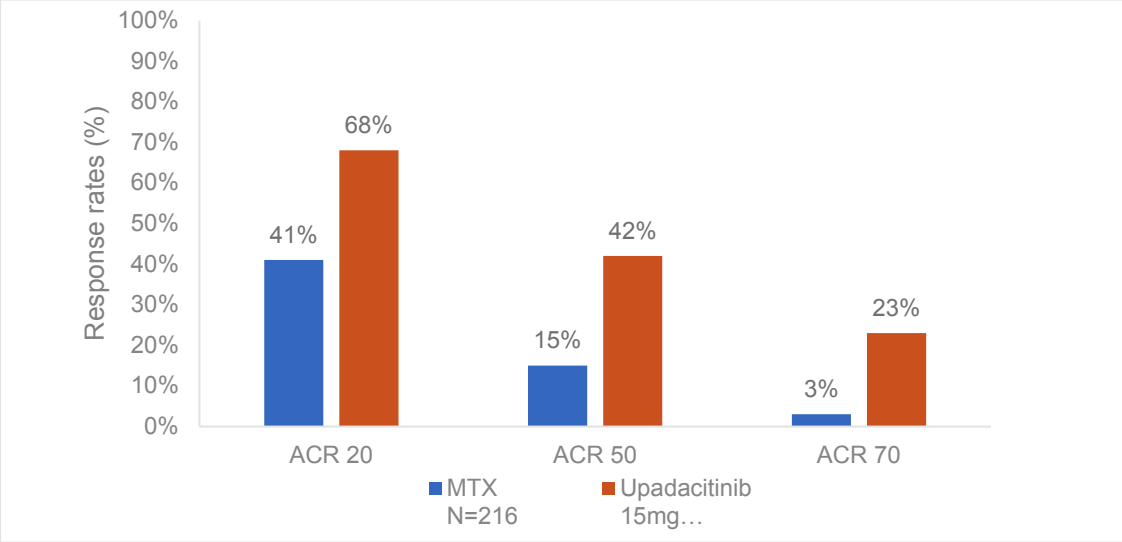
Abbreviations: ACR20/50/70, American College of Rheumatology 20%, 50%, 70% response; CFB, Change From Baseline; CRP, C-reactive protein; DAS-28, Disease Activity Score 28; HAQ-DI, Health Assessment Questionnaire – Disability Index; LDA, low disease activity; PCS, physical component summary; PBO, placebo; QD, once daily; SF-36, 36-item Short Form questionnaire; UPA, upadacitinib

Notes: ** Statistically significant at 0.01 level; *** Statistically significant at 0.001 level

Reproduced from CS, Section B.2.6.3, p.68

The primary outcomes demonstrated that at Week 14, a significantly greater proportion of patients receiving UPA 15 mg QD achieved an **ACR20 response** compared with patients receiving MTX monotherapy (67.7% versus 41.2% respectively, p<0.001; refer to Figure 7). **DAS28 (CRP) 3·2 or lower** was met by 42 (19%) of 216 (95% CI 14–25) receiving MTX, 97 (45%) of 217 (38–51) receiving UPA 15 mg QD monotherapy (p<0·0001).

Figure 7. ACR response rates at Week 12 in SELECT-MONOTHERAPY†



Abbreviations: ACR20/50/70 = American College of Rheumatology 20%, 50%, 70% response; MTX = Methotrexate

Notes: †All Week 14 endpoints shown in the table achieved p-values of <0.001 versus MTX for both doses. Not all ranked secondary endpoints shown. ACR50 and ACR70 were not ranked secondary endpoints. MTX patients shown are patients who continued on their baseline MTX dose in a blinded manner.

Reproduced from CS, Section B.2.6.3, Figure 11, p.69

The CS also highlighted analyses for the following secondary endpoints: clinical remission at 14 weeks, ACR 50 and 70 (Table 14), LDA (based on DAS-28 (CRP) <2.6), HAQ-DI HRQoL (EQ-5D-5L, SF-36), and duration of morning stiffness (Table 14).

At Week 14, a significantly greater proportion of patients receiving UPA 15 mg QD monotherapy achieved **clinical remission** (based on DAS-28(CRP) <2.6) compared with patients receiving MTX monotherapy (28% versus 8% respectively, p<0.001).

Improvements from baseline in **physical function** on the basis of HAQ-DI were observed with UPA 15 mg QD monotherapy versus continued MTX at Week 14: least square mean (LSM) change from baseline in HAQ-DI of −0·65 (95% CI −0·73 to −0·57) for UPA 15 mg QD monotherapy versus −0·32 (−0·41 to −0·24) for continued MTX (p<0·001). The minimum clinically important difference (≤−0·22) was achieved by 140 (66%) of 213 patients (95% CI 59–72) on UPA 15 mg QD monotherapy, and 98 (48%) of 205 patients (95% CI 41–55) on continued MTX (p<0·0001).

HRQoL was assessed using the EQ-5D-5L and SF-36 PCS. Patients reported an improved HRQoL as indicated by improvements in SF-36 PCS for UPA 15 mg QD monotherapy (8·3; 95% CI 7·2–9·4) versus continued MTX (4·3; 3·2–5·4) at Week 14 (p<0·001). Patients also reported an improvement from baseline in mean current health

status as measured by EQ-5D-5L for UPA 15 mg QD monotherapy versus continued MTX (0.2 vs 0.1, p=0.001).

ERG comment

When checking the results reported in the CS against the respective CSRs, no discrepancies were identified.[20,22,24,26]

The ERG noted that here was some variation between the studies in the primary and secondary outcomes used to assess clinical and functional efficacy and HRQoL of UPA (refer to Section 4.2.2.4).

The ERG also noted that, for three of the trials, between-group data were reported only at 12-14 weeks (14 weeks in SELECT MONOTHERAPY and 12 weeks in SELECT NEXT and SELECT COMPARE). For SELECT COMPARE, data are reported at 12 weeks and also at 26 weeks. It is important to consider that the 26 week data include patients who switched treatments (rescue therapy - from PBO to UPA, UPA to ADA, or ADA to UPA - could be implemented at weeks 14, 18, 22, or 26 for patients with <20% improvement in TJC and SJC). Rates of rescue therapy up until 26 weeks were as follows: PBO group not rescued 346 (53.1%), rescued 305 (46.9%); ADA group not rescued 250 (76.5%), rescued 77 (23.5%); UPA group not rescued 526 (80.8%), rescued 125 (19.2%).

[redacted].

In ERG has provided a comment on the results of the pivotal trials for the following key outcomes: ACR response, clinical remission and HRQoL.

ACR response:

ACR response was assessed in all four trials. When compared with PBO over a 12-week period (SELECT-NEXT and SELECT-BEYOND), and over a 14-week period (SELECT-MONOTHERAPY), UPA 15 mg QD demonstrated higher ACR20/50/70 and clinical remission in, despite differences between trials in concomitant treatments. The SELECT-COMPARE trial (through Week 26), a head-to-head comparison with ADA, demonstrated that the ACR20 response rate at Week 12 was significantly higher among UPA 15 mg QD treated patients compared with the 327 ADA-treated patients, at 71% versus 63% (p<0.05).

Clinical remission:

Clinical remission was assessed in all four trials based on DAS-28 CRP <2.6. Clinical remission with UPA 15 mg at 12-14 weeks (14 weeks in SELECT MONOTHERAPY and 12 weeks in the other three trials) was consistent across all trials (28.7%, 30.8%, 28% and 28.7% in SELECT COMPARE, SELECT NEXT, SELECT MONOTHERAPY and SELECT BEYOND respectively), despite differences between trials in concomitant treatments. Clinical remission was consistently higher with UPA 15 mg than with PBO: the clinical remission rates for PBO at 12-14 weeks (across the three PC trials) were 6.1%, 10.0% and 9.5% for SELECT COMPARE, SELECT NEXT and SELECT BEYOND respectively.

At 14 weeks, the clinical remission rate with UPA 15 mg QD monotherapy was significantly higher than that for MTX monotherapy (28% versus 8%, p<0.001). When taken in combination with MTX, UPA 15 mg QD also resulted in a significantly higher remission rate than ADA combined with MTX at both 12 weeks (UPA 15 mg 28.7% ADA 18.0%, p<0.001) and 26 weeks (UPA 15 mg 40.9% ADA 26.9%, p<0.001).

Health-related quality of life:

The EQ-5D-5L and the SF-36 PCS were used to assess HRQoL at 12-14 weeks in all four trials (14 weeks for SELECT MONOTHERAPY). For SELECT COMPARE, EQ-5D-5L data were also reported at 26 weeks.

In all three PC trials (SELECT COMPARE, SELECT NEXT and SELECT BEYOND), and despite differences in concomitant treatments, UPA 15mg resulted in greater improvement on the EQ-5D-5L index at 12-14 weeks (0.2 versus 0.10 respectively in all three studies, p<0.001 in all three trials). Similar results were found for the SF-36 PCS at 12 weeks: there was greater improvement with UPA 15 mg QD than with PBO (mean change from baseline 7.9 versus 3.6 respectively, p<0.001 for SELECT COMPARE, 7.6 versus 3.0 respectively, p≤0.001 for SELECT NEXT; 5.8 versus 2.4, p<0.001 for SELECT BEYOND). In SELECT COMPARE there was also greater improvement on the EQ-5D-5L with UPA 15 mg QD versus PBO at 26 weeks (EQ-5D-5L 0.22 versus 0.11 respectively, p<0.001).

At 14 weeks, there was greater improvement on both the EQ-5D-5L index and the SF-36-PCS with UPA 15 mg QD monotherapy compared with MTX monotherapy (EQ-5D-5L 0.2 vs 0.1 respectively, p=0.001; SF-36 PCS 8·3 versus 4·3 respectively, p<0·001). When taken in combination with MTX, UPA 15 mg QD resulted in a similar improvement

on the EQ-5D-5L index as ADA combined with MTX at both 12 weeks (UPA 15 mg 0.21 ADA 0.17) and 26 weeks (UPA 15 mg 0.22 ADA 0.20). Change from baseline in SF-36 PCS scores was also similar with UPA 15 mg and ADA at 12 weeks (7.9 versus 6.3 respectively).

4.2.4.5 Subgroup analyses

In Section B.2.7 of the CS, the company presented post-hoc subgroup analyses (for ACR20, clinical remission (DAS-28-CRP ≤2.6), and LDA based on DAS-28 (CRP) ≤3.2) for patients with moderate RA. Similar data were not provided in the CS for patients with severe RA. This was queried by the ERG, and in the clarification response from the company, baseline data and clinical effectiveness data were provided separately for the moderate and severe populations. These data are summarised in Table 15 (moderate RA population) and Table 16 (severe RA population).

ERG comment

The ERG noted that the data for the moderate sub-group differed slightly in the CS and in the clarification response from the company (for SELECT COMPARE, SELECT NEXT and SELECT BEYOND) data were provided for fewer participants in the clarification response than the CS). As the most recently provided data, the data taken from the clarification response are presented and discussed here. The ERG highlight that comparisons based on these moderate and severe RA sub-groups were post-hoc analyses and, likely due to this, there was insufficient data in the CSRs with which to check the accuracy of these data. It does appear that, overall, lower p values were found in these between-treatment clinical efficacy analyses for the severe RA subgroup than for the moderate RA subgroup.

Table 15. Baseline characteristics and efficacy outcomes for the moderate RA subgroup across all four registration trials

Study		SELECT-COMPARE			SELECT-NEXT		SELECT-MONOTHERAPY		SELECT-BEYOND
Treatment	**PBO**	**ADA**	**UPA 15 mg**	**PBO**	**UPA 15 mg**	**MTX**	**UPA 15 mg**	**PBO**	**UPA 15 mg**
Total N (moderate)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline demographics & clinical characteristics									
Sex, n (%)									
Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age (years) mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Duration of RA diagnosis (years) – continuous, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TJC68, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SJC66, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HAQ-DI mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DAS 28 based on CRP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Efficacy outcomes timepoint		**Week 12**			**Week 12**		**Week 14**		**Week 12**
ACR20 response rate (% week 12)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical remission (DAS-28- CRP ≤2.6) (responder %)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LDA based on DAS-28 (CRP) ≤3.2 (responder %)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ACR20, America College of Rheumatology 20% response; ADA, adalimumab; CRP, C-reactive protein; csDMARD, conventional synthetic disease modifying antirheumatic drug; DAS-28, ; HAQ-DI, health assessment questionnaire disability index; LDA, low disease activity; MTX, methotrexate; PBO, placebo; RA, rheumatoid arthritis; SD, standard deviation; SJC, swollen joint count; TJC, tender joint count; UPA, upadacitinib

Notes: Values rounded to 1 decimal place ; *p<0.05; ** p<0.01; *** p<0.001 vs placebo

Source: CS, Section B.2.7, Table 13 (p.80) and Table 14 (p.81)

Table 16. Baseline characteristics and efficacy outcomes for the severe RA subgroup across all four registration trials

Study	SELECT-COMPARE			SELECT-NEXT		SELECT-MONOTHERAPY		SELECT-BEYOND	
Treatment	**PBO**	**ADA**	**UPA 15 mg**	**PBO**	**UPA 15 mg**	**MTX**	**UPA 15 mg**	**PBO**	**UPA 15 mg**
Total N (severe)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline demographics & clinical characteristics									
Sex, n (%)									
Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age (years) mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Duration of RA diagnosis (years) – continuous, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TJC68, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SJC66, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HAQ-DI mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DAS 28 based on CRP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Efficacy outcomes timepoint	**Week 12**			**Week 12**		**Week 14**		**Week 12**	
ACR20 response rate (% week 12)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical remission (DAS-28- CRP ≤2.6) (responder %)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LDA based on DAS-28 (CRP) ≤3.2 (responder %)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ACR20, America College of Rheumatology 20% response; ADA, adalimumab; CRP, C-reactive protein; csDMARD, conventional synthetic disease modifying antirheumatic drug; DAS-28, ; HAQ-DI, health assessment questionnaire disability index; LDA, low disease activity; MTX, methotrexate; PBO, placebo; RA, rheumatoid arthritis; SD, standard deviation; SJC, swollen joint count; TJC, tender joint count; UPA, upadacitinib

Notes: *** p<0.001 vs PBO

Source: Company clarification response, Table 4 (p.11), Table 10 (p.23), Table 13 (p.26), Table 19 (p.29). Table 22 (p.31)

The company also presented results with both moderate and severe patient populations combined, stratified by rheumatoid factor status, anti-CCP status and after one and two or more csDMARD failures, in order to understand the efficacy of UPA in patients who could be classified as moderate RA displaying poor prognostic factors as determined by EULAR criteria (refer to Section B.2.7, Table 16 [p.85] and Table 17 [p.85] of the CS). The relative efficacy of UPA was reported in the CS as numerically similar or slightly improved for those with poor prognostic factors (positive rheumatoid factor anti-CCP antibody status and after two csDMARD or more failures) than those without.

4.2.5 Results of any standard meta-analyses of upadacitinib studies

No standard meta-analyses of UPA trials were presented (see Section 4.1.5 for the ERG critique of this decision).

4.2.6 Applicability to clinical practice

The profile of demographic and clinical characteristics was in largely line with clinical expectations, although there may be an overrepresentation of White patients in the trials. All four trials were international with a [redacted] (no UK sites in SELECT-MONOTHERAPY [redacted]), and therefore will include patients undergoing treatment in settings where treatment context and treatment pathways differ considerably from routine practice in England and Wales. An ERG critique of the treatment sequences used in the company economic model is provided in Section 5.2.4.

In addition, the ERG noted that while the trials covered a range of potential treatment scenarios, including comparisons between UPA monotherapy and in combination with csDMARDs against csDMARDs and against bDMARDs, each trial as designed also addressed a range of populations. This is important because decisions for treatment of moderate RA will have different options in the first instance as compared to treatments for severe RA. In response to clarification question A8, the company clarified that treatment severity was not a stratifying factor at randomisation. While subgroup analyses by DAS score were pre-planned, it is not clear that analyses by disease activity were sufficiently powered. In addition, the diverse treatment histories in the included trials mean that estimates from each trial do not map precisely onto different points in the treatment pathway, requiring an assumption of exchangeability of effect among these different points in the treatment pathway.

4.2.7 Safety of UPA

The company provided the key safety data for the four pivotal trials in Section B.2.10 of the CS. Further safety data were provided in Appendix F of the CS. The ERG has checked these safety data against the published data for each trial and, where relevant, the data provided in the clinical study report (CSR). The ERG noted that, for all four studies, the unit of reporting of safety data in the CS was the number of patients experiencing adverse events rather than the number of events. Where relevant, the ERG has supplemented these data with the event rates provided in the CSRs.[20,22,24,26]

4.2.7.1 Safety data from SELECT-COMPARE

For SELECT COMPARE, the company summarised safety data for both the PBO-controlled and active comparator periods of the study (i.e. at 14 weeks and at 26 weeks; refer to B.2.10 and Appendix F of the CS). Table 28 of the CS (p. 112), summarised the key safety data from SELECT-COMPARE. The ERG has checked the data in Table 28 of the CS against the CSR and published papers for the study.[19,20,33,35] For clarity, this table has been reproduced below (Table 17).

The ERG noted that, through to Week 14,

[redacted]

[20] This was not highlighted in the CS, but is highlighted in the CSR.

[redacted]

Table 17. Summary of key safety events from SELECT-COMPARE

	SELECT-COMPARE					
	Week 14			Week 26		
	PBO (N=651)	ADA (N=327)	UPA (N=651)	PBO (N=651)	ADA (N=327)	UPA (N=651)
Any AE, n (%)	303 (46.5)	158 (48.3)	348 (53.5)	347 (53.2)	197 (60.2)	417 (64.2)
Any SAE, n (%)	14 (2.1)	8 (2.4)	18 (2.8)	19 (2.9)	14 (4.3)	24 (3.7)
Any AE leading to discontinuation of study drug, n (%)	12 (1.8)	16 (4.9)	18 (2.8)	15 (2.3)	20 (6.1)	24 (3.7)
Any severe AE[a], n (%)	22 (3.4)	10 (3.1)	20 (3.1)	26 (4.0)	15 (4.6)	29 (4.5)
Any AE with reasonable possibility of being related to study drug[b], n (%)	119 (18.3)	74 (22.6)	174 (26.8)	144 (22.1)	94 (28.7)	212 (32.6)
Any AE leading to death, n (%)	2 (0.3)	1 (0.3)	0	2 (0.3)	2 (0.6)	0
Deaths[c], n (%)	2 (0.3)	1 (0.3)	0	2 (0.3)	2 (0.6)	0

Abbreviations: AE, adverse event; PBO, placebo; ADA, adalimumab; SAE, serious adverse event; UPA, Upadacitinib

Notes: a: Severe AEs were defined as events with Grade 3 or above based on the Rheumatology CTC for AEs; b: As assessed by investigator; c: Any death including non-treatment-emergent deaths

Reproduced from CS, Table 28, page 111

The ERG cross-checked data on deaths and specific AEs through to 26 weeks, censored at treatment switching: no deaths were reported in the UPA 15 mg group (two deaths occurred in the ADA group and two deaths in the PBO group); the most frequently reported AEs (≥5% of patients) in the UPA 15 mg group were upper respiratory tract infection (5.7%) and nasopharyngitis (5.5%); the most frequently reported SAEs in the UPA 15 mg group were appendicitis (0.3%), gastroenteritis (0.3%) and spontaneous abortion (0.3%); and rates of serious infections were 1.8% in the UPA group, 1.5% in the ADA group and 0.8% in the PBO group (noting that all patients were taking MTX).

Adverse events of special interest were described in the text of the CS (refer to B.2.10) and also in Table 42, Appendix F of the CS. The ERG checked the accuracy of these data against the CSR. The ERG noted that rates of treatment-emergent anaemia were not highlighted in Section B.2.10 of the CS (although these data are provided in Table 42, Appendix F of the CS), but for clarity, the ERG highlighted that these rates were comparable across groups at both 14 and 26 weeks (for UPA, ADA and PBO

respectively, these rates were 1.2%, 1.5% and 2.1% at 14 weeks and 1.4%, 1.8% and 2.6% at 26 weeks).

4.2.7.2 Safety data from SELECT-MONOTHERAPY

For SELECT-MONOTHERAPY, 14-week safety data were summarised (i.e. data for the controlled period of the study, refer to B.2.10 and Appendix F of the CS). Table 30 of the CS (p. 115), summarised the key safety data from SELECT-MONOTHERAPY and this has been reproduced below (Table 18).

[redacted][24] As a result, the ERG checked the 14-week data provided in the CS against the available published data for this study.[23,34,36,37]

Table 18. Summary of key safety events from SELECT-MONOTHERAPY

	Week 14		
	cMTX (N=216)	**UPA 15 mg QD (N=217)**	**UPA 30 mg (N=215)**
Any AE, n (%)	102 (47.2)	103 (47.5)	105 (48.8)
Any SAE, n (%)	6 (2.8)	11 (5.1)	6 (2.8)
Any AE leading to discontinuation of study drug, n (%)	6 (2.8)	8 (3.7)	6 (2.8)
Any severe AE, n (%)	5 (2.3)	7 (3.2)	9 (4.2)
Any AE with reasonable possibility of being related to study drug[a], n (%)	43 (19.9)	49 (22.6)	56 (26.0)
Any AE leading to death, n (%)	0	1 (0.5)	0
Deaths[b], n (%)	0	1 (0.5)	0

Abbreviations: AE, adverse event; cMTX, continuing methotrexate; SAE, serious adverse event; UPA, upadacitinib

Notes: a As assessed by investigator; b Any death including non-treatment-emergent deaths

Reproduced from CS, Table 30, page 114

The ERG confirmed that through to 14 weeks, TEAEs occurred, and led to discontinuation, in similar proportions across the three study groups (refer to Table 18). However, SAEs were more common in the UPA 15 mg group than the continuation MTX and UPA 30 mg groups (5.1%, 2.8% and 2.8% respectively). The ERG confirmed that there was one death (haemorrhagic stroke due to a ruptured aneurysm) in the UPA 15 mg group, and no deaths in the other two groups, during the 14-week initial study period.

[redacted]

[redacted]

With regards to specific AEs, the CS stated that there were no AEs that occurred in ≥5 of patients and that for those receiving UPA 15 mg, the most frequently reported AEs during the initial 14 weeks of the study were urinary tract infection (4.1%), upper respiratory tract infection (4.1%), increased blood creatine phosphokinase (2.3%) and bronchitis (1.8%). Further data on specific AEs were given in Appendix F, Table 46 of the CS.

The main publication for SELECT-MONOTHERAPY reported that the lowest rates of infection through to Week 14 were in in the UPA 15 mg arm of the study (19% versus 26% in the continuation MTX arm and 25% in the UPA 30 mg arm).[34] Consistent with the main publication for the study, [34] the CS reported that there was a single treatment emergent serious infection in the UPA 15 mg group (and another in the continuation MTX group) and that there was one MACE event in the UPA 15 mg group and two in the 30 mg group.

The ERG noted that the following 14-week safety data are highlighted in the main publication for SELECT-MONOTHERAPY,[34] and whilst reported in Table 46, Appendix F of the CS, are not highlighted: i) herpes zoster occurred in 2.8% of patients in the UPA 30 mg arm, 1.4% patients in the UPA 15 mg arm and 0.5% of patients in the continued MTX arm; ii) there were two malignancies in the UPA 15 mg arm (non-Hodgkin's lymphoma, breast cancer); iii) Grade 3 haemoglobin decrease was more frequent in the UPA 30 mg than the updacitinib 15 mg and continuation MTX arms, and there was one patient with a Grade 4 haemoglobin decrease in the UPA 30 mg arm. The ERG confirmed that through to Week 14, there were no reports of renal dysfunction in any group.

4.2.7.3 Safety data from SELECT-NEXT

For SELECT-NEXT, 12-week safety data were summarised, i.e. data for the PBO-controlled period of the study (refer to B.2.10 and Appendix F of the CS). Table 29 of the CS (pp.113-114), summarised the key safety data for this study, and this has been reproduced below (Table 19). The ERG checked the data provided in the CS against both the available published data and the CSR.[21,22,38-43] It is important to consider that in SELECT-NEXT, all patients were continuing on csDMARDS.

The ERG confirmed that AEs were reported at similar rates in the UPA 15 mg (56.6%) and UPA 30 mg group (53.9%) compared with 48.9% in the PBO group. However, discontinuations due to AEs occurred in 3.2% of those in the UPA 15 mg and PBO groups and at a higher rate in the upadacitinb 30 mg group (5.9%) even though SAEs were highest in the UPA 15 mg group (4.1%; refer to Table 19). The ERG confirmed that, through to 12 weeks, there were no deaths reported.

Table 19. Summary of key safety events from SELECT-NEXT

	SELECT-NEXT		
	Week 12		
	PBO (N=221)	UPA 15 mg (N=221)	UPA 30 mg (N=219)
Any AE, n (%)	108 (48.9)	125 (56.6)	118 (53.9)
Any SAE, n (%)	5 (2.3)	9 (4.1)	6 (2.7)
Any AE leading to discontinuation of study drug, n (%)	7 (3.2)	7 (3.2)	13 (5.9)
Any severe AE[a], n (%)	5 (2.3)	8 (3.6)	7 (3.2)
Any AE with reasonable possibility of being related to study drug[b], n (%)	45 (20.4)	47 (21.3)	52 (23.7)
Any AE leading to death, n (%)	0	0	0
Deaths[c], n (%)	0	0	0

Abbreviations: AE, adverse event; PBO, placebo; ADA, adalimumab; SAE, serious adverse event; UPA, upadacitinib
Notes: a Severe AEs were defined as events with Grade 3 or above based on the Rheumatology CTC for AEs; b As assessed by investigator; c Any death including non-treatment-emergent deaths
Reproduced from CS, Table 29, page 112

In the UPA 15 mg group, the most commonly reported AEs (≥5% of patients) were nausea (7.2%), nasopharyngitis (5.4%) and upper respiratory tract infection (5.4%). The ERG additionally highlights that [redacted] Table 43, Appendix F of the CS reported lower values for these AEs because only AEs that were assessed as having a reasonable possibility of being related to the study drugs were included.

As stated in Section B.2.10 of the CS, the most commonly reported SAEs in the UPA 15 mg group were wrist fractures (0.9%), coronary artery disease (05%), enterocolitis infectious (0.5%), spinal compression fracture (0.5%), osteoarthritis (0.5%), ovarian germ cell teratoma benign (0.5%), suicide attempt (0.5%) and nephrolithiasis. SAEs across all groups were provided by the company in Appendix F of the CS.

The company noted that the incidence of infection was higher in both groups receiving upadactinib compared with the PBO group (29% in the UPA 15 mg group, 31.5% in the upadactinib 30 mg group, and 21.3% in the PBO group) and these data have been checked against the CSR by the ERG. Similarly, the ERG confirms that serious infections were reported in one patient in the UPA 15 mg group, one patient in the PBO group but in three patients in the UPA 30 mg group and that there were no malignancies or major adverse cardiac events (MACE) reported with UPA 15 mg (there was a single MACE and two malignancies reported with UPA 30 mg). However, there were two patients in the UPA 15 mg group who experienced other cardiovascular events (refer to Table 45, Appendix F of the CS).

The ERG additionally noted that, with respect to other TEAEs of special interest, neutropenia and increased blood creatine phosphokinase was more common in the UPA 15 mg group and the UPA 30 mg group than in the PBO group. Furthermore, the ERG highlights that there were no cases of TE anaemia reported in the UPA 15 mg group, whilst there were three cases each in the UPA 30 mg and PBO groups. These data are provided in Table 45, Appendix F of the CS.

4.2.7.4 Safety data from SELECT-BEYOND

For SELECT-BEYOND, safety data were summarised in Section B.2.10 of the CS, for both the PBO-controlled period (up until 12 weeks) and the extension phase (12–24 weeks) of the study. The extension phase data reported in Section B.2.10 of the CS were provided separately for patients who started the study in the two UPA groups and for patients who started in the PBO group, resulting in four groups (UPA 15 mg, UPA 30 mg, PBO to UPA 15 mg and PBO to UPA 30 mg). Table 31 of the CS (p.118), summarised these data; for clarity these data have also been reproduced below (Table 20). Cumulative safety data (i.e. across the two study periods) were given in Appendix F of the CS as EAIRs.

[redacted]

The ERG checked the data provided in the CS against the available published data and the CSR for the study.[25,26,44-50] In the interpretation of the safety data from SELECT BEYOND, is important to consider that patients were receiving continuation csDMARDS and this may account for adverse events in any of the study arms.

The CS reported that, during the first 12 weeks of the study, rates of TEAEs were similar in the PBO and UPA 15 mg arms (56.2% and 55.5% respectively), but higher in the UPA 30 mg arm (67.3%). The ERG highlighted that during Weeks 12 to 24, rates of TEAEs were similar in the two groups that had received UPA from the start of the study (53% for UPA 15 mg and 56% for UPA 30 mg), lower for the group that switched from PBO to UPA 15 mg (42%) and higher for the group that switched from PBO to UPA 30 mg (67%).

The ERG agreed with the company that during the first 12 weeks of the study, SAEs were more common in the UPA 30 mg group (7.3%) than the UPA 15 mg group (4.9%), and highlights that there were no SAEs in the PBO group during this time. During the extension phase of the study, SAEs were more common in the groups that switched from PBO to UPA 15 mg or 30 mg (7% for each group), than those who started the study with UPA 15 mg or 30 mg (3% in each group). The CSR additionally confirmed

Section B.2.10 of CS reported that AEs leading to discontinuations were highest with UPA 30 mg (9.1%) and lowest with UPA 15 mg (2.4%) during the initial phase of the study. The ERG checked and agreed this and also agreed that discontinuations due to AEs were similar across all four groups between 12 and 24 weeks (4% in the group that switched from PBO to UPA 30 mg and 3% in the groups receiving UPA from baseline and in the group that switched from PBO to UPA 15 mg). The CSR reported

There were two deaths reported across the two SELECT-BEYOND study periods, both in patients taking UPA. One death occurred during the PBO-controlled phase of the study (cardiac failure and pulmonary embolism in a patient receiving UPA 30 mg,). The other death occurred during the extension phase of the study in a patient receiving UPA 15 mg (unwitnessed death due to cardiac arrest and adjudicated as an undetermined/unknown cause of death

[redacted]

In the UPA 15 mg group, the ERG confirmed that during the first 12 weeks of the study, the most frequently reported AEs (>5% of patients) were urinary tract infections (9.1%) and upper respiratory tract infections (7.9%). In the UPA 30 mg the rates of urinary tract infections and upper respiratory tract infections were 5.5% and 6.1% respectively, and these data are correctly reported in Appendix F of the CS, but mislabelled as data pertaining to the upadacitibib 15 mg group in Section B.2.10 of the CS. The ERG additionally noted that the rates of urinary tract infections and upper respiratory tract infections in the PBO group during the same period were 5.9% and 7.7% respectively.

The company reported that although serious infections were more common with UPA 30 mg (2.4%) than UPA 15 mg (0.6%) during the first 12 weeks of the study, and that there were no serious infections in the PBO group during that time, the rates of serious infections were similar across groups during Weeks 12 to 24 of the study, when all groups were receiving UPA. The ERG agreed with this, but additionally confirmed that although rates of serious infection were low during the extension period of the study, they were highest in the group that switched from PBO to UPA 15 mg (refer to Table 20). Details on opportunistic infections are provided in Appendix F and in the text of the main body of the CS (Section B.2.10). These were checked by the ERG against the CSR and appeared to be correct.

Table 20. Summary of key safety events from SELECT-BEYOND

	Weeks 0–12			Weeks 12–24			
	PBO	UPA 15 mg	UPA 30 mg	PBO to UPA 15 mg	PBO to UPA 30 mg	UPA 15 mg	UPA 30 mg
	n=169	n=164	n=165	n=72	n=75	n=156	n=148
AE	95 (56%)	91 (55%)	111 (67%)	30 (42%)	50 (67%)	82 (53%)	83 (56%)
AE leading to discontinuation	9 (5%)	4 (2%)	15 (9%)	2 (3%)	3 (4%)	5 (3%)	5 (3%)
SAE	0	8 (5%)	12 (7%)	5 (7%)	5 (7%)	5 (3%)	5 (3%)
Infection	51 (30%)	54 (33%)	55 (33%)	16 (22%)	31 (41%)	43 (28%)	47 (32%)
Serious infection	0	1 (1%)	4 (2%)	2 (3%)	1 (1%)	1 (1%)	2 (1%)
Opportunistic infection	0	1 (1%)	2 (1%)	0	0	0	1 (1%)
Herpes zoster	1 (1%)	1 (1%)	4 (2%)	0	1 (1%)	2 (1%)	2 (1%)
Malignancy (excluding non-melanoma skin cancer)	0	1 (1%)	2 (1%)	0	0	1 (1%)	0
Hepatic disorder	2 (1%)	2 (1%)	3 (2%)	0	2 (3%)	4 (3%)	4 (3%)
Gastrointestinal perforation	0	0	0	0	0	0	1 (1%)
Pulmonary embolism events	0	1 (1%)	0	2 (3%)	1 (1%)	0	0
Cardiovascular events	0	1 (1%)	0	0	1 (1%)	2 (1%)	0
Major adverse cardiovascular event	0	1 (1%)	0	0	1 (1%)	0	0
Other cardiovascular events	0	0	0	0	0	1 (1%)	0
Undetermined or unknown cause of death	0	0	0	0	0	1 (1%)	0
Deaths	0	0	1 (1%)	0	0	1 (1%)	0

Abbreviations: AE, adverse event; PBO, placebo; SAE, serious adverse event; UPA, upadacitinib

Reproduced from CS, Table 31, page 117

Other AEs of special interest for SELECT-BEYOND are provided in Table 51, Appendix F of the CS. The ERG confirmed that throughout the study there were two patients who experienced a MACE (one whist receiving UPA 15 mg, and one whilst receiving UPA 30 mg), and three reports of renal dysfunction (one in the UPA 15 mg group and two in the 30 mg group). The ERG also noted that in the first 12 weeks of the study there were three malignancies (one in the UPA 15 mg group and two in the UPA 30 mg group), and that from baseline to Week 24 there were four malignancies (two in patients who received UPA 15 mg and two in participants who received UPA 30 mg). From baseline to Week 24, there were 11 patients who experienced TE anaemia (four whilst receiving UPA 15 mg and seven in whilst receiving UPA 30 mg). Similarly, TE neutropenia was seen in patients whilst receiving UPA, but not in patients whilst receiving PBO (refer to Appendix F, Table 51 of the CS).

4.2.7.5 Summary of safety data across the SELECT studies

When considering the four pivotal studies together, the company stated that there was a comparable safety profile for UPA 15 mg and comparators (ADA, MTX and PBO). Whilst this largely appears to be the case, the ERG highlighted that in the PBO-controlled period of SELECT-COMPARE, [redacted]; in the initial period of SELECT-MONOTHERAPY a greater proportion of patients in the UPA 15 mg group experienced SAEs than the continuation MTX and UPA 30 mg groups (5.1%, 2.8% and 2.8% respectively); in the PBO controlled period of SELECT-NEXT a higher proportion of patients in the UPA 15 mg group experienced SAEs than those in the UPA 30 mg group and the PBO group; and in the PBO-controlled phase of SELECT-BEYOND, SAEs occurred in those taking UPA (30 mg group 7.3%; 15 mg group 4.9%) but not in those taking PBO.

The company also summarised that, in patients who received UPA 15 mg, fewer than 7.5% had SAEs, only two SAEs were reported in >0.5% of that sample, and that there were two deaths (haemorrhagic stroke, cardiac arrest). For clarity, the ERG summarised all deaths that occurred across the four studies: across 26 weeks of SELECT-COMPARE there were no deaths with UPA 15 mg, two with ADA and two with PBO; across 14 weeks of SELECT-MONOTHERAPY there was one death with UPA 15 mg, none with UPA 30 mg and none with continuation MTX [redacted]; there were no deaths reported across the 12-week

initial phase of SELECT-NEXT; and there were two deaths reported during SELECT-BEYOND, one in the PBO-controlled phase with UPA 30 mg, and one in the extension phase with upadactinib 15 mg
([redacted]).

With regard to serious infections, the ERG agreed with the company that frequencies of serious infections were similar to those seen in patients taking bDMARDS: in SELECT-COMPARE rates of serious infection through to week 26 were 1.8% in the UPA 15 mg group and 1.5% in the ADA group. The rates of serious infection with UPA 15 mg in the remaining studies was as follows: 0.5% during the initial period of SELECT-MONOTHERAPY, 0.5% during the initial period of SELECT-NEXT and 1% in both treatment periods of SELECT-BEYOND (amongst those who received UPA from the start of the study, but 3% during the extension period of SELECT-BEYOND amongst patients who switched from PBO to UPA 15 mg).

The ERG also agreed with the company that malignancies and MACE were uncommon, but they did occur in the UPA groups of two of the pivotal trials: in SELECT-MONOTHERAPY there was a single MACE in the UPA 15 mg group, and in SELECT-BEYOND there were two MACE (one in a patient who received 15 mg, and one in a patient who received 30 mg, of UPA). Malignancies were also uncommon: in SELECT-COMPARE there were no malignancies in the UPA group, and similarly there were no malignancies in the UPA 15 mg group in SELECT-NEXT. There were, however, two malignancies in the UPA 15 mg group in SELECT-MONOTHERAPY and two malignancies in patients who received UPA 15 mg in SELECT-BEYOND.

The company reported, and the ERG agreed, that across the trials the most commonly reported adverse events in patients receiving UPA were: upper respiratory tract infections, nausea, cough and increased blood creatine phosphokinase (CPK). The ERG additionally noted the following commonly reported AEs: urinary tract infections (in SELECT-MONOTHERAPY and SELECT-BEYOND), and
[redacted]).

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

4.3.1 Search strategy

The company did not conduct a separate search to identify relevant RCTs for comparators for inclusion in the NMA.

ERG comment:

The searches for the clinical effectiveness SLR (including comparators) are critiqued in Section 4.1.1. These searches also encompass the identification of trials for the NMA.

4.3.2 Feasibility assessment

Feasibility assessment was not explicitly reported for the NMAs undertaken. This is a major omission that threatens the credibility of the NMAs presented. Ideally, feasibility assessment should have considered the quantity and quality of included evidence, with a view towards similarity of trials within networks of evidence. As discussed below in Section 4.3.3, feasibility assessment should have considered the similarity of trials within the networks comprised of csDMARD-experienced and bDMARD-experienced populations. This examination should also have explicitly considered transitivity, which includes, among other characteristics, the similarity of populations across trials in each network, the relevance of all included treatments to the population targeted by the NMA, and the quality of evidence included.

The ERG regarded that the included characteristics of studies within each network (discussed further in Section 4.3.4), together with the application of inclusion and exclusion criteria for the NMA, provided some evidence of balance in terms of population characteristics across each network. However, the high rate of missingness for key population characteristics in included trials precludes confidence that trial populations are similar within each NMA. For example, number of previous DMARDs, an important indicator of treatment 'stage', was frequently unreported in the included trials. Relatedly, the broad characteristics used to shape each network—namely inadequate response to csDMARDs and inadequate response to bDMARDs, regardless of disease severity—obscure potential heterogeneity in disease stage and treatment sequence that may be clinically relevant or predictive of treatment response. While the ERG acknowledged that there is some basis to proceed with NMAs based on the evidence provided, it would urge caution in the interpretation of the NMAs.

4.3.3 Study selection criteria

Following inclusion in the SLR (see Section 4.1.2 for ERG critique), trials were further assessed for potential inclusion in the NMA.

The NMA was divided into two populations (CS, p. 53): i) csDMARD-experienced: patients with RA who had an inadequate response or were intolerant to at least one

csDMARD and ii) bDMARD-experienced: patients with RA who had an inadequate response or were intolerant to at least one bDMARD.

Furthermore, in order to be included in the NMA, trials had to be:

- A Phase III or higher RCT
- EMA licensed treatments for moderate-to-severe RA approved by NICE
- Reporting ACR outcomes between 9- and 15 weeks (12-week network) and between 20 and 30 weeks (24-week network)

Assessment windows allowed for the inclusion of additional clinical evidence, although the majority of clinical evidence is reported at the 12- and 24-week time points. This was in accordance with precedence from TA375[31], TA466[51] and TA480[32] in RA. However, the ERG noted an inconsistency between inclusion criteria in CS Appendix D.1.6, which states that three-month follow-up data could range from 9 to 15 week follow-up, findings as presented in CS Appendix D.1.13, Table 12, which describes three-month findings as ranging from 12 to 16 week follow-up; similarly, six-month follow-up is described in CS Appendix D.1.6 as 20 to 30 weeks, whereas Table 13 describes these as 18 to 30 weeks.

Studies comparing two methods of administration of the same agent were included. Based on the NICE recommendations for these particular agents, GOL, IFX, ABT, and RTX were only considered in combination therapies. RCTs from any geographical location were considered. Trials with early escape were only included if an appropriate imputation of data was employed.

The list of trials included in the SLR but excluded from the NMA is presented in the CS Appendix D Table 4 for the csDMARD experienced population and Appendix D Table 5 for the bDMARD inadequate response population.

For the csDMARD-experienced population, the listed reasons for exclusion were:

- Study design – Phase 2
- Study design – phase unclear
- Study design – other
- Treatments – biosimilar

- Treatments – no intervention
- Treatments – no comparator
- Outcomes – timepoint
- Outcomes – not of interest
- Study population – bio experienced
- Study population – MTX naïve
- Study population – disease severity and study population – other.

For the bDMARD-experienced population, the reasons listed for exclusion were: study design –early termination, study design – other, treatments – no intervention, treatments – no comparator, treatments – biosimilar, outcomes – not of interest and study population – bio naïve.

ERG comment:

The ERG considered the inclusion criteria for the NMA to be largely appropriate. However, the ERG sought further information at the clarification stage regarding the restriction to phase III or higher trials, the use of MTX-naïve as a possible exclusion criterion and the criterion related to early escape. The ERG critiqued the list of studies excluded from the NMA and the listed reasons for exclusion. The inclusion criteria for the csDMARD-experienced population NMA in the CS did not specify that prior treatment had to be with MTX. The NICE final scope for this appraisal[11] stated that prior combination therapy should include MTX, but does not make this stipulation for prior csDMARD monotherapy. "Study population – MTX naïve" was listed in the CS as a reason for exclusion in the csDMARD-experienced population. In the clarification response (A16), the company stated that MTX "was not required as a previous csDMARD for included trials [and that] trials were only excluded if the results of the results of the subgroup of csDMARD-experienced patients were not reported". Ambiguities in the time points included in the analysis also present a potential source of uncertainty in interpretation of NMAs arising from this SLR.

Furthermore, the ERG noted that studies of biosimilars had been excluded and that this was not a stated exclusion criterion. Indeed, the NICE final scope[11] states that: "the availability and cost of biosimilar products should be taken into account" (p.4).

The ERG considered the categories “study population – other” and “study design – other” (at times written just as “study population” and “study design” due to inconsistency in the terminology in the CS Appendix D (Table 4, p. 106-142) to be too imprecise to make a definitive judgement on appropriateness.

With regard to the bDMARD-experienced population, the ERG noted the same concerns as above regarding the “study design – other” and “treatments – biosimilar” reasons for exclusion as described above for the csDMARD-experienced population.

The ERG considered that the potential of inappropriate exclusion of trials from the NMAs could not be ruled out.

4.3.4 Included studies

4.3.4.1 csDMARD-experienced population

The csDMARD-experienced population NMA included 55 unique studies profiled across 207 publications. The included studies are profiled in the CS Appendix D (Table 7, pp.152-69), and reproduced below as Table 21.

The ERG checked the reasons for inclusion or exclusion of the studies identified in TA375[31] and TA485[52] with regards to the SLR and NMAs, to determine whether studies that had not been included in the company’s SLR or NMAs for this appraisal would have qualified. A number of these studies contained relevant interventions but were not included by the company’s SLRs: AUGUST II[53], ETN Study 309[54,55], IIBCREATE[56], Wong 2009[57] and Zhang 2006[58]. AUGUST II and ETN Study 309 were excluded in the company’s SLR for reasons of study design, but the studies by Wong and by Zhang were identified in the ERG’s replication of the company search but were not included in the company’s SLR nor on the list of full-text excluded studies. The ERG regarded that Wong 2009[57] was excluded on the basis of study outcome, as ACR was not reported, and that IIBCREATE[56] was excluded on the basis of study design, as it was described as a phase II trial. The ERG could not definitively consider whether Zhang 2006[58] should have been excluded, though the title of the study characterises its design as ‘preliminary’, which suggests it may have been excluded on the basis of phase II design.

The study by Wajdula et al. 2000[59] was identified in the SLR of cost-effectiveness evidence and included in the economic evaluation (see the inclusion of Chen 2006[60] in the CS, Appendix D [Table 53, p.322-331), but was not identified in the SLR of clinical-effectiveness evidence. However, the ERG did not agree with the company’s exclusion of the RCT by Kay et al. 2008[61] on the grounds of the timepoint of the study outcomes,

despite ACR data at Week 16 being reported. This may be related to an ambiguity in time points used in NMAs, described above in Section 4.3.3.

Table 21. Study details of all studies included in the NMA (csDMARD-experienced population)

Study name (Author year) (ref), Country	Treatment name	Study design	Study duration; Primary endpoint	Outcomes reported	Main prior treatment criteria	Inclusion criteria	Secondary Reference
ACQUIRE[62] Global	• ABT 10 mg/kg q4w + MTX • ABT 125 mg weekly + MTX	RCT, DB, DD, MC, PG (Phase 3b)	26 weeks	• ACR20/50/70 • DAS 28 • HAQ-DI score	Patients had to have had an inadequate response to 3 months of MTX therapy	• RA who were in functional classes I, II or III	63-68
ACT-RAY[69] UK	• TCZ 8 mg/kg q4w + MTX • TCZ 8 mg/kg q4w + PBO	RCT, DB (Phase 3)	24 weeks, 12 weeks	• ACR20/50/70 • EULAR • DAS-28 Score • HAQ-DI score	Anti TNF-α naïve	• RA, DAS-28-ESR >4.4	70-75
ADACTA[76] US/Global	• ADA 40 mg q2w • TCZ 8 mg/kg q4w	RCT, DB, PG (Phase 4)	25 weeks; 12 Weeks	• DAS-28 score • ACR20/50/70 • EULAR • HAQ-DI score	Anti TNF-α naive	• Age ≥18 years • Active RA, intolerant to MTX	77-79
AIM[80] US, Mexico, Europe	• ABT ~10 mg/kg + MTX ≥10 mg/week • PBO + MTX ≥10 mg/week	RCT, DB, MC, PC (Phase 3)	52 weeks/26 weeks	• ACR20/50/70 • HAQ-DI score • DAS 28	Treated with MTX (15 mg/w) for 3 months or longer, with a stable dose for 28 days before enrolment.	• Age ≥18 years • RA for at least 1 year	81-88
Amano, 2015[89] Japan	• ABT 125 mg SC weekly + MTX + PBO • ABT ~10 mg/kg IV + MTX + PBO	MC, RCT, DB, DD (Phase 2/3)	24 Week/ day 169	• ACR20/50/70 • DAS 28 • HAQ-DI score	Patients had an inadequate response to MTX (patients had to have received MTX for 3 months at a stable dose (6-8 mg/week) prior to entry)	• Japanese adults • Age 20 years • RA, who were MTX-IR • ≥10 SJC/ ≥12 TJC joints	90

Study name (Author year) (ref), Country	Treatment name	Study design	Study duration; Primary endpoint	Outcomes reported	Main prior treatment criteria	Inclusion criteria	Secondary Reference
						• CRP levels of ≥0.8 mg/dL	
AMPLE[91] Global (reported as multinational study)	• ABT 125 mg weekly + MTX • ADA 40 mg q2w + MTX	RCT (Phase 3b)	52 weeks/ 24 weeks	• ACR20/50/70 DAS 28 HAQ-DI score	Patients had an inadequate response to MTX	• Patients with an inadequate response to MTX	92-101
APPEAL[102] Asia-Pacific	• ETN 25 mg twice weekly + MTX • csDMARD + MTX	RCT, PG, MC, OL (Phase 4)	16 weeks	• ACR20/50/70 • EULAR • DAS-28 score HAQ-DI score	Subjects were currently receiving an adequate dose of oral MTX 1 day/week	• Age 18-70 years • DAS-28 ≥3.2	
ARMADA[103] US and Canada	• ADA 40 mg q2w + MTX • PBO + MTX	RCT, DB, PC (Phase 2/3)	24 weeks	• ACR20/50/70 • HAQ-DI score	Anti TNF-α naïve	• Age ≥18 years • Active RA	104
ATTEST[105] Multiple countries	• ABT 10 mg/kg q4w + MTX • IFX 3 mg/kg q8w + MTX • MTX	RCT, DB, DD, PC (Phase 3)	52 weeks/28 weeks	• ACR20/50/70 • EULAR DAS 28	Anti TNF-α naïve; MTX: ≥15 mg/week for ≥3 months	• Age ≥18 years • RA, inadequate response to MTX, • >10 SJC, >12 TJC • CRP levels >1	106,107
ATTRACT[108] US/Global	• IFX 3 mg/kg q8w + MTX • PBO + MTX	RCT, DB, PC (Phase 3)	30 Weeks	• ACR20/50/70 • HAQ-DI score	Anti TNF-α naïve	• RA, despite treatment with MTX • SJC ≥6, TJC of ≥6 • ESR >28 mm/h,	109-111

Study name (Author year) (ref), Country	Treatment name	Study design	Study duration; Primary endpoint	Outcomes reported	Main prior treatment criteria	Inclusion criteria	Secondary Reference
						• CRP > 2 mg/dL	
BREVACTA[112] US/Global	• TCZ 162 mg q2w + MTX • PBO + DMARDs	RCT, DB, PC, PG, MC (Phase 3)	24 weeks	• ACR20/50/70 • DAS-28 Score • HAQ-DI score	Anti TNF-α naïve	• Age ≥18 years • SJC= 6 (66-joint count) and TJC= 8 (68-joint count) • CRP level 10 mg/litre and/or • ESR 28 mm/hour • Inadequate response to 1 DMARD	113-115
CERTAIN[116] Europe	• CTZ 200 mg q2w + csDMARD • PBO + csDMARDs	RCT, DB, PC (Phase 3b)	52 weeks, 24 weeks	• ACR20/50/70 • EULAR • DAS-28 score • HAQ-DI score	Patients must have received mono or combination DMARD therapy	• Age ≥18 years • Moderate • ≥2 TJC, ≥2 SJC • ESR ≥28 mm/h • CRP >10 mg/L).	117,118
CHANGE[119] Japan	• ADA 40 mg q2w • PBO	RCT, DB, MC, PC (Phase 2/3)	24 weeks	• ACR20/50/70 • HAQ-DI score	Anti TNF-α naive	• Japanese 20 years or older • Active RA, had failed treatment with at least	

Study name (Author year) (ref), Country	Treatment name	Study design	Study duration; Primary endpoint	Outcomes reported	Main prior treatment criteria	Inclusion criteria	Secondary Reference
						one prior DMARD • 10 SJC,12 TJC • CRP 2 mg/dl	
DE019[120] US, and Canada	• ADA 40 mg q2w + MTX • PBO + MTX	RCT, DB, PC, PG (Phase 3)	52 weeks/ 24 weeks	• ACR20/50/70 • HAQ-DI score	Anti TNF-α naïve	• Age ≥18 years • Active RA • ≥9 TJC of 68 evaluated), ≥6 SJC (of 66 evaluated • CRP >1 mg/dl, • Rheumatoid factor positive	[121,122]
EXXELERATE[123] Multiple countries	• CTZ 200 mg q2w + MTX • ADA 40 mg q2w + MTX • SRL 150 mg q2w + MTX • SRL 200 mg q2w + MTX • PBO + MTX	RCT, DB (DB until Week12, SB thereafter), PG, MC (Phase 4)	104 Weeks, 12 weeks	• ACR20	Patients were bDMARD-naive and with active disease despite a minimum 12-week course of MTX therapy.	• Age ≥18 years • DAS-28-ESR higher than 3·2, • SJC ≥4 • CRP ≥10 mg/L • ESR ≥28 mm/h allowed, if the	
Go-Forth[124] Japan	• GOL 50 mg q4w + MTX	RCT, DB, MC, PC, PG (Phase 2/3)	24 weeks, 14 weeks	• ACR20/50/70 • EULAR	Anti TNF-α naïve	• Age 20-75 years	[125-128]

Study name (Author year) (ref), Country	Treatment name	Study design	Study duration; Primary endpoint	Outcomes reported	Main prior treatment criteria	Inclusion criteria	Secondary Reference
	• PBO + MTX			• DAS-28 score • HAQ-DI score		• Active RA	
GO-FORWARD[129] Multiple countries	• GOL 50 mg q4w + MTX • PBO + MTX	RCT, DB Multicentre (Phase 3)	24 weeks, 14 weeks	• ACR20/50/70 • EULAR • HAQ-DI score	Anti TNF-α naïve	• Age ≥18 years • Active RA	[130-136]
JESMR[137] Japan	• ETN 25 mg q2w + MTX • ETN 25 mg q2w	RCT, OL (Phase 3)	24 weeks	• ACR20/50/70 • EULAR • DAS-28 score • HAQ-DI score	Patients also had to be ACR functional class I-III, receiving not less than 6 mg/week of MTX for a minimum of 3 months, and be dose stable for at least 4 weeks at the time of study enrolment	• Age ≥18 years • At least 6 TJC and 6 SJC • CRP level of more than 2 mg/dl • ESR of no less than 28 mm	
J-RAPID[138] Japan	• CTZ 200 mg q2w + MTX • PBO + MTX	RCT, DB, MC, PC (Phase 2/3)	24 weeks; 12 weeks	• ACR20/50/70 • EULAR • DAS-28 score • HAQ-DI score	Anti TNF-α naive	• Age 20-74 years • Active RA	
Kim, 2007[139] Korea	• ADA 40 mg q2w + MTX • PBO + MTX	RCT, DB, PC (Phase 3)	24 weeks	• ACR20/50/70 • HAQ-DI score	Anti TNF-α naïve	• Age ≥18 years • Active RA • ≥6 SJC and ≥9 TJC	
Kim, 2013[140] Korea	• IFX 3 mg/kg q8w + MTX • PBO + MTX	RCT, DB, PC (Phase 3)	84 Weeks, 30 weeks	• ACR20/50/7 • HAQ-DI score	Anti TNF-α naïve	• Active RA despite MTX • ≥6 SJC, ≥6 TJC • ESR >28 mm/h, • CRP >2 mg/dL	

Study name (Author year) (ref), Country	Treatment name	Study design	Study duration; Primary endpoint	Outcomes reported	Main prior treatment criteria	Inclusion criteria	Secondary Reference
LARA[141] Latin America	• ETN 50 mg qw SC + MTX • csDMARD + MTX	RCT, PG (Phase 4)	24 weeks	• ACR20/50/70 • EULAR • HAQ-DI score	Prior nonbiologic DMARDs other than MTX could not have been received within 3 months before screening.	• Active RA	
Li, 2016[142] China	• GOL 50 mg q4w + MTX • PBO + MTX	RCT, DB, MC, PC, PG (Phase 3)	25 weeks, 14 weeks	• ACR20/50/70 • DAS Score • HAQ-DI score	Anti TNF-α naïve	• RA ≥18 years • ≥4/66 SJC, ≥4/68 TJC • CRP ≥15 mg/L • ESR ≥28 mm/	[143]
LITHE[144] US/Global	• TCZ 8 mg/kg q4w + MTX • PBO + MTX	RCT, DB, PC (Phase 3)	52 weeks/12 and 24 Week	• ACR20/50/70 • DAS 28 • HAQ-DI score	Patients had an inadequate response to MTX (stable at a dosage of 10-25 mg/week for ≥8 weeks)	• RA, inadequate response to MTX • SJC ≥6, TJC of ≥8 • CRP ≥1 mg/dl • ESR ≥28 mm/h	[145-147]
MOBILITY[148] Global	• SAR150 mg q2w + MTX • SRL 200 mg q2w + MTX • PBO + MTX	RCT, DB, PC, MC (Phase 3)	52 week/16 and 24 weeks	• ACR20/50/70 • DAS 28 • HAQ-DI score	Patients had an inadequate response to MTX	• Age ≥18 years • SJC ≥6, TJC ≥8; • CRP ≥0.6 mg/dl	[149-152]
MONARCH[153] Multiple countries	• ADA 40 mg q2w • SRL 200 mg q2w	RCT, DB, DD (Phase 3)	24 weeks	• DAS-28 score • ACR20/50/70 • HAQ-DI score	Active RA, defined as ≥6 of 66 swollen and ≥8 of 68 tender joints	• Age ≥18 years • Active RA	[154,155] [156-160]

Study name (Author year) (ref), Country	Treatment name	Study design	Study duration; Primary endpoint	Outcomes reported	Main prior treatment criteria	Inclusion criteria	Secondary Reference
						• ≥6 of 66 SJC and ≥8 of 68 TJC • CRP ≥8 mg/L • ESR (ESR) ≥28 mm/hours • DAS-28-ESR) >5.1	
Moreland, 1999[161] North America	• ETN 25 mg q2w • PBO	RCT, DB, PC (Phase 3)	26 weeks, 13weeks	• ACR20/50/70	Inadequate response to one to four DMARDs	• Age ≥18 years • RA, inadequate response to one to four DMARDs	
OPTION[162] Global	• TCZ 8 mg/kg q4w + MTX • PBO + MTX	RCT, DB, PC, MC International (Phase 3)	24 weeks/24 weeks	• ACR20/50/70 • EULAR • Change from baseline in DAS 28 • HAQ-DI score	Adult patients with moderate to severe active RA	• Moderate to severe active RA	
ORAL SCAN[163] US/Global	• TFC 5 mg bid + MTX • PBO + MTX	RCT, DB, PC, PG (Phase 3)	26 weeks, 13weeks	• ACR20/50/70 • EULAR • DAS-28 Score • HAQ-DI score	Anti TNF-α naïve	• Age ≥18 years • Active RA	164-168 169
ORAL Standard[170] Global	• TFC 5 mg bid + MTX • ADA 40 mg q2w + MTX	RCT, PC (Phase 3)	52 weeks, 26 weeks	• ACR20/50/70 • EULAR • DAS-28 score • HAQ-DI score	Anti TNF-α naive	• Age ≥18 years • Active	171-175

Study name (Author year) (ref), Country	Treatment name	Study design	Study duration; Primary endpoint	Outcomes reported	Main prior treatment criteria	Inclusion criteria	Secondary Reference
	• PBO Followed by TFC, 5 mg						
ORAL Strategy[176] Global	• TFC 5mg bid • TFC 5mg bid + MTX • ADA 40 mg q2w + MTX	RCT, TD, DB, MC (phase3b/4)	6 months	• ACR 20/50/70 • EULAR • DAS 28	Adult patients with active RA despite treatment with MTX 15-25 mg per week	• Age ≥18 years • ≥4 tender or painful joints on motion and ≥4 SJC	177-180
ORAL Sync[181] Global	• TFC 5 mg bid + MTX • PBO + csDMARD	RCT, DB, MC (Phase 3)	52 weeks, 13 weeks	• ACR20/50/70 • EULAR • DAS-28 Score • HAQ-DI score	Anti TNF-α naïve	• RA diagnosis, ≥18 years • ≥4 TJC, ≥4 or SJC • ESR ≥28 mm/h • CRP >66.7 nmol/L • Inadequate response DMARDs	182
RA0025[183] Korea	• CTZ 200 mg q2w + MTX • PBO + MTX	RCT, DB, PC (Phase 3)	24 weeks	• ACR20/50/70 • HAQ-DI score	Anti TNF-α naïve	• Active RA • ≥9 TJC/SJC • CRP >15 mg/L • ESR ≥30 mm/h	184
RA-BEAM[185] Global	• ADA 40 mg q2w + MTX • BAR 4 mg QD + MTX; PBO + MTX	RCT, DB, PC (Phase 3)	52 weeks, 12 weeks	• ACR20/50/70 • DAS-28 score • HAQ-DI score	Anti TNF-α naive	• Age ≥18 years • Active RA • ≥6/68 TJC, ≥6/66 SJC	186-201

Study name (Author year) (ref), Country	Treatment name	Study design	Study duration; Primary endpoint	Outcomes reported	Main prior treatment criteria	Inclusion criteria	Secondary Reference
						• CRP ≥6 mg/L • Patients had inadequate response to MTX	
RA-BUILD[202] Global	• PBO + csDMARD • BAR 2 mg qd + csDMARD • BAR 4 mg qd + csDMARD	RCT, DB, DD, PC, MC International (Phase3)	24 weeks/ 12 and 24 weeks	• ACR20/50/70 • DAS-28 score	An insufficient response (despite prior therapy) or intolerance to ≥1 csDMARDs	• Age ≥18 years • Active RA • ≥6/68 TJC and ≥6/66 SJC • CRP ≥3.6 mg/L • Insufficient response ≥1 csDMARDs	203-206
RACAT[207] US and Canada	• SSZ 1 g daily + HCQ 400 mg daily + MTX + PBO + ETN weekly • ETN 50 mg weekly + PBO SSZ and HCQ daily	RCT, MC, DB, (Phase 4)^	48 week/24 weeks	• DAS-28 score • ACR20/50/70 • HAQ-DI score	MTX at stable doses of 15 to 25 mg weekly for at least 12 weeks	• Age ≥18 years • Active RA	
RAPID-1[208] US, and Europe	• CTZ 200 mg q2w + MTX • PBO + MTX	RCT, DB, MC, PC, PG (Phase 3)	52 weeks, 24 weeks	• ACR20/50/70 • HAQ-DI score	Anti TNF-α naïve (patients excluded if any within the last 6 months)	• Age ≥18 years • >9 TJC, >9 SJC • ESR >30 mm/h • CRP >15 mg/litre	209-218

Study name (Author year) (ref), Country	Treatment name	Study design	Study duration; Primary endpoint	Outcomes reported	Main prior treatment criteria	Inclusion criteria	Secondary Reference
RAPID-2[219] US and Europe	• CTZ 200 mg q2w + MTX • PBO + MTX	RCT, DB, MC, PC (Phase 3)	24 weeks; 12 weeks	• ACR20/50/70 • DAS-28 score • HAQ-DI score	10% anti TNF-α exposed	• Age ≥18 years • Active RA	[220-224]
RA BALANCE[225] China, Brazil, Argentina	• BRC 4 mg QD • PBO	RCT, DB, PC, MC (Phase 3)	52 weeks; 12 weeks	• ACR20/50/70 • DAS 28 • HAQ-DI score	Previously treated with MTX	• Active RA (tender joint counts >=6 & swollen joint counts >=6 & hsCRP >=6 mg/L)	[226,227]
RA-SCORE[228] Europe	• PBO + MTX • RTX 2x500 mg q24w + MTX • RTX 2x1000 mg q24w + MTX	RCT, DB, PC, MC International (Phase3b)	52 weeks/24 weeks	• ACR20/50/70 • EULAR DAS-28	patients had experienced an Inadequate response to MTX	• DAS-28-CRP score ≥3.2 • inadequate response to MTX	
REALISTIC[229] US, Canada and Europe	• CTZ 200 mg q2w + csDMARD • PBO + csDMARD	RCT, DB, MC (Phase 3b)	12 weeks/ 12 weeks	• ACR20/50/70	Unsatisfactory response or intolerance to at least one DMARD	• Age ≥18 years • 5 TJC, 4 SJC • ≥10 mg/l CRP • ≥28 mm/h ESR	[230-236]
SAMURAI[237] Japan	• TCZ 8 mg/kg q4w • csDMARD	RCT, MC (Phase 3), SB (reader blind)	52 week/12 and 24 weeks	• ACR20/50/70 • DAS-28 • HAQ-DI score	All candidates had an inadequate response to at least one DMARD or immunosuppressant	• Age >20 years • >6 TJC (of 49 evaluated), >6 SJC (of 46 evaluated)	

Study name (Author year) (ref), Country	Treatment name	Study design	Study duration; Primary endpoint	Outcomes reported	Main prior treatment criteria	Inclusion criteria	Secondary Reference
						• ESR of >30 mm/h • CRP of >20 mg/l	
SATORI[238] Japan	• TCZ 8 mg/kg q4w + csDMARD • MTX	RCT, DB, MC (Phase 3)	24 weeks	• ACR20/50/70 • EULAR • DAS-28 Score • HAQ-DI score	Assumed Anti TNF-α naive	• Age 20 and 75 years • 6 TJC (of 49 evaluated), 6 SJC (of 46 evaluated) • ESR 30 mm/h • CRP 10 mg/l • Inadequate response to MTX	[239]
SELECT–COMPARE[19]	• PBO • UPA 15 mg QD • ADA 40 mg EOW	RCT, DB, AC, MC (Phase 3)	26 weeks; 12 weeks	• ACR20/50/70 • DAS 28 • HAQ-DI score	Previously treated with MTX	• Active RA patients • Previously treated with MTX	-
SELECT MONOTHERAPY[23]	• UPA 15 mg QD • UPA 30 mg QD • cMTX	RCT, DB (Phase 3)	14 weeks	• ACR20 • DAS 28 • HAQ-DI score	MTX treatment	• Active RA (TJC >=6, SJC>=6, hsCRP >=3 mg/L) • Stable dose of MTX previously	[36,37]
SELECT NEXT[21]	• UPA15 mg QD • UPA 30 mg QD • PBO	RCT, DB, PC (Phase 3)	12 weeks	• ACR20/50/70 • DAS-28 score • HAQ-DI score	Patients with prior exposure to any JAK inhibitor, and patients who are considered	• Patients with RA	[38-43]

Study name (Author year) (ref), Country	Treatment name	Study design	Study duration; Primary endpoint	Outcomes reported	Main prior treatment criteria	Inclusion criteria	Secondary Reference
					inadequate responders to csDMARD	• Inadequate response to csDMARDs	
SELECT SUNRISE[27] Japan	• UPA 7.5 mg QD • UPA 15 mg QD • UPA 30 mg QD • PBO	RCT, DB, PC (Phase 2/3)	12 weeks	• ACR20/50/70 • DAS 28 • HAQ-DI score	csDMARDs	• Active RA Japanese patients	-
SERENE[240] Global	• RTX 2x1000 mg q24w + MTX • PBO + MTX	RCT, DB, PC, MC (Phase 3)	24 weeks	• ACR20/50/70 • EULAR • DAS-28 Score • HAQ-DI score	Anti TNF-α naïve	• Active RA, inadequate response to MTX	[241]
STAR[242] US, Canada	• ADA 40 mg q2w • PBO	RCT, DB, PC, MC (Phase 3)	24-week/ 24 weeks	• Safety • ACR20/50/70 • EULAR • DAS-28	standard antirheumatic therapy in patients with active RA not adequately responding to such therapies	• Age ≥18 years • Active RA • At least 6 SJC and at least 9 TJC	
START[243] North/South America, Europe	• IFX 3 mg/kg q8w + MTX • PBO + MTX	RCT, PC (Phase 3)	22 weeks	• ACR20/50/70 • EULAR • DAS-28 Score • HAQ-DI score	Anti TNF-α naïve	• Active RA	
SURPRISE[244] Japan	• TCZ 8 mg/kg q4w + MTX • TCZ 8 mg/kg q4w	RCT (Phase 4)	52 weeks, 24 weeks	• ACR20/50/70 • EULAR • DAS-28 Score • HAQ-DI score	Anti TNF-α naïve	• DAS-28 based on the ESR of more than 3.2	[245-247]
TEMPO[248] Europe, Israel, Australia	• ETN 25 mg q2w • ETN 25 mgq2w + MTX • MTX	RCT, DB, PG, (Phase 3)	52 weeks, 24 weeks	• ACR20/50/70 • DAS-28 Score • HAQ-DI score	Anti TNF-α naïve	• Inadequate response to at least DMARD	[249-252]

Study name (Author year) (ref), Country	Treatment name	Study design	Study duration; Primary endpoint	Outcomes reported	Main prior treatment criteria	Inclusion criteria	Secondary Reference
						other than MTX	
TOWARD[253] US/Global	• TCZ 8 mg/kg q4w + csDMARD • PBO + csDMARD	RCT, DB, MC, PC (Phase 3)	24 weeks	• ACR20/50/70 • EULAR • DAS-28 Score • HAQ-DI score	Anti TNF-α naïve	• Age ≥18 years • Moderate-to severe RA • SJC of 6, and TJC of 8 • CRP level 1 mg/dl • ESR 28 mm/h	[254]
VAN DE PUTTE, 2004[1] Europe, Canada, Australia	• ADA 40 mg q2w • PBO	RCT, DB, PC (Phase 3)	26 weeks	• ACR20/50/70 • EULAR • DAS-28 score • HAQ-DI score	Anti TNF-α naive	• Age ≥18 years • >12 TJC,>10	
WEINBLATT, 1999[255] US	• ETN 25 mg q2w + MTX • PBO + MTX	RCT, DB, (Phase 2/3)	24 weeks, 12 weeks	• ACR20/50/70 • HAQ-DI score	Anti TNF-α naïve	• Age ≥18 years • Active RA	

Abbreviations: ABT, abatacept, ACR, American College of Rheumatology; ACR20/50/70, American College of Rheumatology 20%/50%/70% response; ADA, adalimumab, BID, twice daily, BIW, twice weekly, CRP, C-reactive protein; csDMARD, conventional synthetic disease modifying antirheumatic drugs; CTZ, certolizumab pegol, DAS-28, disease activity score 28-joint count; DB, double blind, DMARD, disease-modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; ETN, etanercept, EULAR, European League Against Rheumatism; g, gram, HAQ-DI, health assessment questionnaire disability index; HCQ, hydroxychloroquine, IQR, Interquartile range, IFX, infliximab, ITT, intention to treat, IV, intravenous, Kg, kilogram, M, median; MC, multicentre; mg, milligram, MTX, methotrexate, NMA, network meta-analysis, NR, not reported, OL, open-label, QW, once weekly, PBO, placebo; PC, placebo-controlled; PG, parallel group; qd, once weekly; q2w, every two weeks, q4w, every four weeks, q8w, every 8 weeks; RA, rheumatoid arthritis; RCT, randomised controlled trial, RTX, rituximab, SRL, sarilumab; SB, single blind, SC, subcutaneous, SD, standard deviation, SE, standard error, SJC, swollen joint, SRK, sirukumab, SSZ, sulfasalazine, TJC, tender joint count; TNF, tumour necrosis factor; TCZ, tocilizumab, TFC, tofacitinib

Source: CS Appendix, Table 7, pp. 152-69. References have been checked and updated where necessary.

ERG comment:

The ERG performed a 10% check on the company's data extraction for the csDMARD-experienced population NMA, and the results of this are presented in Section 4.5.2. One trial was conducted in a UK-specific population.[69] The majority of trials were either global or conducted across a wide range of countries. Seven trials were conducted in an exclusively North American population, while 14 trials were conducted exclusively in Asia or the Asia-Pacific region. All included trials were RCTs, although study duration ranged from 12 to 104 weeks. The outcomes considered varied across trials, but there was an outcome – ACR20 response – that was common to all trials in the csDMARD-experienced population NMA.

4.3.4.2 bDMARD-experienced population

The bDMARD-experienced population NMA included 12 unique studies profiled across 68 publications. The included studies are profiled in CS, Appendix D (Table 9, pp.171-4), and provided below in Table 22. The ERG checked the reasons for inclusion or exclusion of the studies identified in TA375 and TA485 with regards to the NMA, to determine whether studies that had not been included in the NMA for this appraisal would have qualified. This was not the case for the biologic experienced population.

Table 22. Study details of all studies included in the NMA (bDMARD-experienced population)

Study name (Author year) (ref)	Treatment name	Study design	Study duration; Primary endpoint	Outcomes reported	Main prior treatment criteria	Inclusion criteria	Secondary reference
ASCERTAIN[256]	• SRL 150 mg q2w • SRL 200 mg q2w • TCZ 4 mg/kg q4w	RCT, DB, DD MC, Phase 3	24 weeks	• ACR20/50/70	bDMARDs	• Age ≥18 years • RA more than 3 months	257
ATTAIN[258] North America and Europe	• ABT 10 mg/kg q4w + DMARDs • PBO + DMARDs	RCT, DB, MC, PC, Phase 3	24 weeks	• ACR 20/50/70 • DAS-28 • HAQ-DI score	3 months of anti-TNF-α therapy either ETN or IFX or both	• Age ≥18 years • At least 10 SJC, an at least 12 TJC	259-262
BREVACTA[112] Global	• TCZ 162 mg + DMARDs • PBO + DMARDs	RCT, DB, MC, PC, Phase 3	24 weeks	• ACR 20/50/70 • DAS-28 • HAQ-DI score	Inadequate response to ≥1 DMARD	• Age ≥18 years • Active RA • SJC ≥6 (66-joint count), TJC ≥8 (68-joint count),	113-115
GO-AFTER[263] Austria, Australia, Canada, Finland, Germany, Netherlands, New Zealand, Spain, UK, and US	• GOL SC 50 mg q4w ± DMARD • PBO	RCT, DB, MC, PC, Phase 3	24 weeks/ 12 weeks	• ACR 20/50/70 • HAQ-DI score	Had been treated with ≥1 dose of a TNF inhibitor	• Age ≥18 years • ≥4 SJC, ≥4 TJC	264-271
MOBILITY[148] Global	• SRL 150 mg q2w + MTX • SRL 200 mg q2w + MTX • PBO + MTX	RCT, DB, PC, MC, International, phase-3	52 weeks/24 weeks	• ACR20/50/70	Patients with prior exposure to tumour necrosis factor-α inhibitor (TNF-I)	• Patients with Moderate-to-Severe Rheumatoid Arthritis and with/without prior biologic use.	149-152
ORAL-STEP[272] North America, Europe, and Latin America	• TFC 5mg bid • PBO	RCT, DB, MC, PC, Phase 3	24 weeks/12 weeks	• ACR 20/50/70 • DAS-28 • HAQ-DI score	Patients had previous inadequate response or intolerance to 1 or more approved TNF inhibitors	• Age ≥18 years • CRP >66·67 nmol/L • Inadequate response to TNFi	273

Study name (Author year) (ref)	Treatment name	Study design	Study duration; Primary endpoint	Outcomes reported	Main prior treatment criteria	Inclusion criteria	Secondary reference
RA- BEACON[274] North America, South America, Europe, Asia and UK	• BAR 2 mg QD • BAR 4mg QD • PBO	CT, DB, MC, PC, Phase 3	12 weeks, 24 weeks	• ACR 20/50/70 • DAS-28	Patients with inadequate response or intolerance to ≥1 TNF inhibitor (TNFi).	• Active RA • TJC & SJC ≥6 • CRP ≥3mg/L	275-279
RADIATE[280] North America and western Europe	• TCZ 4 mg/kg + MTX • TCZ 8 mg/kg + MTX • PBO + MTX	RCT, DB, PC (Phase-3)	24 weeks/12 weeks	• ACR20/50/70 • EULAR • DAS-28 Score • HAQ-DI score	Moderate to severe active RA and failure to respond or intolerance to one or more TNF antagonists	• Age ≥18 years • Moderate to severe active RA • SJC ≥6, TJC ≥8 CRP >1.0 mg/dl • ESR >28 mm/h	281-284
REALISTIC[229] US, Canada, Europe	• CTZ 400-200 mg qw • PBO	RCT, DB, MC, PC, Phase 3b	12 weeks	• ACR 20/50/70 • DAS-28	Patients showed an unsatisfactory response or intolerance to DMARD (MTX, LEF, SSZ, chloroquine or HCQ, AZA, and/or gold)	• Age ≥18 years • RA intolerance to at least one DMARD	230-236
REFLEX[285] US, Europe, Canada, and Israel	• RTX 1,000 mg + MTX • PBO + MTX	RCT, DB, PC, Phase 3	24 weeks/ 12 weeks	• ACR20/50/70 • EULAR • DAS-28 Score • HAQ-DI score	Patients had inadequate response to previous or current treatment with the anti-TNF	• Active RA • ≥8 SJC, ≥8 TJC, • CRP level 1.5 mg/dl • ESR ≥28 mm/h	286,287
SELECT BEYOND[25]	• PBO • UPA 15 mg QD • UPA 30 mg QD	RCT, DB, DD, MC, PC, Phase 3	24 weeks/12 weeks	• ACR 20/50/70 • DAS-28 • HAQ-DI score	3 months of bDMARD treatment	• Age ≥18 years • Active RA • SJC ≥6 (66-joint count), TJC ≥6 (68-joint count),	44,47 45,46,48-50

Study name (Author year) (ref)	Treatment name	Study design	Study duration; Primary endpoint	Outcomes reported	Main prior treatment criteria	Inclusion criteria	Secondary reference
TARGET[288] Global	• SRL 200 mg q2w + csDMARDs • SRL 150 mg q2w + csDMARDs • PBO + csDMARDs	RCT, DB, PC, MC, Phase-3	24 weeks/12 weeks	• ACR20/50/70 • DAS-28 Score • HAQ-DI score	Moderate to-severely active disease; disease duration ≥6 months; inadequate responses or intolerance to ≥1 TNFi	• TNFi intolerant adults • Age ≥18 years • Moderate to severely active RA • SJC ≥6, TJC ≥8, • CRP ≥0.6 mg/dL	289-298

Abbreviations: ABT, abatacept, ACR, American College of Rheumatology; ACR20/50/70, American College of Rheumatology 20%/50%/70% response; ADA, adalimumab, bDMARDs, biologic disease modifying antirheumatic drugs; BID, twice daily, BIW, twice weekly, CRP, C-reactive protein; csDMARD, conventional synthetic disease modifying antirheumatic drugs; CT, controlled trial; CTZ, certolizumab pegol, DAS-28, disease activity score 28-joint count; DB, double blind, DMARD, disease-modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; ETN, etanercept, EULAR, European League Against Rheumatism; g, gram, HAQ-DI, health assessment questionnaire disability index; HCQ, hydroxychloroquine, IQR, Interquartile range, IFX, infliximab, ITT, intention to treat, IV, intravenous, Kg, kilogram, M, median; MC, multicentre; mg, milligram, MTX, methotrexate, NMA, network meta-analysis, NR, not reported, OL, open-label, QW, once weekly, PBO, placebo; PC, placebo-controlled; PG, parallel group; qd, once weekly; q2w, every two weeks, q4w, every four weeks, q8w, every 8 weeks; RA, rheumatoid arthritis; RCT, randomised controlled trial, RTX, rituximab, SRL, sarilumab; SB, single blind, SC, subcutaneous, SD, standard deviation, SE, standard error, SJC, swollen joint, SRK, sirukumab, SSZ, sulfasalazine, TJC, tender joint count; TNF, tumour necrosis factor; TCZ, tocilizumab, TFC, tofacitinib.

Source: CS Appendix, Table 9, pp. 171-4. References have been checked and updated where necessary.

ERG comment:

The ERG performed a check on the company's data extraction for all studies in the bDMARD-experienced population NMA, and the results of this are presented in Section 4.5.2. Included trials covered a wide range of countries and none were restricted to non-European populations. All trials were listed as RCTs, except for RA-BEACON which was listed as a controlled trial (CT). Having checked the primary reference,[274] the ERG noted that this trial is described as randomised. Study duration ranged from 12 to 52 weeks, although all but one study reported results at 24 weeks. Only 12-week data were available for the REALISTIC trial.[229]

4.3.5 Quality assessment of studies included in network meta-analysis

The company appraised the quality of the 61 trials included in the two NMAs (55 that were included in the NMA for the csDMARD-experienced population and 12 that were included in the NMA for the bDMARD-experienced population, noting that six trials were included in both NMAs). The methods used to assess risk of bias for these studies were the same as those used for the four pivotal trials (refer to Sections 4.1.4 and 4.2.3), and the company's QA ratings can be found in Tables 30 and 31, Appendix D.1.17 of the CS.

ERG comment:

In order to provide a general check of accuracy of these 61 QA assessments, the ERG randomly selected seven of these studies (≈10%) with a view to performing a full check of the company's QA for these studies in order to estimate the likelihood of inaccuracies in the QA ratings for the remainder of the studies. One of the studies randomly selected by the ERG was the SELECT-BEYOND study; a critique of the QA for SELECT-BEYOND had already been performed (refer to Section 4.2.3). The remaining six randomly selected studies were assessed by the ERG. Table 23 provides a summary of pertinent comments and disagreements in ratings between the company and ERG.

For five of the six selected studies, the ERG was mostly in agreement with the ratings made by the company, although some additional points and clarifications were noted (refer to Table 23. Critique of the QA for the randomly selected trials). However, for one of these studies,[1] the ERG found errors in the QA that are likely to underestimate the quality of this study. These errors are outlined in Table 23.

Table 23. Critique of the QA for the randomly selected trials

Study	QA Item	Company or ERG	Ratings and comments
ARMADA[103]	Blinding	Company	Yes – Double-blind
		ERG	The ERG agrees that the study was described as double-blind but also notes that (with the exception of patients) it is unclear exactly who was blind (e.g. treating clinicians only, all clinical site personnel, all assessors)
ASCERTAIN[256]	Blinding	Company	Yes – Double-blind
		ERG	The ERG agrees that the study was described as double-blind but also notes that (with the exception of patients) it is unclear exactly who was blind (e.g. treating clinicians only, all clinical site personnel, all assessors)
	Drop-outs	Company	Yes - Higher discontinuation observed in SRL 150 mg q2w group
		ERG	The ERG notes that although higher discontinuation rates were found in the SRL 150 mg q2w group, it was not reported whether this difference was statistically significant
	ITT analyses	Company	Yes, ITT; Unclear[a]
		ERG	The ERG disagrees that ITT analyses were reported - only safety analyses are reported and these were based on all randomised participants according to actual treatment received. Efficacy analyses were not available for the final sample and it remains unclear whether ITT data will be provided
CERTAIN[116]	Blinding	Company	Yes – Double-blind
		ERG	The ERG noted that although the study was described as double-blind, the clinicians administering treatments were not blind
	ITT analyses	Company	Yes ITT: Yes ITT; LOCF
		ERG	Yes ITT: Yes ITT; NRI/LOCF
J-RAPID[138]	Blinding	Company	Yes – Double-blind
		ERG	The ERG notes that patients and assessors were blind but clinicians administering treatments were not blind
	Drop-outs	Company	No
		ERG	The ERG agrees that there were no unexpected differences between groups in drop-outs, but noted an expected difference (more withdrawals and fewer completions in the PBO+MTX group than the CTZ + MTX group)
LI[142]	Blinding	Company	Yes – Double-blind
		ERG	The ERG agrees that the study was described as double-blind but also notes that (with the exception of patients) it is unclear exactly who was blind (e.g. treating clinicians only, all clinical site personnel, all assessors)
VAN DE PUTTE [1]	Blinding	Company	Yes – Double-blind
		ERG	The ERG agrees that the study was described as double-blind but also notes that (with the exception of patients) it is unclear exactly who was blind (e.g. treating clinicians only, all clinical site personnel, all assessors)
		Company	Yes[b]

Study	QA Item	Company or ERG	Ratings and comments
	Prognostic indicators	ERG	The ERG disagrees with the company's rating that the groups were not similar at baseline: the main publication for the study explicitly states that they were similar and the ERG did not detect any evidence to the contrary
	Drop-outs	Company	Yes - Higher withdrawals observed in ADA group
		ERG	The ERG disagrees with the company that there were higher withdrawals with ADA; in fact the publication states that "Withdrawals occurred in 118/434 (27.2%) ADA treated patients and 62/110 (56.4%) PBO treated patients"[1]
	ITT analyses	Company	Yes ITT: Yes ITT; study did not use imputation
		ERG	The ERG disagrees that the study did not use imputation and instead felt that the handling of missing data were not clearly reported; the publication mentioned that non-completers were assumed to be non-responders, but the handling of other missing data was not reported

Abbreviations: ADA, adalimumab; CTZ, certolizumab pegol; ITT, intention-to-treat; LOCF, last observation carried forward; MTX, methotrexate; NRI, non-responder imputation; PBO, placebo; q2w, every two weeks; QA, quality appraisal; SRL, sarilumab

Notes: a Refers to methods used to account for missing data; b Refers to an imbalance between groups at baseline on prognostic indicators

Due to the errors found, the ERG noted the possibility of further errors in the company's QA of the remaining 51 studies across the two NMAs. However, the ERG also noted that the QA was not used to select or weight studies in the NMA, or in the economic modelling. The ERG considered, therefore, that any errors or potential errors in the QA of the remaining studies could affect transitivity of networks in NMA, but would not necessarily impact choice of studies for NMA or economic modelling.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

4.4.1 Summary of analyses undertaken

The CS presented NMAs for ACR outcomes, integrating findings from studies reporting one or more of ACR20, ACR50 or ACR70, for each of csDMARD-experienced and bDMARD-experienced populations (see CS B.2.9.7). Meta-analyses for additional outcomes were not undertaken (see clarification response A19). To integrate findings from each of these response thresholds, especially when studies reported more than one of them, response was modelled as a latent probit-distributed variable with fixed effects for threshold. Put otherwise, the underlying difference in response between each pair of treatments was modelled as a continuous variable, with empirically derived thresholds used to convert this continuous variable into odds ratios for each pair of treatments comparing the probability of achieving each of ACR20, ACR50 and ACR70. This is

broadly the analysis approach recommended in NICE Technical Support Document 2.[18] Networks integrated evidence for response at three months with evidence for response at six months using a meta-regression based method, with a random effect at the trial level to capture the dependence of measures. This was done to compare findings from the pivotal SELECT trials, which primarily captured data at three months instead of six months, to the broader network of evidence. Put otherwise, findings at six months for UPA in the NMA are based on meta-regression estimates 'projecting' the three-month data forward using a common effect for the difference in effectiveness between three and six months.

Results were presented as probabilities of response for each threshold for each treatment. To estimate these probabilities, the probability of non-response in a reference treatment was calculated, and the odds ratios generated from the NMA estimated. The ERG queried this at clarification and in response to question A23, the company noted that: "non-response for the csDMARD arm was estimated using the maximum likelihood estimator based on the observed ACR20 non-response data from observed data of all csDMARD arms". While this is at face a reasonable approach, no further details were presented to determine what was meant by "maximum likelihood estimation" and whether this was undertaken in a separate analysis. ACR outcomes were then mapped onto EULAR response using a probabilistic algorithm.

Analyses were undertaken in a Bayesian framework using JAGS (see clarification response A18), with convergence assessed using the Gelman-Rubin diagnostic (see clarification response A20). Several alternative models were considered, including random and fixed effects for the distribution of treatment effects, and sensitivity analyses testing imputation strategies to extrapolate data from the SELECT trials to six months. Models were compared using the deviance information criterion (DIC), as well as the between study variance parameter tau and the residual deviance. Inconsistency was tested for each network by comparing an inconsistency model against a consistency model in terms of model fit and parameter estimates.

ERG comment:

Methods used to undertake the NMAs were broadly appropriate and in line with NICE Technical Support Document recommendations. However, the DIC is a suboptimal index to compare model fit when models are sparse, as was especially the case in the bDMARD-experienced population NMA. Model choice should be driven by substantive considerations.

The ERG noted the remaining ambiguity in how non-response probabilities in reference arms were estimated. It was unclear from the clarification response and from the code presented whether the pooling of non-response probabilities in the reference arm was undertaken separately. While it appears that the analysis was not undertaken as a 'simultaneous model', which would have the inappropriate impact of analysis of reference arm non-response influencing analysis of relative treatment effects, the assumptions used to estimate the pooled probability of non-response remained vague. In addition, mapping of treatment effects to EULAR response required additional clarification to understand how this was undertaken probabilistically. Because of this, results from the NMA should be interpreted with caution. In addition, ambiguities in the exact time period considered for inclusion at three-month and six-month follow-up preclude clear interpretation of findings.

Finally, the company made several references to ranking of treatments in presentation of results. It appeard that this was undertaken 'numerically', that is by ranking parameter estimates. The ERG regarded that use of a ranking measure that incorporated uncertainty in estimation was more suitable and requested surface under the cumulative ranking curve (SUCRA) estimates in clarification, which were provided. The ERG uses these to consider treatment ranking throughout the results presented here.

4.4.2 Critique of network meta-analysis assumptions

NMAs presented required several statistical assumptions. Vague prior distributions were assumed for all model parameters with the exception of the between-study standard deviation in the bDMARD-experienced population analysis (see CS p 90). This relied on a standard informative prior distribution of log normal form with mean -2.56 and standard deviation 1.74. The use of an informative prior can be useful to stabilise estimation when information is sparse, as would be expected for between-study standard deviation, estimation of which is frequently underpowered in NMAs. In addition, treatment effects were assumed exchangeable, consistency was assumed, and thresholds used to convert the latent probit response variable to probabilities of response were assumed to be fixed. Clarification elicited several additional assumptions used to estimate NMA models (see clarification response A22): between-study variance was assumed equal across all relative treatment effects, the meta-regression coefficient used to compare three-month and six-month results was assumed equal across all relative treatment effects, and trial-specific baselines were treated as nuisance parameters.

4.4.3 Correspondence to NICE scope population

The analysis as undertaken considered two populations: csDMARD-experienced people with inadequate response, and bDMARD-experienced people with inadequate response. A similar approach has been undertaken in the last three key STAs to assess new treatments for rheumatoid arthritis.[32,51,52] Focusing on csDMARD-experienced and bDMARD-experienced populations as major groupings for NMA has several benefits. These include relative tractability in terms of data extraction from included trials and mapping against a key decision points in existing treatment pathways (i.e. the transition from csDMARD-only strategies to bDMARD-included strategies after two or more csDMARDs have not induced an adequate response). To the extent that all relevant comparators were included in the search for trials and inclusion and exclusion criteria generally matched the NICE final scope (see 4.3.4), the NMAs as presented met the NICE final scope.

However, this approach also requires several conceptual assumptions. These include the similarity of treatment effects between moderate and severe RA populations, which may not be reasonable; and exchangeability of treatment effects at different points in the treatment pathway, which may not be appropriate, given that clinical advice provided to the ERG is that the 'prognosis' of drugs' effectiveness decreases with each successive line of treatment attempted. Related to this assumption is the concern that populations from each trial will include people who are not strictly 'at risk' for receiving every other comparator in the network, either due to prior exposure to other comparators or contraindications. As a hypothetical example, included trials elsewhere in the bDMARD-experienced network will likely include at least some patients who are not eligibile for RTX; but data from these patients are used to estimate the comparative efficacy of RTX against other therapies. The approach used also requires locating subgroup data from trials that "blend" csDMARD-experienced and bDMARD-experienced populations, data which it may not always be possible to obtain. In fact, this stipulation led to the exclusion of at least eight trials that did not report findings for csDMARD-experienced subgroups (clarification response A16). It also requires subsuming subgroups defined by the NICE treatment pathway (e.g. patients with severe RA who are intolerant of or who have had an inadequate response to RTX) into a group with all those trialling a second bDMARD.

The ERG acknowledges that the "optimal" approach, which would include stratifying NMAs by line of treatment (e.g. inadequate response to one csDMARD; inadequate response to two or more csDMARDs; inadequate response to two or more csDMARDs and one bDMARD), would not be feasible given the limitations of available data.

Regardless, the strong assumptions relating to similarity of effect and exchangeability between different points in the pathway, and the 'collapsing' of different groups in the NICE scope into one NMA, suggest that the results of the NMA should be used with caution.

It is also of note that only upadactinib in its 15 mg dose, with or without csDMARD, that is considered in the NMAs. As noted above in Section 3.2, this is consistent with the company's general approach to the different dosages tested.

Only ACR response was considered as an outcome in NMAs, at variance with prior TAs that have considered a wider range of outcomes relevant to RA. The company chose to map ACR response onto EULAR response to inform the economic model. Previous TAs have used EULAR outcomes directly,[32,51,52] though in some cases with pre-processing of study-level data via probabilistic mapping of ACR to EULAR. Given the importance of EULAR in the economic model against the high levels of missing data for EULAR response, the ERG regards that the methodological strategy undertaken was not unreasonable, though it does add uncertainty.

A final point relates to the treatment of csDMARD dose escalation, which is noted as a comparator for those with moderate RA that has not responded adequately to therapy with csDMARDs. This is never explicitly defined as a treatment strategy, and it remains unclear how this is operationalised in the included NMAs. One trial (APPEAL[102]) is noted in the CS (Section D.1.12), as including intensive csDMARDs, but it is unclear how this relates to the scoped comparator of csDMARD dose escalation. This is important as treatment effects relating to intensive csDMARDs are included in treatment sequencing as part of the economic model (Section 5.2.4).

4.4.4 Results of network meta-analysis

Results for the NMA undertaken on csDMARD-experienced populations are provided in Table 23 of the CS, with mapping onto EULAR response categories in the CS Table 25. Similarly, results for the NMA undertaken on bDMARD-experienced populations are provided in the CS Tables 26 and 27. On clarification, the company provided probabilities of superiority of each treatment compared to PBO, csDMARDs generally, UPA and UPA in combination with csDMARDs. The company also provided updated results for the bDMARD-experienced population as inaccurate results were presented in the CS.

4.4.4.1 NMA findings for the csDMARD-experienced population

Findings for the csDMARD-experienced population at six months are reproduced in Table 24 below. UPA 15 mg yielded a probability of ACR20 of [redacted] and of ACR70 of [redacted] UPA 15 mg in combination with csDMARDs yielded a probability of [redacted]) and of ACR70 of [redacted] For both regimens, the probability of inferiority as compared to PBO was <0.001, and as compared to csDMARDs alone was <0.001 as well. It is of note that these data are 'extrapolated' in that no six-month data from the SELECT trials were included in the NMA. Findings from the mapped analysis for EULAR can be found in Table 25. [redacted]

Convergence of this model was evidenced via a Gelman-Rubin diagnostic with a value very close to 1 (1.000415; see clarification response A20). The company justifies use of a random effects model by noting that a random effects model had lower total residual deviance and lower deviance information criterion as compared to a fixed effects model (CS p 97). The ERG acknowledged that these summary indices are useful for interpretation, but submits that a random effects model would have been appropriate regardless as this choice should have been driven by substantive considerations. In addition, the company notes that an inconsistency model did not generate meaningful improvements in fit over a consistency model and did not generate meaningfully or systematically different pairwise estimates. It appeared that the company undertook this examination separately for three-month and six-month results, given inconsistencies between CS p 94 and CS appendix D.1.14. However, the ERG accepted the company's conclusion that the NMAs were not notably inconsistent.

Table 24. Estimates of ACR treatment effect in csDMARD-experienced population at six months

Treatment	SUCRA	ACR 20		ACR 50		ACR 70		Posterior probability of treatment effect difference			
		Posterior Median	(95% CrI)	Posterior Median	(95% CrI)	Posterior Median	(95% CrI)	Pr (Trt < PBO)	Pr (Trt < csDMARD)	Pr (Trt < UPA 15 mg)	Pr (Trt < UPA 15 mg + csDMARDs)
csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ABT 10 mg/kg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ABT 125 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 40 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 40 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BRC 2 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BRC 4 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CTZ 200 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ETN 50 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ETN 50 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GOL 50 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFX 3 mg/kg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Intensive csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RTX 2,000 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SRL 150 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Treatment	SUCRA	ACR 20		ACR 50		ACR 70		Posterior probability of treatment effect difference			
		Posterior Median	(95% CrI)	Posterior Median	(95% CrI)	Posterior Median	(95% CrI)	Pr (Trt < PBO)	Pr (Trt < csDMARD)	Pr (Trt < UPA 15 mg)	Pr (Trt < UPA 15 mg + csDMARDs)
SRL 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SRL 200 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TCZ 8 mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TCZ 8 mg/kg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TCZ 162 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TFC 10 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TFC 5 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TFC 5 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UPA 15 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABT, abatacept; ACR, American College of Rheumatology; ADA, adalimumab; BRC, baricitinib; csDMARD, conventional synthetic disease modifying antirheumatic drug; CrI, credible interval; CTZ, certolizumab pegol; ETN, etanercept; GOL, golimumab; IFX, infliximab; PBO: placebo; RA, rheumatoid arthritis; SRL, sarilumab; TCZ, tocilizumab; TFC, tofacitinib; Trt: treatment; UPA, upadacitinib

Notes: a Posterior probability of treatment effect difference is presented in this table. For example, Pr (Trt < PBO) is the posterior probability that treatment effect difference between active treatment and PBO is less than 0; b The posterior probability of treatment effect difference is the same for ACR 20, ACR 50 and ACR 70.

Source: Clarification response A21, A29

Table 25. Estimates of EULAR treatment effect in csDMARD-experienced population at six months

Treatment	Response						Posterior probability of treatment effect difference			
	No Response (95% CrI)		Moderate Response (95% CrI)		Good Response (95% CrI)		Pr (Trt < PBO)	Pr (Trt < csDMARD)	Pr (Trt < UPA 15 mg)	Pr (Trt < UPA 15 mg + csDMARDs)
csDMARD	[redacted]									
ABT 10 mg/kg + csDMARD	[redacted]									
ABT 125 mg + csDMARD	[redacted]									
ADA 40 mg	[redacted]									
ADA 40 mg + csDMARD	[redacted]									
BRC 2 mg + csDMARD	[redacted]									
BRC 4 mg + csDMARD	[redacted]									
CTZ 200 mg + csDMARD	[redacted]									
ETN 50 mg	[redacted]									
ETN 50 mg + csDMARD	[redacted]									
GOL 50 mg + csDMARD	[redacted]									
IFX 3 mg/kg + csDMARD	[redacted]									
Intensive csDMARD	[redacted]									
PBO	[redacted]									

Treatment	Response						Posterior probability of treatment effect difference			
	No Response (95% CrI)		Moderate Response (95% CrI)		Good Response (95% CrI)		Pr (Trt < PBO)	Pr (Trt < csDMARD)	Pr (Trt < UPA 15 mg)	Pr (Trt < UPA 15 mg + csDMARDs)
RTX 2,000 mg + csDMARD	[redacted]		[redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
SRL 150 mg + csDMARD	[redacted]		[redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
SRL 200 mg	[redacted]		[redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
SRL 200 mg + csDMARD	[redacted]		[redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
TCZ 8 mg/kg	[redacted]		[redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
TCZ 8 mg/kg + csDMARD	[redacted]		[redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
TCZ 162 mg + csDMARD	[redacted]		[redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
TFC 10 mg + csDMARD	[redacted]		[redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
TFC 5 mg	[redacted]		[redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
TFC 5 mg + csDMARD	[redacted]		[redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
UPA 15 mg	[redacted]		[redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
UPA 15 mg + csDMARD	[redacted]		[redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABT, abatacept; ADA, adalimumab; BRC, baricitinib; csDMARD, conventional synthetic disease modifying antirheumatic drug; CrI, credible interval; CTZ, certolizumab pegol; ETN, etanercept; EULAR, European League Against Rheumatism; GOL, golimumab; IFX, infliximab; PBO: placebo; RA, rheumatoid arthritis; SRL, sarilumab; TCZ, tocilizumab; TFC, tofacitinib; Trt: treatment; UPA, upadacitinib

Notes: a Posterior probability of treatment effect difference is presented in this table. For example, Pr (Trt < PBO) is the posterior probability that treatment effect difference between active treatment and PBO is less than 0; b The posterior probability of treatment effect difference is the same for EULAR response categories

Source: clarification response A29

4.4.4.2 NMA findings for the bDMARD-experienced population

Findings for the bDMARD-experienced population at six months are reproduced in Table 26 below. UPA 15 mg in combination with csDMARDs yielded a probability of ACR20 of [redacted] and of ACR70 of [redacted] The probability of inferiority as compared to csDMARDs alone was 0.003. As above, these data are "extrapolated" in that no six-month data from the SELECT trials were included in the NMA. Findings from the mapped analysis for EULAR can be found in Table 27. [redacted]

Convergence of this model was evidenced via a Gelman-Rubin diagnostic with a value very close to 1 (1.000943; see clarification response A20). As above, the company justified the use of a random effects model based on similarity of total residual deviance and lower DIC as compared to a fixed effects model (CS, p 98). Again, the ERG considered that a random effects model would have been appropriate regardless as this choice should have been driven by substantive considerations. In this case, estimation of a random effects model was facilitated by use of an informative prior for the between-study variance. In addition, the company noted that consideration of inconsistency was not relevant to this network given the absence of head-to-head evidence. The ERG noted that this assertion was not strictly accurate, given the inclusion of trials testing non-csDMARD treatments against each other, but accepted that a test of inconsistency would not be meaningful for this analysis.

4.4.4.3 Additional sensitivity analyses undertaken by the company

A number of sensitivity analyses were undertaken to impute six-month data for the relevant UPA trials using an 'optimistic' approach, with six-month data for patients on UPA and three-month data from the csDMARD arms carried forward, and a 'conservative' approach, with three-month data used for six-month data. Results are presented in CS Appendix D.1.15 and are substantially similar to those from the main analyses; however, 'conservative' imputation yielded different results for ACR response for patients with upadactinib 15 mg with csDMARD in the csDMARD-experienced population ([redacted]).

Table 26. Estimates of ACR treatment effect in bDMARD-experienced population at six months

Treatment	SUCRA	ACR 20		ACR 50		ACR 70		Posterior probability of treatment effect difference	
		Posterior Median	(95% CrI)	Posterior Median	(95% CrI)	Posterior Median	(95% CrI)	Pr (Trt < csDMARD)	Pr (Trt < UPA 15 mg + csDMARDs)
csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ABT 10 mg/kg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BRC 2 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BRC 4 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CTZ 200 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GOL 50 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RTX 2,000 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SRL 150 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SRL 200 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TCZ 8 mg/kg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TCZ 162 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TFC 10 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TFC 5 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UPA 15 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABT, abatacept; ACR, American College of Rheumatology; ADA, adalimumab; BRC, baricitinib; csDMARD, conventional synthetic disease modifying antirheumatic drug; CrI, credible interval; CTZ, certolizumab pegol; ETN, etanercept; GOL, golimumab; IFX, infliximab; PBO, placebo; RA, rheumatoid arthritis; SRL, sarilumab; TCZ, tocilizumab; TFC, tofacitinib; Trt, treatment; UPA, upadacitinib

Notes: a Posterior probability of treatment effect difference is presented in this table. For example, Pr (Trt < csDMARD) is the posterior probability that treatment effect difference between active treatment and csDMARD is less than 0; b. The posterior probability of treatment effect difference is the same for ACR 20, ACR 50 and ACR 70

Source: Clarification response A21, A29

Table 27. Estimates of EULAR treatment effect in bDMARD-experienced population at six months

Treatment	Response						Posterior probability of treatment effect difference	
	No Response (95% CrI)		Moderate Response (95% CrI)		Good Response (95% CrI)		Pb (Trt < csDMARD)	Pr (Trt < UPA 15 mg + csDMARDs)
csDMARD	[redacted]							
ABA10 mg/kg + csDMARD	[redacted]							
BRC 2 mg + csDMARD	[redacted]							
BRC 4 mg + csDMARD	[redacted]							
CTZ 200 mg + csDMARD	[redacted]							
GOL 50 mg + csDMARD	[redacted]							
RTX 2,000 mg + csDMARD	[redacted]							
SRL 150 mg + csDMARD	[redacted]							
SRL 200 mg + csDMARD	[redacted]							
TCZ 8 mg/kg + csDMARD	[redacted]							
TCZ 162 mg + csDMARD	[redacted]							
TFC 10 mg + csDMARD	[redacted]							
TFC 5 mg + csDMARD	[redacted]							
UPA 15 mg + csDMARD	[redacted]							

Abbreviations: ABT, abatacept; ADA, adalimumab; BRC, baricitinib; csDMARD, conventional synthetic disease modifying antirheumatic drug; CrI, credible interval; CTZ, certolizumab pegol; ETN, etanercept; EULAR, European League Against Rheumatism; GOL, golimumab; IFX, infliximab; PBO: placebo; RA, rheumatoid arthritis; SRL, sarilumab; TCZ, tocilizumab; TFC, tofacitinib; Trt: treatment; UPA, upadacitinib

Notes:a Posterior probability of treatment effect difference is presented in this table. For example, Pr (Trt < PBO) is the posterior probability that treatment effect difference between active treatment and PBO is less than 0; b The posterior probability of treatment effect difference is the same for EULAR response categories

Source: clarification response A29

In addition, the ERG requested at clarification a set of NMA analyses excluding data from SELECT-SUNRISE, given the dissimilarity in population between SELECT-SUNRISE and the trials used for regulatory approval. Findings from this NMA, which relate to the csDMARD-experienced population, are presented below in Table 28 and Table 29. On the whole, the impact of excluding SELECT-SUNRISE on results and their interpretation was minimal.

4.4.5 Overall comment on network meta-analysis

While the company's approach to the NMAs followed precedent in terms of using csDMARD-experienced and bDMARD-experienced groupings and used appropriate statistical techniques, the ERG raised a number of concerns that suggest caution is required when interpreting the results of the NMAs. For example, the ERG noticed some inconsistencies between studies included in this appraisal and included in prior appraisals; inconsistencies in the presentation of results; a number of ambiguities relating to the inclusion and exclusion of trials and the formation of nodes (e.g. for intensive csDMARDs as a treatment strategy). From a statistical perspective, the ERG noted a persisting lack of clarity on how trial arms from reference groups were pooled to generate probabilities across all treatments. The ERG also noted strong assumptions required for the interpretation and application of findings across different points in the treatment pathways, eligibility of populations in networks for all relevant treatments, severities of disease and treatment sequencing, and exclusion of data from potentially informative trials that did not include subgroups.

4.5 Additional work on clinical effectiveness undertaken by the ERG

4.5.1 Additional searches undertaken by the ERG

The ERG conducted a search on Ovid MEDLINE (search completed 6 August 2019) with additional free-text terms for biosimilars and brand names, and using the validated RCT filter (sensitivity and precision maximising version) developed by Cochrane.[13] We used Boolean NOT to identify unique records not retrieved by the company's original search (as reported in Appendix D of the CS). The search retrieved 882 records, and these were single-screened by the ERG. The ERG's full search strategy is available in Appendix 1. The modified search did not identify additional relevant randomized controlled trials for UPA or comparators (from database inception to April 2019, the date of the company's updated review searches).

Table 28. Estimates of ACR treatment effect in csDMARD-experienced population at six months, excluding SELECT-SUNRISE

	ACR 20		ACR 50		ACR 70	
Treatment	**Posterior Median**	**(95% CrI)**	**Posterior Median**	**(95% CrI)**	**Posterior Median**	**(95% CrI)**
csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ABT 10 mg/kg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ABT 125 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 40 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 40 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BRC 2 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BRC 4 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CTZ 200 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ETN 50 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ETN 50 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GOL 50 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFX 3 mg/kg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Intensive csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RTX 2,000 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SRL 150 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SRL 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SRL 200 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TCZ 8 mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TCZ 8 mg/kg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TCZ 162 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TFC 10 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TFC 5 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TFC 5 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UPA 15 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABT, abatacept; ACR, American College of Rheumatology; ADA, adalimumab; BRC, baricitinib; csDMARD, conventional synthetic disease modifying antirheumatic drug; CrI, credible interval; CTZ, certolizumab pegol; ETN, etanercept; GOL, golimumab; IFX, infliximab; PBO: placebo; SRL, sarilumab; TCZ, tocilizumab; TFC, tofacitinib; UPA, upadacitinib; Source: Clarification response A25

Table 29. Estimates of EULAR treatment effect in csDMARD-experienced population at six months, excluding SELECT-SUNRISE

	No response		Moderate Response		Good Response	
Treatment	**Posterior Median**	**(95% CrI)**	**Posterior Median**	**(95% CrI)**	**Posterior Median**	**(95% CrI)**
csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ABT 10 mg/kg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ABT 125 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 40 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 40 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BRC 2 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BRC 4 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CTZ 200 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ETN 50 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ETN 50 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GOL 50 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFX 3 mg/kg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Intensive csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RTX 2000 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SRL 150 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SRL 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SRL 200 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TCZ 8 mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TCZ 8 mg/kg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TCZ 162 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TFC 10 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TFC 5 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TFC 5 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UPA 15 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABT, abatacept; ACR, American College of Rheumatology; ADA, adalimumab; BRC, baricitinib; csDMARD, conventional synthetic disease modifying antirheumatic drug; CrI, credible interval; CTZ, certolizumab pegol; ETN, etanercept; EULAR, European League Against Rheumatism; GOL, golimumab; IFX, infliximab; PBO: placebo; RA, rheumatoid arthritis; SRL, sarilumab; TCZ, tocilizumab; TFC, tofacitinib; UPA, upadacitinib

Source: Clarification response A25

4.5.2 Additional work on network meta-analysis undertaken by the ERG

The ERG checked the patient demographics, baseline characteristics, ACR response rates and the inclusion and exclusion criteria for all of the studies included in the NMA for the bDMARD experienced population and for 10% of the studies included in the NMA for the csDMARD experienced population (as referred to in Section 4.3). For the 10% of studies checked for the csDMARD experienced population, the values matched those reported in Appendix D of the company's submission. There were discrepancies in the baseline characteristics reported in Appendix D for the biologic experienced population in studies for which DAS28 had been assessed using both CRP and ESR, mostly likely due to a pasting error. The patient demographics, baseline characteristics and ACR response rates for patients allocated TFC 10 mg BID + csDMARD in the ORAL-STEP trial were missing from Tables 11 and 16 in Appendix D of the company's submission, and a few minor errors for other studies (for example, the reported follow-up for the GO-AFTER trial) were identified in Table 16 and Table 17 in Appendix D of the company's submission. Corrected versions of these tables (Table 30, Table 31, and Table 32).

Where the values reported in Appendix D of the company's submission could not be checked using the sources referenced, alternative sources were identified for this purpose and have been referenced in the tables. The ERG has checked the data extraction file used in the NMA and these errors were not present. However, there were significant differences between the ACR response rates at week 24 for the bDMARD experienced population in the REFLEX trial in the data extraction R file and the values reported by Cohen et al. 2006, which those reported in Table 17 in Appendix D. This reinforces the need for caution in interpreting the company's NMA results.

The NMA was implemented using a nonstandard package for R that was not available on the Comprehensive R Archive Network (CRAN). The ERG checked the R code provided by the company in their clarification response but, despite extensive efforts to 'debug' the code, the ERG was unable to reproduce the NMA results provided in section B.2.9.8 of Appendix D, due to the code structure rather than an error to the probability distributions parameterised. Within the timeline of this STA, the ERG was unable to reconstruct the company's NMA in alternative software to confirm results presented.

Table 30. Corrected patient demographics and baseline characteristics of studies included in the NMA (bDMARD-experienced population)

Study name (Author year) (ref)	Treatment name	ITT N	Age mean (SD)	Female (%)	Mean (SD) DAS28 [CRP/ESR]	Rheumatoid factor (% positive)	Mean no. of previous DMARDs (SD)	Mean disease duration in years (SD)	Mean swollen joint count (SD)
ATTAIN Genovese, 2005[258]	ABT 10 mg/kg q4w + DMARDs	258	53.4 (12.4)	77.1	CRP: 6.5 (0.9)	189 (73.3)	NR	12.2 (8.5)	22.3 (10.2)
	PBO + DMARDs	133	52.7 (11.3)	79.7	CRP: 6.5 (0.8)	97 (72.9)	NR	11.4 (8.9)	22.0 (10.0)
ASCERTAIN Emery, 2019[256]	SRL 150 mg q2w	49	54.8 (12.1)	83.7	CRP: 5.85 (0.92)	39 (83.0)	NR	13.6 (8.2)	16.0 (8.9)
	SRL 200 mg q2w	51	51.7 (13.1)	76.5	CRP: 5.88 (0.97)	29 (58.0)	NR	10.5 (7.6)	16.0 (8.1)
	TCZ 4 mg/kg q4w	102	50.4 (13.0)	80.4	CRP: 5.91 (1.01)	79 (78.2)	NR	10.8 (8.9)	15.2 (7.6)
BREVACTA Kivitz, 2014[112]	TCZ 162 mg + DMARDs	432	52.1 (11.4) ††	85.8††	6.70 (0.9) ††	349 (80.8) ††	1.3 (0.7) ††	11.1 (8.2) ††	17.5 (10.3) ††
	PBO + DMARDs	218	52.0 (11.7) ††	82.6††	6.60 (0.9) ††	178 (81.7) ††	1.4 (0.8) ††	11.1 (8.4) ††	17.6 (9.9) ††
GO-AFTER Smolen, 2009[263]	GOL 50 mg q4w SC ± DMARD	153	55.0 (46.0-63.0) †	74	6.3 (5.6-7.2)	108 (72)	NR	9.6 (5.6-17.2) †	14.0 (9.0-25.0) †
	PBO	155	54.0 (46.0-64.0)†	85	6.3 (5.5-7.1)	110 (73)	NR	9.8 (4.9-17.6) †	14.0 (9.0-23.0) †
ORAL-STEP Burmester, 2013[272]	TFC 5 mg bid + MTX	132	55.4 (11.5)	85	CRP: 5.4 (1.0) ESR: 6.5 (1.1)	80 (60.6)	NR	13.0 (1.2-55.0)§	16.2 (10.1)
	TFC 10 mg bid + MTX	133	55.1 (11.3)	86.6	CRP: 5.3 (0.9) ESR: 6.4 (0.9)	83 (61.9)		12.6 (0.7 – 42.0)	16.6 (9.9)
	PBO	131	54.4 (11.3)	80.3	CRP: 5.4 (1.0) ESR: 6.4 (1.1)	86 (65.6)	NR	11.3 (0.4-47.0)§	17.2 (10.7)
MOBILITY Genovese, 2015[148]	SRL 150 mg q2w + MTX	400	50.1 (11.9)	79.8	CRP: 6.0 (0.9)	(87.1)	NR	9.5 (8.5)	16.6 (9.0)
	SRL 200 mg q2w + MTX	399	50.8 (11.8)	84.5	CRP: 6.0 (0.9)	(82.6)	NR	8.6 (7.0)	16.8 (9.7)

Study name (Author year) (ref)	Treatment name	ITT N	Age mean (SD)	Female (%)	Mean (SD) DAS28 [CRP/ESR]	Rheumatoid factor (% positive)	Mean no. of previous DMARDs (SD)	Mean disease duration in years (SD)	Mean swollen joint count (SD)
	PBO + MTX	398	50.9 (11.2)	80.7	CRP: 5.9 (0.9)	(84.4)	NR	9.1 (8.1)	16.7 (9.3)
RADIATE Emery, 2008[280]	TCZ 4mg/kg + MTX	161	50.9 (12.5)	81	Unclear: 6.78 (1.0)	(73)	2.0 (1.6)	11.0 (8.5)	19.5 (10.4)
	TCZ 8mg/kg + MTX	170	53.9 (12.7)	84	Unclear: 6.8 (0.9)	(79)	1.9 (1.7)	12.6 (9.3)	18.9 (10.9)
	PBO + MTX	160	53.4 (13.3)	79	Unclear: 6.8 (1.1)	(75)	2.1 (1.6)	11.4 (9.2)	18.9 (11.1)
RA- BEACON Genovese, 2015[274]	BRC 2 mg OD	174	55.1 (11.1)	78.7	CRP: 6.03 (0.9) ESR: 6.7 (1.0)	128 (74)	NR	14 (8)	19 (12)
	BRC 4 mg OD	177	55.9 (11.3)	84.2	CRP: 5.87 (1.0) ESR: 6.6 (1.06)	128 (72)	NR	14 (9)	16 (9)
	PBO	176	56 (10.7)	82.4	CRP: 5.89 (0.94) ESR: 6.6 (0.9)	130 (74)	NR	14 (10)	17 (11)
REALISTIC Weinblatt, 2012[229]	CTZ 400-200 mg OD	851	55.4 (12.4) ††	77.6††	CRP: 5.7 (0.9) †† ESR: 6.4 (0.9) ††	555 (73.9)	NR	8.6 (8.8) ††	11.8 (5.6) ††
	PBO	212	53.9 (12.7) ††	79.7††	CRP: 5.7 (0.9) †† ESR: 6.4 (0.9) ††	137 (76.5)	NR	8.9 (9.1) ††	11.1 (5.2) ††
REFLEX Cohen, 2006[285]	RTX 1,000 mg + MTX	308	52.2 (12.2)	81	Unclear: 6.9 (1.0)	242 (79)	2.6 (1.8)	12.1 (8.3)	23.4 (11.8)
	PBO + MTX	209	52.8 (12.6)	81	Unclear: 6.8 (1.0)	165 (79)	2.4 (1.8)	11.7 (7.7)	22.9 (12.7)
SELECT BEYOND Genovese, 2018[25]	PBO	169	57.6 (11.4)	85	CRP: 5.8 (1.0)	113 (67)	NR	13.2 (9.5)	16.3 (9.6)
	UPA 15 mg QD	164	56.3 (11.3)	84	CRP: 5.9 (1.0)	119 (73)	NR		17.0 (10.8)
	UPA 30 mg QD	165	57.3 (11.6)	84	CRP: 5.8 (0.9)	113 (68)	NR		17.2 (11.4)
TARGET Fleischmann, 2017[288]	SRL 200 mg q2w + csDMARDs	184	52.9 (12.9)	82.1	CRP: 6.3 (1.0)	132 (72.9)	NR	12.7 (9.6)	20.0 (11.9)
	SRL 150 mg q2w + csDMARDs	181	54.0 (11.7)	78.5	CRP: 6.1 (0.9)	135 (74.6)	NR	11.6 (8.6)	19.6 (11.2)

Study name (Author year) (ref)	Treatment name	ITT N	Age mean (SD)	Female (%)	Mean (SD) DAS28 [CRP/ESR]	Rheumatoid factor (% positive)	Mean no. of previous DMARDs (SD)	Mean disease duration in years (SD)	Mean swollen joint count (SD)
	PBO + csDMARDs	181	51.9 (12.4)	85.1	CRP: 6.2 (0.9)	142 (78.9)	NR	12.0 (10.0)	20.2 (11.3)

Abbreviations: ABT, Abatacept; ADA, adalimumab; bid, twice a day; CTZ, certolizumab pegol ; ETN, Etanercept; HCQ, hydroxychloroquine; g, gram; IQR, Interquartile range; IFX, infliximab; ITT, intention to treat; IV, intravenous; Kg, kilogram; mg, milligram; M: Median; MTX, methotrexate; NMA, network meta-analysis; NR, not reported; PBO, placebo; PsA, psoriatic arthritis; OD, once weekly; q2w, every 2 weeks; q4w, every 4 weeks; q8w, every 8 weeks; RTX, rituximab; SRL, sarilumab; SC, subcutaneous; SD, standard deviation; SE, standard error; SRK, Sirukumab; SSZ, sulfasalazine; TCZ, Tocilizumab; TFC, Tofacitinib

Notes: † = median (IQR), ‡ = median (range), § = mean (range); †† = Baseline demographics captured for overall population

Table 31. Corrected ACR response rate at 12-16-week follow-up (bDMARD-experienced population)

Author, year	Intervention	Follow-up, weeks	Analysis (e.g. ITT)	N	ACR 20 (patients achieving 20% improvement)		ACR 50 (patients achieving 50% improvement)		ACR 70 (patients achieving 70% improvement)	
					#	%	#	%	#	%
ORAL-STEP Burmester, 2013[272]	TFC 5mg bid	12	mITT	132	55	41.7	35	26.5	18	13.6
	TFC 10mg bid			133	64	48.1	37	27.8	14	10.5
	PBO			131	32	24.4	11	8.4	2	1.5
RA-BEACON Genovese, 2015[274]	BRC 4 mg QD	12	mITT	177	NR	55.4	NR	28.2	NR	11.3
	BRC 2 mg QD			174	NR	48.9	NR	20.1	NR	12.6
	PBO			176	NR	27.3	NR	8	NR	2.3
REALISTIC Weinblatt, 2012[229]	CTZ 400-200 mg QOW	12	ITT	320	NR	47.2	NR	21.6	NR	9.1
	PBO			80	NR	27.5	NR	11.3	NR	3.8
SELECT BEYOND Genovese, 2018[25]	PBO	12	FAS	169	48	28	20	12	11	7
	UPA 15 mg OD			164	106	65	56	34	19	12
	UPA 30 mg OD			165	93	56	59	36	38	23
GO-AFTER Smolen, 2009[263]	GOL 50 mg	14	ITT	153	54	35	25	16	16	10
	PBO			155	28	18	10	6	3	2
TARGET STUDY Fleischmann 2017[288]	PBO + csDMARDs	12	ITT	181	NR	37.6	NR	13.3	NR	2.2
	SRL 150 mg q2w + csDMARDs			181	NR	54.1	NR	30.4	NR	13.8
	SRL 200 mg q2w + csDMARDs			184	NR	62.5	NR	33.2	NR	14.7

Abbreviations: ACR, American College of Rheumatology; BRC, baricitinib; CTZ, certolizumab pegol GOL, golimumab; ITT, intention to treat; mITT, modified intention to treat; NR, not reported; PBO, Placebo; QD, once daily; SRK, sirukumab; SRL, sarilumab; RTX, rituximab; TFC, tofacitinib

Table 32. Corrected ACR response rate at 18-30-week follow-up (bDMARD-experienced population)

Author, year	Intervention	Follow-up, weeks	Analysis (e.g. ITT)	N	ACR 20 (patients achieving 20% improvement)		ACR 50 (patients achieving 50% improvement)		ACR 70 (patients achieving 70% improvement)	
					#	%	#	%	#	%
ASCERTAIN^ Emery, 2019[256]	SRL 150 mg q2w	24	ITT	49	NR	63.3	NR	36.7	NR	18.4
	SRL 200 mg q2w			51	NR	68.6	NR	41.2	NR	13.7
	TCZ 4 mg/kg q4w			102	NR	75.5	NR	41.2	NR	22.5
ATTAIN Genovese, 2005[258]	ABT 10 mg/kg q4w + DMARDs	24	mITT	258	NR	50.4	NR	20.3	NR	10.2
	PBO + DMARDs			133	NR	19.5	NR	3.8	NR	1.5
BREVACTA Kivitz, 2014[112]	TCZ-SC	24	mITT	89	NR	48	NR	28	NR	14
	PBO-SC			47	NR	17	NR	13	NR	2
MOBILITY Genovese, 2015[148]	PBO + MTX	24	Unclear	109	NR	33	NR	12	NR	4
	SRL 150 mg q2w + MTX			108	NR	59	NR	36	NR	20
	SRL 200 mg q2w + MTX			110	NR	64	NR	41	NR	19
TARGET Fleischmann, 2017[288]	PBO + csDMARDs	24	ITT	181	61	33.7	33	18.2	13	7.2
	SRL 150 mg q2w + csDMARDs			181	101	55.8	67	37	36	19.9
	SRL 200 mg q2w + csDMARDs			184	112	60.9	75	40.8	30	16.3
RADIATE Emery, 2008[280]	4 mg/kg TCZ + MTX	24	ITT	161	NR	30.4	NR	16.8	NR	5
	8 mg/kg TCZ + MTX			170	NR	50	NR	28.8	NR	12.4
	PBO + MTX			158	NR	10.1	NR	3.8	NR	1.3
RA- BEACON Genovese, 2015[274]	PBO	24	mITT	176	NR	27.3	NR	13.1	NR	3.4
	BRC 2 mg QD			174	NR	44.8	NR	23	NR	13.2
	BRC 4 mg QD			177	NR	46.3	NR	29.4	NR	16.9
REFLEX Cohen, 2006[285]	PBO + MTX	24	mITT	201	NR	18	NR	5	NR	1
	RTX 1,000 mg + MTX			298	NR	51	NR	27	NR	12

Author, year	Intervention	Follow-up, weeks	Analysis (e.g. ITT)	N	ACR 20 (patients achieving 20% improvement)		ACR 50 (patients achieving 50% improvement)		ACR 70 (patients achieving 70% improvement)	
					#	%	#	%	#	%
GO-AFTER Smolen, 2009[263]	PBO	24	ITT	155	26	17	8	5	5	3
	50 mg GOL			153	52	34	28	18	18	12

Abbreviations: ABT, abatacept; ACR, American College of Rheumatology; BRC, baricitinib; csDMARD, conventional disease modifying anti-rheumatic drug; GOL, golimumab; ITT, intention to treat;, IV, intravenous; mITT, modified intention to treat; MTX, methotrexate; NR, not reported; PBO, Placebo; Q2W, every 2 weeks; QD, once daily; RTX, rituximab;, SRK, sirukumab; SRL, sarilumab; TCZ, tocilizumab.

4.6 Conclusions of the clinical effectiveness section

The company conducted a SLR that was appropriately aligned with the NICE final scope. The ERG considered the company's search strategies to be well-conducted and reported. Although some issues were noted, the ERG was broadly satisfied that the company identified all relevant RCTs for UPA and comparators. The ERG was broadly satisfied with the study selection and quality assessment (QA) methods for the UPA trials. The ERG noted however that there was a lack of detail on how the study selection criteria were applied, meaning that the ERG could not definitively confirm that no trials for the technology of interest were inappropriately excluded during the screening process. Moreover, the ERG considered that the SELECT-SUNRISE trial did meet the inclusion criteria for the SLR and therefore detailed clinical effectiveness evidence should have been provided for this trial, especially since it informs the NMA and economic modelling.

The ERG considered the four trials that were included as pivotal trials in the clinical evidence submission to be appropriate and fulfilled the inclusion criteria. All were RCTs and the study designs were in line with the NICE final scope and the SLR inclusion criteria. The ERG noted that UPA was used as monotherapy in one of the pivotal trials (SELECT-MONOTHERAPY), and was administered in combination with MTX and other csDMARDs in other trials. The included trials were a mixture of PBO and/or active controlled trials – active control was with ADA in SELECT-COMPARE and with MTX in SELECT-MONOTHERAPY. The ERG noted that there were no UK sites in SELECT-MONOTHERAPY and that the [redacted] The ERG considered the study populations in all four trials to be relevant to the decision problem and to exhibit a large degree of between-trial comparability, although differences in prior medication regimens were noted. The ERG also noted that the range of populations in each trial means that each trial 'evidences' multiple points on the NICE treatment pathway, which could pose a challenge to interpretation and application of study findings.

Head-to-head evidence is provided for certain comparisons, although the key clinical effectiveness comparisons that serve as inputs to the economic model are comparative data derived from an NMA, in order to take into account the totality of the available evidence across the network. The evidence presented in the CS broadly covered the range of outcomes included in the NICE final scope, although it was noted that only safety data were available for extra-articular manifestations. The ERG agreed that there was generally a low risk of bias in the four pivotal trials for the technology of interest.

The ERG found no discrepancies in trial results compared to the respective CSRs. The ERG noted that there was some variation between the studies in the primary and secondary outcomes used to assess clinical and functional efficacy and HRQoL of UPA. The ERG also noted that, for three of the trials, between-group data were reported only at 12-14 weeks. It is important to consider that the 26 week data include patients who switched treatments.

Feasibility assessment was not explicitly reported for the NMAs undertaken. This is a major omission that threatens the credibility of the NMAs presented. The ERG considered the inclusion criteria for the NMA to be largely appropriate. However, due to a lack of clarity in the reasons of exclusion, the ERG could not rule out the potential of inappropriate exclusion of trials from the NMAs. While the ERG found errors in the QA of included trials, the ERG also noted that the QA was not used to select or weight studies in the NMA, or in the economic modelling. The ERG considered, therefore, that any errors or potential errors in the QA of the remaining studies could affect transitivity of networks in NMA, but would not necessarily impact choice of studies for NMA or economic modelling.

The results of the NMA evidenced the effectiveness of UPA both as monotherapy, where appropriate, and in combination with csDMARDs relative to comparators. These findings were generally robust to sensitivity analysis. UPA ranked highly against other treatment options in both the csDMARD-experienced and bDMARD-experienced treatment networks. The statistical methods and assumptions described were appropriate, though specific ambiguities (including the generation of reference group probabilities) remain. However, the ERG urges caution in the interpretation of NMAs due to the strong conceptual assumptions of exchangeability between populations and treatment pathways required; challenges in replicating inclusion and exclusion decisions and the analyses undertaken; and the ERG’s inability to recreate the findings of the NMA.

5 Cost-effectiveness

5.1 ERG comment on companies review of cost-effectiveness evidence

5.1.1 Objective

The company performed a literature search in order to identify economic evaluations of interventions used to treat people with moderate or severe RA.

5.1.2 Search strategy

The company completed searches to identify cost-effectiveness studies relevant to UPA (and comparators) in patients with rheumatoid arthritis in December 2017, and these were updated in April 2019. The cost effectiveness searches are reported in Appendix G of the CS.

The following bibliographic databases were searched: Ovid Embase, MEDLINE, EBM Reviews (incorporating the Cochrane Library databases), and EconLit. The search strategy uses a combination of indexing (e.g. MeSH in MEDLINE) and free text (i.e. title and abstract terms), and searches were not limited by language. Additional searches were conducted for cost effectiveness studies in reference lists of included studies, conference proceedings, HTA websites, the CEA Registry and EconPapers in RePEc.

The cost effectiveness searches use a combination of terms for the population (rheumatoid arthritis), intervention (UPA), comparators, and study design (cost utility analyses, cost effectiveness analyses, cost-benefit analyses, cost-minimisation analyses), combined appropriately using Boolean logic.

The ERG noted several issues with the cost-effectiveness searches. Searches for all biosimilars and brand names for comparators were not included in the cost-effectiveness search strategies. Update searches completed in April 2019 did not use all relevant date fields to limit searches (see Section 4.1.1 for further details). The company has not cited a validated filter for the identification of cost-effectiveness studies, and subject headings have not been adapted for each bibliographic databases. Several relevant subject headings have not been included (for e.g. health economics/ in Embase). The NHS Economic Evaluation Database was searched as part of EBM Reviews, and economic terms have been applied unnecessarily. As a result of these issues, all relevant cost-effectiveness studies may not have been identified.

Supplementary searches have not been fully reported, and search strategies have not been provided for CEA Registry or EconPapers. The conference proceeding searches

were not updated in April 2019 to include 2018 abstracts; however, these were checked for the clinical effectiveness and cost/resource use searches.

The company also conducted searches for health utilities (reported in Appendix H of the CS) and cost/resource use literature (reported in Appendix I of the CS). Further detail is provided in Appendix 2.

ERG comment

The ERG noted several issues with the searches for cost-effectiveness, health utilities and cost outlined above. It is possible that all relevant cost effectiveness studies, health utilities and cost literature may not have been identified, but this risk is likely to have been mitigated by the use of multiple sources and supplementary search approaches. The ERG is broadly satisfied with the search approach utilized by the company.

5.1.3 Inclusion/exclusion criteria

The inclusion and exclusion criteria of the company's review of economic evaluations are presented in Table 33

Table 33. Eligibility criteria for review of cost-effectiveness studies

	Inclusion criteria	Exclusion criteria
Population	• Adult patients (≥18 years of age) • Meeting the ACR Classification criteria for RA, and • An inadequate response to conventional DMARDs (csDMARDs) or biological DMARDs	Patients with disease other than RA
Interventions	Upadicitinib 15mg or 30mg QD in monotherapy or in combination	
Comparators	JAK-inhibitor • TFC (Xeljanz®) • BRC (Olumiant®) • Filgotinib • Peficitinib **bDMARDs** TNF-α inhibitors • ADA (Humira®) • ETN (Enbrel®) • IFX (Remicade®) • GOL (Simponi®) • CTZ (Cimzia®) Anti-B-cell therapy • RTX (Rituxan®) Co-stimulatory inhibitor molecules • ABT (Orencia®)	

	Inclusion criteria	Exclusion criteria
	Anti-IL-6 therapy • TCZ (Actemra®) • SRK • SRL Anti-IL-1 therapy • Anakinra (Kineret®) Biosimilars to any of the interventions listed above PBO Interventions may be used alone or in combination with any other biological/ conventional DMARDs. No restrictions to drug dose or formulation, mode of delivery or duration of treatment. However, studies with at least one treatment arm with a licensed dose are of primary interest.	
Outcomes	**Main outcomes:** • ICER: Cost per QALY • ICER: Cost per DALY • ICER: Cost per event avoided **Additional outcomes:** • Range of ICERs as per sensitivity analyses • Assumptions underpinning model structures • Key costs drivers • Sources of clinical, cost and quality of life inputs • Discounting of costs and health outcomes • Model summary and structure	Outcome(s) not listed
Study design	• Cost-utility analyses • Cost-effectiveness analyses • Cost-benefit analyses • Cost-minimisation analyses	
Language restrictions	English abstracts of foreign publications will be considered.	Foreign language publications without an English abstract
Date of publication	No restriction	-
Countries/global reach	No restriction	-

Key: ABT, abatacept; ACR, American College of Rheumatology, ADA, adalimumab; bDMARDs, biologic disease modifying antirheumatic drugs; BRC, baricitinib; csDMARDs, Conventional Disease-modifying Antirheumatic Drugs; CTZ, certolizumab pegol; ETN, etanercept; GOL, golimujmab; IFX, infliximab; NICE, National Institute for Health and Care Excellence; RA, rheumatoid arthritis; RTX, rituximab; SRK, sirukumab; SRL, sarilumab; TCZ, tocilizumab; TFC, tofacitinib; UK, United Kingdom

Source: CS, Appendix G, p292

The criteria set out by the company in Table 38 of the CS (CS, Appendix G) were aligned with NICE scope. The ERG noted that the company specified economic evaluations comparing UPA (15 mg or 30 mg QD) versus biological DMARDs; however, given the list

of studies included the ERG consider it more likely that the inclusion criteria reflect those specified for the company's reviews of health-related quality of life and of cost and healthcare resource use whereby studies evaluating any biological DMARD (as mono- or combination therapy) (in line with NICE scope) compared with another biological DMARD (in line with NICE scope). The ERG considers, however, that this is likely a reporting error.

The company also presented eligibility criteria for its reviews of HRQoL and of cost and healthcare resource use (CS, Appendix H [Table 65], and CS, Appendix I [Table 69], respectively). The criteria for these reviews were broadly aligned with the NICE final scope.

5.1.4 Results

The review was conducted in two stages: an initial review was conducted in December 2017 and an update was performed in April 2019 (refer to CS Appendix G, Section G.7.1 and G.7.2). A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram combining the original and update reviews is presented by the company in Figure 36 of the CS (CS, Appendix G). The ERG queried a discrepancy in the PRISMA flow diagram which the company satisfactorily addressed in the clarification response (refer to clarification response B1). A total of 241 publications (reporting 238 economic evaluations) were considered eligible for inclusion in the review. Of these, 228 publications were economic evaluations, and 13 publications reported health technology assessment (HTA) reports with economic models. Among the included studies the company identified 32 UK-based economic evaluations, of which 17 were NICE technology appraisals.

The company focused on published cost-effectiveness reviews that were set within a UK context. The ERG considers this to be a pragmatic way in which to reduce the number of studies to summarise. A description and critical appraisal using the Drummond checklist of these economic evaluations was provided by the Company in Appendix G of the CS (CS Appendix G, Section G.8 and G.10, respectively). Although the non-UK economic evaluations were not discussed further, a list of studies was provided by the company in Section G.9 (Table 55; Appendix G) of the CS.

The company reported that the economic model developed was "consistent with the assessment group (AG) model/approach in TA375,[31] and the recent submissions of BRC (TA466),[51] TFC (TA480),[32] and SRL (TA485)[52] for the treatment of RA; with necessary adaptations or additions in order to incorporate the modelling of UPA therapy and

additional patient populations." (CS Document B, Section B.3.2). The model for TA375[31] has been published in a peer-reviewed journal.[299]

In the review of HRQoL, the ERG queried the exclusion of 131 studies on publication date (year ≤2017). In clarification response B3, the company confirmed that these studies had indeed been identified in the original search. The review of HRQoL followed the same approach as the review of economic evaluations in that the company focused on studies that compared interventions (aligned with NICE scope), that were set within a UK context. A list of non-UK studies was also provided (CS, Appendix H, Table 66). Outcomes of interest were utilities for health states or mode of administration, and mapping studies. Eligible studies were not summarised although some had been captured in the review of economic evaluations. Studies were, however, quality assessed (CS Appendix H, Table 68).

In the review of cost and healthcare resource use, a total of 17 unique studies from 18 publications were identified (CS Appendix I, Figure 40). Eligible studies were summarised (CS, Appendix I, Table 70), and methodological limitations were assessed using the checklist reported by Molinier and colleagues[300] (CS Appendix I, Table 71 and Table 72).

5.1.5 Conclusions

None of the economic evaluations identified included UPA. As such, the company developed a de novo health economic model to assess the cost effectiveness of UPA (Section 5.2). Studies identified in the reviews of utilities and of cost and healthcare resource use were used to inform model parameters.

5.2 Summary of company's submitted economic evaluation

The company developed a *de novo* economic model to assess the cost effectiveness of UPA in adults with moderate-to-severe RA, though much of it mirrors the structure and inputs of the TA375 model.

The company model is programmed in Visual Basic for Applications (VBA) with a Microsoft Excel front end acting as a database store of input values and model outputs. In discussion with NICE, the ERG has treated the VBA programming as a black box model.

The evaluation of the company's submitted economic evaluation has been hampered by a series of staggered changes subsequent to the ERG receiving the original submission on 5 July 2019. At different times over the course of the assessment:

- The UPA PAS was changed.
- The list of bDMARD PASs plus a CMU price for biosimilar IFX was extended to CMU prices for all the biosimilars.
- The company model was revised to alter the time to discontinuation of treatment curves, but this introduced further errors.
- The company model was revised a second time to correct the first model revision but additional errors were identified around the implementation of comparator PASs, requiring a 3rd model revision.

The final set of company results was received by the ERG on the 27 August 2019. The final company model was received by the ERG on the 29 August 2019. The deadline for the ERG report was the 10 September 2019.

The following subsections describe the company's methods in more detail based upon the written submissions of the company, including the model structure, the data sources used and applicability of the analysis in comparison to the NICE reference case.

5.2.1 NICE reference case checklist

The NICE reference case checklist is given in Table 34.

Table 34. NICE reference case checklist

Attribute	Reference case and TA Methods guidance	Does the *de novo* economic evaluation match the reference case
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice.	Among moderate RA patients UPA is compared with BSC, MTX and intensified csDMARDs. Among severe RA patients UPA is compared with other advanced DMARDs. The ERG agrees with the general approach but questions the logic of some of the treatment sequences.
Patient group	As per NICE scope. "Adults with moderate to severe active rheumatoid arthritis whose disease has responded inadequately to or who are intolerant of one or more DMARDs, including csDMARDs or bDMARDs"	Yes
Perspective costs	NHS & Personal Social Services	Yes.

Attribute	Reference case and TA Methods guidance	Does the *de novo* economic evaluation match the reference case
Perspective benefits	All health effects on individuals	Yes.
Form of economic evaluation	Cost-effectiveness analysis	Cost utility analysis.
Time horizon	Sufficient to capture differences in costs and outcomes	45 years. This is sufficient to be a lifetime horizon for the vast majority of patients.
Synthesis of evidence on outcomes	Systematic review	The company applies the clinical effectiveness estimates of its two NMAs: the csDMARD-IR NMA and the bDMARD-IR NMA. Given the NICE methods guide, it can be argued that the head to head results of the SELECT trials should be applied in the modelling where UPA is being compared to BSC, control or PBO.
Outcome measure	Quality adjusted life years	Yes.
Health states for QALY	Described using a standardised and validated instrument	The approach to quality of life involves mapping from the modelled HAQ scores to pain scores, and applying the combination of these to map onto an EQ-5D quality of life function from the literature. This is the same approach as in TA375, but the company derives its own HAQ to pain mapping function from SELECT trials' data.
Benefit valuation	Time-trade off or standard gamble	The EQ-5D mapping function is not stated in the paper, but the lowest feasible value corresponds with that of the usual UK tariff.
Source of preference data for valuation of changes in HRQL	Representative sample of the public	Yes, for the EQ-5D values within the HAQ and pain mapping function taken from the literature.
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes.
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes.
Probabilistic modelling	Probabilistic modelling	Yes. The ERG has not undertaken any probabilistic modelling due to time constraints.

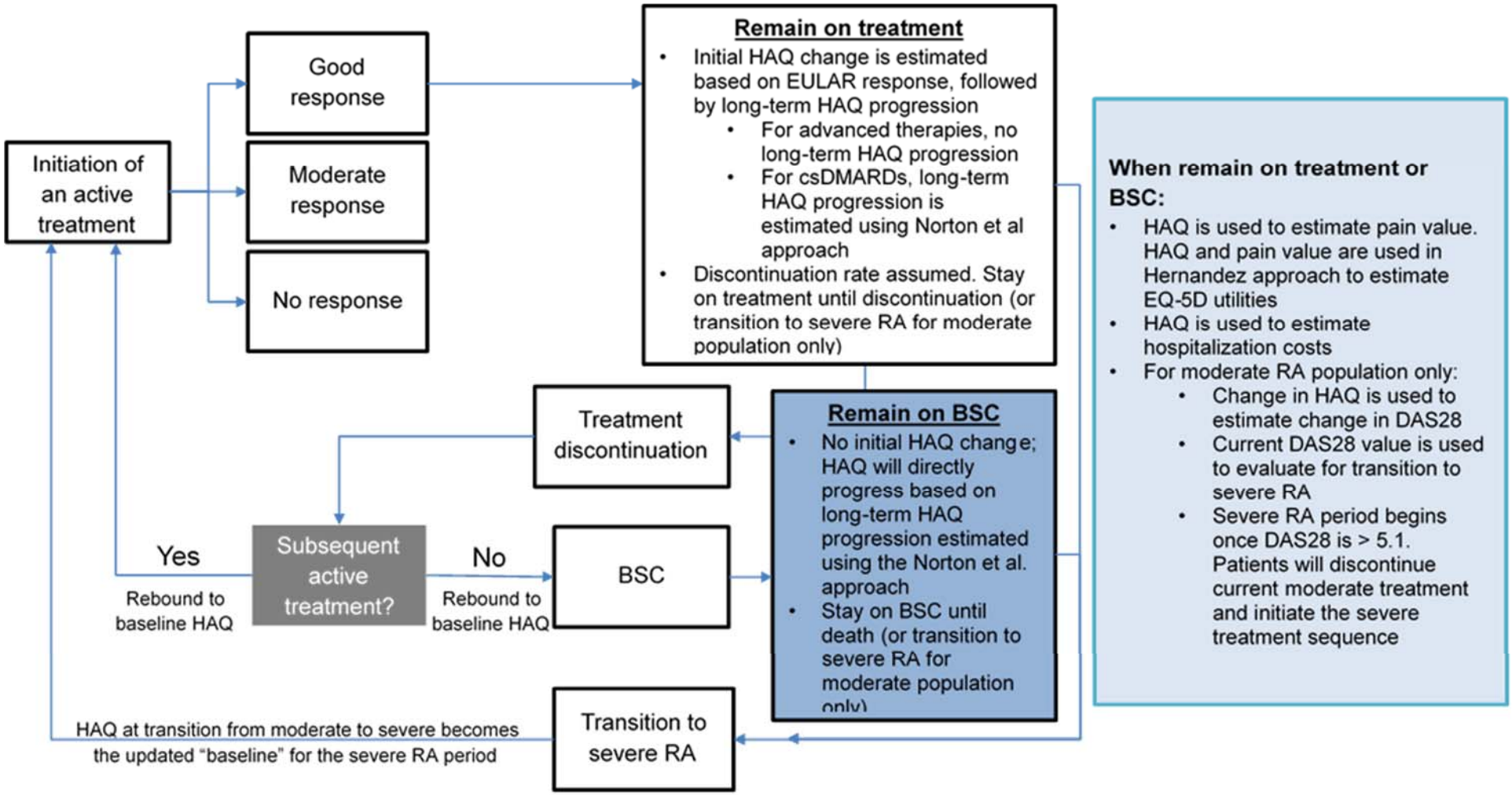
Attribute	Reference case and TA Methods guidance	Does the *de novo* economic evaluation match the reference case
Sensitivity analysis		A wide range of univariate sensitivity analyses are included.

Abbreviations: bDMARD, biologic disease modifying antirhumatic drug; BSC, best supportive care; csDMARD, conventional synthetic disease modifying antirheuamtic drug; DMARD, disease modifying antirheumatic drug; EQ-5D, Euroqol five dimensions; ERG, Evidence Review Group; HAQ, health assessment questionnaire; HRQoL, health-related quality of life; MTX, methotrexate; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; QALY, quality adjusted life year; TA, tehcnology appraisal

5.2.2 Model structure

The company has updated the model structure diagram to take into account the possibility of worsening from moderate RA to severe RA. In general, patients trial a first-line treatment and if they achieve a EULAR response at six months remain on it and have a corresponding reduction in their HAQ. Those not achieving a EULAR response at six months go on to trial the next treatment in the sequence. Treatment cessation curves are also modelled. When a patient ceases treatment their HAQ score rebounds to baseline, but will improve if they have a EULAR response to their next in line treatment.

Figure 8. Model structure



Abbreviations: BSC, best supportive care; DAS28, disease activity score in 28 joints; EQ-5D, EuroQol Five Dimensions; EULAR, European League Against Rheumatism; HAQ, health assessment questionnaire; RA, rheumatoid arthritis

5.2.3 Population

The company models the following 10 population subgroups:

- 1a: Moderate RA, MTX intolerant, RTX tolerant, failed one csDMARD
- 1b: Moderate RA, MTX tolerant, RTX tolerant, failed one csDMARD
- 2a: Moderate RA, MTX intolerant, RTX tolerant, failed ≥2 csDMARD
- 2b: Moderate RA, MTX tolerant, RTX tolerant, failed ≥2 csDMARD
- 3a: Severe RA, MTX intolerant, RTX tolerant, failed ≥2 csDMARD
- 3b: Severe RA, MTX tolerant, RTX tolerant, failed ≥2 csDMARD
- 4a: Severe RA, MTX intolerant, RTX tolerant, failed one bDMARD
- 4b: Severe RA, MTX tolerant, RTX intolerant, failed one bDMARD
- 5: Severe RA, MTX tolerant, RTX tolerant, failed one bDMARD
- 6: Severe RA, MTX tolerant, RTX tolerant, failed RTX

The baseline characteristics of the patient subgroups are based upon the pooled SELECT trial data (Table 35).

Table 35. Patient baseline characteristics

	csDMARD-IR				bDMARD-IR	
	Moderate RA		Severe RA		Severe RA	
	Mean	(SD)	Mean	(SD)	Mean	(SD)
Age	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HAQ	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weight	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DAS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease duration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: bDMARD, biologic disease modifying antirheumatic drugs; csDMARD, conventional synthetic disease modifying antirheumatic drugs; DAS, disease activity score; HAQ, health assessment questionnaire; IR, inadequate response; RA, rheumatoid arthritis; SD, standard deviation

The model is an individual patient discrete event simulation. The company samples 10,000 patients using the above distributions. It appears that the model shows reasonable convergence when 10,000 patients are run through it.

5.2.4 Interventions and comparators

In common with the previous NICE assessments in RA, individual treatments are not directly compared. Rather, treatment sequences are compared. For the modelling of moderate RA patients UPA is typically assumed to lengthen the treatment sequence, and a longer UPA containing treatment sequence is compared with a shorter non-UPA treatment sequence. For the modelling of severe RA patients UPA is typically assumed to displace another treatment and treatment sequences of the same length are compared.

5.2.4.1 Position: 1a: Moderate RA: MTX intolerant, RTX tolerant, failed one csDMARD

The treatment sequences for those remaining with moderate RA are provided in Table 36.

Table 36. Sequence: 1a: Moderate RA: MTX intolerant, RTX tolerant, failed one csDMARD: Among moderate patients

Sequence	First-line	Second-line	Third-line
1.	UPA	Int.csDMARD	BSC
2.	Int.csDMARD	BSC	..

Abbreviations: bDMARD, biologic disease modifying antirheumatic drugs; BSC, best supportive care; csDMARD, conventional synthetic disease modifying antirheumatic drugs; int, intensified; UPA, upadacitinib

Those progressing to severe RA receive a different treatment sequence depending upon their treatment when they were moderate (Table 37). Those worsening to severe having been on Sequence 1 when moderate receive Sequence 3 when severe. Similarly, those worsening to severe having been on Sequence 2 when moderate receive Sequence 4 when severe.

Table 37. Sequence: 1a: Moderate RA: MTX intolerant, RTX tolerant, failed one csDMARD: Among patients who have progressed to severe

Sequence	First-line	Second-line	Third-line	Fourth-line
3.	ADA	SRL	BSC	..
4.	BRC	ADA	SRL	BSC

Abbreviations: ADA, adalimumab; BRC, baricitinib; BSC, best supportive care; SRL, sarilumab; UPA, upadacitinib

In the above BRC monotherapy is assumed to have the same efficacy as BRC+MTX in the cDMARD-IR NMA.

5.2.4.2 Position: 1b: Moderate RA: MTX tolerant, RTX tolerant, failed one csDMARD

The treatment sequences for those remaining with moderate RA are provided in Table 38.

Table 38. Sequence: 1b: Moderate RA: MTX tolerant, RTX tolerant, failed one csDMARD: Among moderate patients

Sequence	First-line	Second-line	Third-line	Fourth-line
1.	UPA+MTX	Int.csDMARD	MTX	BSC
2.	UPA	Int.csDMARD	MTX	BSC
3.	Int.csDMARD	MTX	BSC	..

Abbreviations: BSC, best supportive care; csDMARD, conventional synthetic disease modifying antirheumatic drugs; int, intolerant; MTX, methotrexate; SRL, sarilumab; UPA, upadacitinib

As with the treatment sequences for the MTX intolerant, among the MTX tolerant those progressing to severe RA receive a different treatment sequence depending upon their treatment when they were moderate: Sequence 1 to Sequence 4, Sequence 2 to Sequence 5 and Sequence 3 to Sequence 6 (Table 39).

Table 39. Sequence: 1b: Moderate RA: MTX tolerant, RTX tolerant, failed one csDMARD: Among patients who have progressed to severe

Sequence	First-line	Second-line	Third-line	Fourth-line	Fifth-line	Sixth-line
4.	ADA+MTX	RTX+MTX	TCZ_{IV}+MTX	MTX	BSC	..
5.	ADA+MTX	RTX+MTX	TCZ_{IV}+MTX	MTX	BSC	..
6.	BRC+MTX	ADA+MTX	RTX+MTX	TCZ_{IV}+MTX	MTX	BSC

Abbreviations: ADA, adalimumab; BRC, baricitinib; BSC, best supportive care; IV, intravenous; MTX, methotrexate; RTX, rituximab; TCZ, tocilizumab

5.2.4.3 Position: 2a: Moderate RA: MTX intolerant, RTX tolerant, failed ≥2 csDMARDs

The treatment sequences for those remaining with moderate RA are provided in Table 40.

Table 40. Sequence: 2a: Moderate RA: MTX intolerant, RTX tolerant, failed ≥2 csDMARD: Among moderate patients

Sequence	First-line	Second-line
1.	UPA	BSC
2.	BSC	..

Abbreviations: BSC, best supportive care; UPA, upadacitinib

As before, those progressing to severe RA receive a different treatment sequence depending upon their treatment when they were moderate (Table 41).

Table 41. Sequence: 2a: Moderate RA: MTX intolerant, RTX tolerant, failed ≥2 csDMARDs: Among patients who have progressed to severe

Sequence	First-line	Second-line	Third-line	Fourth-line
3.	ADA	SRL	BSC	..
4.	BRC	ADA	SRL	BSC

Abbreviations: ADA, adalimumab; BRC, baricitinib; BSC, best supportive care; SRL, sarilumab

In the above, BRC monotherapy is assumed to have the same efficacy as BRC+MTX, taken from the cDMARD-IR NMA.

5.2.4.4 Position: 2b: Moderate RA: MTX tolerant, RTX tolerant, failed ≥2 csDMARDs

The treatment sequences for those remaining with moderate RA are provided in Table 42.

Table 42. Sequence: 2b: Moderate RA: MTX tolerant, RTX tolerant, failed ≥2 csDMARDs: Among moderate patients

Sequence	First-line	Second-line	Third-line
1.	UPA+MTX	MTX	BSC
2.	UPA	MTX	BSC
3.	MTX	BSC	..

Abbreviations: BSC, best supportive care; MTX, methotrexate; UPA, upadacitinib

Again, the treatment sequences for those worsening to severe RA depend upon which treatment sequence was received when with moderate RA (Table 43).

Table 43. Sequence: 2b: Moderate RA: MTX tolerant, RTX tolerant, failed ≥2 csDMARDs: Among patients who have progressed to severe

Sequence	First-line	Second-line	Third-line	Fourth-line	Fifth-line	Sixth-line
4.	ADA+MTX	RTX+MTX	TCZ_{IV}+MTX	MTX	BSC	..
5.	ADA+MTX	RTX+MTX	TCZ_{IV}+MTX	MTX	BSC	..
6.	BRC+MTX	ADA+MTX	RTX+MTX	TCZ_{IV}+MTX	MTX	BSC

Abbreviations: ADA, adalimumab; BRC, baricitinib; BSC, best supportive care; IV, intravenous; MTX, methotrexate; RTX, rituximab; TCZ, tocilizumab

5.2.4.5 Position: 3a: Severe RA: MTX intolerant, RTX tolerant, failed ≥2 csDMARDs

The company models the following treatment sequences for the comparison of UPA at first-line against the bDMARDs. The bDMARDs are not pooled but considered individually with there being seven treatment sequences with bDMARD comparators at first-line.

Table 44. Sequence: 3a: Severe RA: MTX intolerant, RTX tolerant, failed ≥2 csDMARDs

Sequence	First-line	Second-line	Third-line
1.	UPA	SRL	BSC
2.	bDMARD	SRL	BSC

Abbreviations: bDMARDs, biologic disease modifying antirheumatic drugs; BSC, best supportive care; SRL, sarilumab; UPA, upadacitinib

The seven bDMARDs considered as comparators at first-line are: ADA, BRC, CTZ, ETN, SRL, TFC, TCZ_{IV} and TCZ_{SC}.

For the sequence with SRL at first-line, the second-line treatment is assumed to be BRC.

The effectiveness of BRC and CTZ is assumed to be the same as ADA, taken from the cDMARD-IR NMA. The effectiveness of TCZ_{SC} is assumed to be the same as TCZ_{IV}, taken from the cDMARD-IR NMA.

5.2.4.6 Position: 3b: Severe RA: MTX tolerant, RTX tolerant, failed ≥2 csDMARDs

The company models the following treatment sequences for the comparison of UPA at first-line against the bDMARDs (Table 45). The bDMARDs are not pooled but considered individually with there being 12 treatment sequences with bDMARD+MTX comparators at first-line.

Table 45. Sequence: 3b: Severe RA: MTX tolerant, RTX tolerant, failed ≥2 csDMARDs

Sequence	First-line	Second-line	Third-line	Fourth-line	Fifth-line
1.	UPA+MTX	RTX+MTX	TCZ_{IV}+MTX	MTX	BSC
2.	UPA	RTX+MTX	TCZ_{IV}+MTX	MTX	BSC
3.	bDMARD+MTX	RTX+MTX	TCZ_{IV}+MTX	MTX	BSC

Abbreviations: bDMARDs, biologic disease modifying antirheumatic drugs; BSC, best supportive care; IV, intravenous; MTX, methotrexate; RTX, rituximab; TCZ, tocilizumab; UPA, upadacitinib

The 12 bDMARDs+MTX considered as comparators at first-line are: ABT_{IV}+MTX, ABT_{SC}+MTX, ADA+MTX, BRC+MTX, CTZ+MTX, ETN+MTX, GOL+MTX, IFX+MTX, SRL+MTX, TFC+MTX, TCZ_{IV}+MTX and TCZ_{SC}+MTX.

For the treatment sequences with TCZ_{IV}+MTX and TCZ_{SC}+MTX at first-line, the third-line treatment is assumed to be SRL+MTX.

5.2.4.7 Position: 4a: Severe RA: MTX intolerant, RTX tolerant, failed one bDMARD

The company models the following treatment sequences for the comparison of UPA at "first-line" against the bDMARDs, though obviously this is among patients who have already received and failed on one bDMARD (Table 46). The bDMARDs are not pooled but considered individually with there being eight treatment sequences with bDMARD comparators at first-line.

Table 46. Sequence: 4a: Severe RA: MTX intolerant, RTX tolerant, failed one bDMARD

Sequence	First-line	Seconline
1.	UPA	BSC
2.	bDMARD	BSC

Abbreviations: bDMARDs, biologic disease modifying antirheumatic drugs; BSC, best supportive care; UPA, upadacitinib

The eight bDMARDs considered as comparators at first-line are: ADA, BRC, CTZ, ETN, SRL, TFC, TCZ_{IV} and TCZ_{SC}.

The effectiveness of all treatments is assumed to be the same as BRC+MTX, taken from the bDMARD-IR NMA.

5.2.4.8 Position: 4b: Severe RA: MTX tolerant, RTX intolerant, failed one bDMARD

The company models the following treatment sequences for the comparison of UPA at first-line against the bDMARDs (Table 47). The bDMARDs are not pooled but considered individually with there being treatment sequences with bDMARD+MTX comparators at first-line.

Table 47. Sequence: 4b: Severe RA: MTX tolerant, RTX intolerant, failed one bDMARD

Sequence	First-line	Second-line	Third-line	Fourth-line
1.	UPA+MTX	TCZ_{IV}+MTX	MTX	BSC
2.	UPA	TCZ_{IV}+MTX	MTX	BSC
3.	bDMARD+MTX	TCZ_{IV}+MTX	MTX	BSC

Abbreviations: bDMARDs, biologic disease modifying antirheumatic drugs; BSC, best supportive care; IV, intravenous; MTX, methotrexate; TCZ, tocilizumab; UPA, upadacitinib

The 12 bDMARDs+MTX considered as comparators at first-line are: ABT_{IV}+MTX, ABT_{SC}+MTX, ADA+MTX, BRC+MTX, CTZ+MTX, ETN+MTX, GOL+MTX, IFX+MTX, SRL+MTX, TFC+MTX, TCZ_{IV}+MTX and TCZ_{SC}+MTX.

For the treatment sequences with TCZ_{IV}+MTX and TCZ_{SC}+MTX at first-line, the second-line treatment is assumed to be SRL+MTX.

ABT_{SC}+MTX is assumed to have the same efficacy as ABT_{IV}+MTX, taken from the bDMARD-IR NMA.

ADA+MTX ETN+MTX and IFX+MTX are assumed to have the same efficacy as BRC+MTX, taken from the bDMARD-IR NMA.

5.2.4.9 Position: 5: Severe RA: MTX tolerant, RTX tolerant, failed one bDMARD

The company models the following treatment sequences for the comparison of UPA at first-line against the RTX+MTX (Table 48).

Table 48. Sequence: 5: Severe RA: MTX tolerant, RTX tolerant, failed one bDMARD

Sequence	First-line	Second-line	Third-line	Fourth-line
1.	UPA+MTX	TCZ_{IV}+MTX	MTX	BSC
2.	UPA	TCZ_{IV}+MTX	MTX	BSC
3.	RTX+MTX	TCZ_{IV}+MTX	MTX	BSC

Abbreviations: BSC, best supportive care; IV, intravenous; MTX, methotrexate; RTX, rituximab; TCZ, tocilizumab; UPA, upadacitinib

UPA is assumed to have the same efficacy as BRC+MTX, taken from the bDMARD-IR NMA.

5.2.4.10 Position: 6: Severe RA: MTX tolerant, RTX tolerant, failed RTX

The company models the following treatment sequences for the comparison of UPA at first-line against the RTX+MTX (Table 49).

Table 49. Sequence: 6: Severe RA: MTX tolerant, RTX tolerant, failed RTX

Sequence	First-line	Second-line	Third-line
1.	UPA+MTX	MTX	BSC
2.	UPA	MTX	BSC
2.	SRL+MTX	MTX	BSC
3.	TCZ_{IV}+MTX	MTX	BSC

Abbreviations: BSC, best supportive care; IV, intravenous; MTX, methotrexate; TCZ, tocilizumab; SRL, sarilumab; UPA, upadacitinib

UPA is assumed to have the same efficacy as BRC+MTX, taken from the bDMARD-IR NMA.

5.2.5 Perspective, time horizon and discounting

The perspective and discounting are as per the NICE reference case.

The time horizon is 45 years for the base case. Given mean (SD) [redacted] a reasonable number of people with RA will remain alive at the end of the time horizon: around [redacted], respectively.

If the time horizon is extended to 60 years, for the company modelling at position 2b this only worsens the ICER from £13,434 per QALY to £13,549 per QALY. Given that the model does not anticipate any survival gains, it seems likely that towards the end of the model the patient experience is similar in both arms and so there is little net effect from lengthening the time horizon. The ERG does not explore this further.

5.2.6 Treatment effectiveness and extrapolation

5.2.6.1 Treatment effectiveness: EULAR response rates

The treatment effectiveness estimates are based upon the EULAR response estimates of the two company NMAs: the csDMARD-IR NMA and the bDMARD-IR NMA. An additional "treatment" of BSC is included, which is assumed to have zero EULAR response rates. The mean EULAR response rates that are derived from the company NMA estimates, in order of increasing effectiveness within the cDMARD-IR NMA, are provided in Table 50.

Table 50. Mean EULAR response rates

Treatment	Abbreviation	Company NMA results			
		csDMARD-IR		bDMARD-IR	
		Mod.	Good	Mod.	Good
Best supportive care	BSC	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	PBO	[redacted]	[redacted]	[redacted]	[redacted]
cDMARD	MTX	[redacted]	[redacted]	[redacted]	[redacted]
Intensive cDMARD	Int cDMARD	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept 50mg	ETN	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab 40mg	ADA	[redacted]	[redacted]	[redacted]	[redacted]
Tofacitinib 5mg	TFC	[redacted]	[redacted]	[redacted]	[redacted]
Sarilumab 150mg + cDMARD	n.a.	[redacted]	[redacted]	[redacted]	[redacted]
Sarilumab 200mg	SRL	[redacted]	[redacted]	[redacted]	[redacted]
Rituximab 2g + cDMARD	RTX+MTX	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab 3mg/kg + cDMARD	IFX+MTX	[redacted]	[redacted]	[redacted]	[redacted]
Abatacept 125mg + cDMARD	ABT_{SC}+MTX	[redacted]	[redacted]	[redacted]	[redacted]
Abatacept 10mg/kg + cDMARD	ABT_{IV}+MTX	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept 50mg + cDMARD	ETN+MTX	[redacted]	[redacted]	[redacted]	[redacted]
Baricitinib 2mg + cDMARD	BRC+MTX	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab 40mg + cDMARD	ADA+MTX	[redacted]	[redacted]	[redacted]	[redacted]
Upadacitinib 15mg	UPA	[redacted]	[redacted]	[redacted]	[redacted]
Tofacitinib 5mg + cDMARD	TFC+MTX	[redacted]	[redacted]	[redacted]	[redacted]
Baricitinib 4mg + cDMARD	BRC+MTX	[redacted]	[redacted]	[redacted]	[redacted]
Tocilizumab 162mg + cDMARD	TCZ_{SC}+MTX	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab 50mg + cDMARD	GOL+MTX	[redacted]	[redacted]	[redacted]	[redacted]
Sarilumab 200mg + cDMARD	SRL+MTX	[redacted]	[redacted]	[redacted]	[redacted]
Tocilizumab 8mg/kg + cDMARD	TCZ_{IV}+MTX	[redacted]	[redacted]	[redacted]	[redacted]
Tocilizumab 8mg/kg	TCZ_{IV}	[redacted]	[redacted]	[redacted]	[redacted]
Tofacitinib 10mg + cDMARD	TFC+MTX	[redacted]	[redacted]	[redacted]	[redacted]
Upadacitinib 15mg + cDMARD	UPA+MTX	[redacted]	[redacted]	[redacted]	[redacted]
Certolizumab 200 mg + cDMARD	CTZ+MTX	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: bDMARD, biologic disease modifying antirheumatic drugs; csDMARDs, conventional synthetic disease modifying antirheumatic drugs; EULAR, European League Against Rheumatism; IR, inadequate response; Mod, moderate; NMA, network meta-analysis

Where the NMAs do not provide EULAR response estimates for a treatment, it is assumed to have the same clinical effectiveness as another treatment within the NMA, typically that of BRC or ADA. These assumptions are summarised in more detail in Section 5.2.4 above.

5.2.6.2 Treatment effectiveness: EULAR response rates and the HAQ

The model is largely driven by (1) direct drug and administration costs and (2) the evolution of patients' HAQ scores. The HAQ scores determine quality of life and inpatient costs. EULAR responses are assumed to result in the following improvements in patients' HAQ scores. The base case values are the same as those applied in TA375[31], with the company supplying an additional set of values based upon the pooled SELECT trials' data.

Table 51. EULAR responses relationship with HAQ changes

	Base case		SELECT trials	
	Mean	**(SE)**	**Mean**	**(SE)**
None	0.000	..	-0.123	(0.018)
Moderate	-0.317	(0.048)	-0.481	(0.016)
Good	-0.673	(0.112)	-0.755	(0.019)

Abbreviations: HAQ, health assessment questionnaire; SE, standard error

HAQ changes are not differentiated by whether a patient has moderate RA or severe RA. For the SELECT trials' data the HAQ change for those without a EULAR response appeared to be set to zero.

Given the patient baseline characteristics, the above changes imply that a substantial proportion of those with a good EULAR response will see their HAQ fall to zero: perhaps a little over 20% among those with moderate RA.

The model contains the facility to assume that the HAQ change occurs immediately, evolves linearly over six months or occurs at six months. The company base case assumes that the HAQ changes at six months. It can be argued that this is conservative towards the most effective treatment.

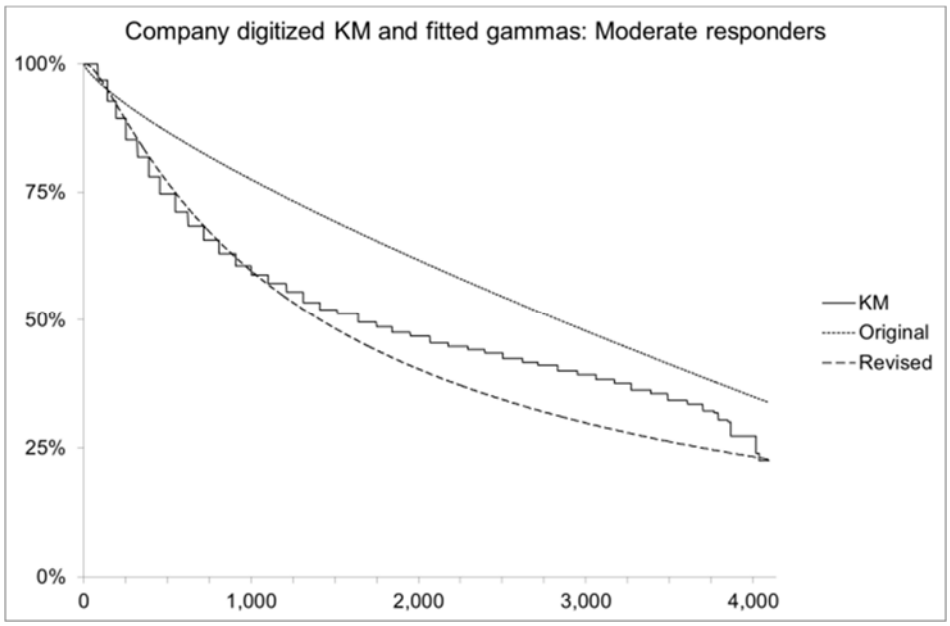
The ERG does not explore applying the SELECT trials' HAQ changes as it appears that the HAQ change for no EULAR response is probably ignored. It can be noted that the net effect relative to no EULAR response is -0.358 for a moderate EULAR response and -0.632 for a good EULAR response. These net effects are not that different from the values of the base case.

5.2.6.3 Extrapolation: Treatment cessation

The company digitised the treatment cessation curves estimated in TA375[31] from the British Society of Rheumatology Biologics Register (BSRBR) data from 7,743 patients,

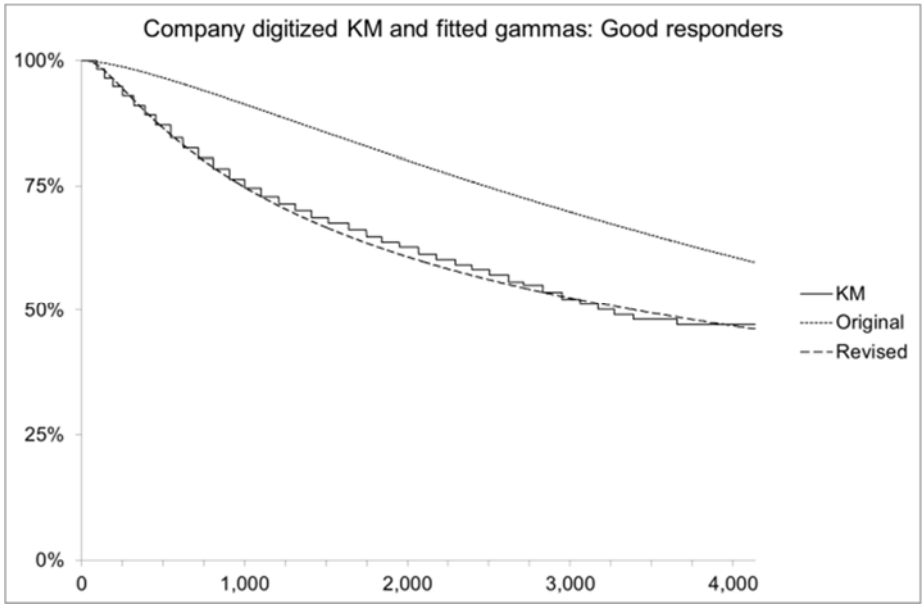
with there being separate curves for moderate RA patients and for severe RA patients. The company then fitted the usual set of functional forms to them. The original company model was found to have errors in the statistical analyses and the company submitted a revised model, with the ERG receiving the final company model on the 29 August. The digitized curves and the fitted generalised gammas derived by the ERG from clarification data are provided in Figure 9, the curves for those with a moderate EULAR response being to the left and for those with a good EULAR response to the right.

Figure 9. Treatment cessation curve: Moderate RA



Abbreviations: KM, Kaplan-Meier

Figure 10. Treatment cessation curve: Severe RA



Abbreviations: KM, Kaplan-Meier

In the original company model the generalised gammas had the best Akaike information criterion (AIC) and Bayesian information criterion (BIC). In the resubmitted model for severe RA patients the generalised gamma had the best AIC and BIC, but for moderate RA patients the log-normal had slightly better AIC, 25,573 vs 25,575, and BIC, 25,587 vs 25,595, than the generalised gamma. The company retained the generalised gamma for all analyses on grounds of consistency of approach. The generalised gamma was also the functional form applied during TA375[31] for both moderate and severe patients.

It is possible that in the modelling of moderate patients the moderate patient treatment cessation curve is applied both to moderate RA patients and to the patients who are modelled as having developed severe RA.

Note that in the original CS a scenario analysis of applying the log-normal treatment cessation curves had little effect upon the cost effectiveness estimates.

5.2.6.4 Extrapolation: Change in DAS-28 and from moderate RA to severe RA

The modelling of moderate RA patients includes the possibility of patients worsening to severe RA, and so moving onto a further sequence of bDMARDs. This requires the evolution of the DAS-28 to be modelled for moderate RA patients, with patients transitioning to severe RA when the DAS-28 worsens to 5.1.

The company ran a repeated measures linear mixed effects model on the SELECT trials' data. Only one functional form was explored, the change in DAS-28 at three or six months being regressed on the change in the HAQ at three and fro SELECT-COMPARE at six months (Table 52).

Table 52. ∆DAS-28 from baseline as a function of ∆HAQ from baseline

	Coefficient	SE	p-value
Intercept	-1.16	0.05	<0.0001
∆HAQ	0.91	0.07	<0.0001

Abbreviations: DAS-28, disease activity score 28-joint count; HAQ, health assessment questionnaire; SE, standard error

5.2.6.5 Extrapolation: HAQ changes

The HAQ of those remaining on bDMARDs is assumed to remain constant.

The HAQ of those remaining on csDMARDs and those on BSC is assumed to worsen through time. The functional forms are based upon the Norton et al[301] analysis of the 1,460 UK csDMARD patients of the ERAS study recruited between 1986 and 1998 and

with 10 years follow up. This was also the source used to model the HAQ of those remaining on cDMARDs in TA375[31]. The worsening of HAQ is limited to 15 years, which the company states is in line with TA375[31].

5.2.6.6 Extrapolation: Mortality

The mortality hazard ratios of TA375[31] are applied using the same method of TA375 to the individual patients' baseline HAQ scores (Table 53).

Table 53. Baseline HAQ and mortality hazard ratios

Baseline HAQ	Mortality HR
0.000	1.0
0.125-0.375	1.4
0.500-0.875	1.5
1.000-1.375	1.8
1.500-1.875	2.7
2.000-2.375	4.0
2.500-3.000	5.5

Abbreviations; HAQ, health assessment questionnaire; HR, hazard ratio

Note that the mortality multipliers are only applied to baseline HAQ scores to estimate individual patients' survival, as per TA375[31]. The model does not anticipate any survival gain from UPA.

5.2.6.7 Adverse event rates

Adverse event rates were estimated from SELECT-COMPARE with the control arm providing estimates for csDMARDs, ADA for bDMARDs and UPA for JAK inhibitors. Annual rates of SAEs were 0.096 for csDMARDs, 0.156 for bDMARDs and 0.129 for JAK inhibitors.

The ERG does not know how rescue therapy was handled within this analysis. The ERG assumes that patients were analysed on the basis of treatment arm with no consideration of rescue treatment. As a consequence, given the higher adverse event rates with UPA and the extent of UPA rescue therapy in the control arm of SELECT-COMPARE, the adverse event rate for csDMARDs may be too high.

5.2.7 Health related quality of life

5.2.7.1 HAQ, Pain and the EQ-5D

In common with TA375[31] the company model first maps the HAQ to pain scores. The HAQ and the resulting pain scores then determine the main quality of life values. But the company model bases its mapping from the HAQ to pain scores upon an analysis of the pooled SELECT trials' data, in contrast to TA375[31] which based it upon an analysis of 100,398 observations from the NDB, as reviewed in greater detail in Section 5.3.4.3 below.

5.2.7.2 Adverse events and quality of life

The submission does not contain any reference to adverse events quality of life effects, and there are no obvious elements of the electronic model relating to this. The ERG assumption is that none are modelled. This will slightly bias the analysis in favour of the advanced DMARDs and against the csDMARDs and BSC.

5.2.8 Resources and costs

5.2.8.1 Direct drug and administration costs

The original CS included a simple UPA PAS of [redacted]. Midway through the ERG review of the CS the company revised the UPA PAS to [redacted]. A complex PAS of 12 weeks free supply applies to CTZ. Simple PASs also apply to:

- ABT: Abatacept
- BRC: Baricitinib
- GOL: Golimumab
- SRL: Sarilumab
- TFC: Tofacitinib

There are also a number of biosimilars available for the older bDMARDs. The company generally applies the list price of the cheapest biosimilar as below:

- ADA: Adalimumab: Hulio®
- ETN: Etanercept: Benepali®
- IFX: Infliximab: Flixabi®

- RTX: Rituximab: Rixathon®

Erelzi® is marginally cheaper than Benepali® at list prices, but the small difference is irrelevant to decision making. In common with TA375[31], the interval between RTX doses is assumed to be nine months. All the older bDMARDs with biosimilars also have confidential discounts. The Commercial Medicines Unit (CMU) has provided these to NICE, which has forwarded them to the ERG.

All results in this document include the revised UPA [redacted] PAS and the CTZ complex PAS, but do not include the other comparators' simple PASs or the CMU price discounts for the older bDMARDs. The results inclusive of all price discounts are presented within the cPAS appendix.

Intravenous (IV) administration costs of £159 are applied, apparently based upon the TA375 cost of £154, marginally uprated for inflation by 3% with the company giving the hospital and community health services (HCHS) index as the source of the inflation uplift.

Subcutaneous (SC) administration costs of £3.14 are applied, apparently based upon the £26.10 TA247[302] cost uprated for inflation by 46% using the HCHS. The TA375 cost was based upon 10% of SC administrations requiring a district nurse at a cost of £30.50, an increase on the £26.10 district nurse cost of TA247.

The drug and administration prices applied in the modelling for the first six months prior to assessment of EULAR response and annually thereafter are provided in Table 54.

Table 54. Direct drug and administration costs: bDMARDs

	1st 6 months			Annual thereafter		
Treatment	**Drug**	**Admin**	**Total**	**Drug**	**Admin**	**Total**
ABT_{IV}: $Abatacept_{IV}$	£7,278	£1,273	£8,551	£11,834	£2,070	£13,904
ABT_{SC}: $Abatacept_{SC}$	£7,889	£82	£7,971	£15,779	£164	£15,943
CTZ: Certoluzumab pegol	£2,518	£41	£2,559	£9,327	£82	£9,409
GOL: Golimumab	£4,976	£20	£4,997	£9,953	£41	£9,994
SRL: Sarilumab	£5,950	£41	£5,991	£11,900	£82	£11,982
TCZ_{IV}: $Tocilizumab_{IV}$	£5,343	£1,035	£6,378	£10,686	£2,070	£12,756
TCZ_{SC}: $Tocilizumab_{SC}$	£5,956	£82	£6,038	£11,911	£164	£12,075
BRC: Baricitinib	£5,254	£0	£5,254	£10,508	£0	£10,508
TFC: Tofacitinib	£4,501	£0	£4,501	£9,001	£0	£9,001
UPA: Upadacitinib	[redacted]	£0	[redacted]	[redacted]	£0	[redacted]
ADA: Adalimumab	£4,019	£41	£4,060	£8,039	£82	£8,121
ETN: Etanercept	£4,279	£82	£4,361	£8,557	£164	£8,721
IFX: Infliximab	£6,233	£874	£7,108	£7,377	£1,035	£8,412
RTX: Rituximab	£2,096	£106	£2,201	£4,191	£212	£4,403

Abbreviations: bDMARDs, biologic disease modifying antirheumatic drugs

Note that no pharmacy costs are included in the model. Most bDMARDs are formulated as four-weekly preparations and, given the cost of bDMARDs, it seems unlikely that relatively minor pharmacy costs which would be similar across the bDMARDs would much affect net results.

The costs for csDMARD of £8 for the initial six months and £17 thereafter are based upon the cost of MTX. The BNF recommends 7.5 mg once weekly, adjusted according to response with a maximum of 20 mg per week. The company chooses the maximum 20 mg dose, but MTX is so cheap this will have little to no impact upon results.

The costs for intensified csDMARDs of £107 for the initial six months and £215 thereafter are based upon the cost of MTX, plus daily 6.5mg/kg hydroxychloroquine, daily 7.5mg prednisolone and 3 g daily sulfasalazine. Again, these are the maxima recommended in the BNF for hydroxychloroquine and sulfasalazine. Given this, the costs cross check with CMU EMIT prices.

5.2.8.2 Inpatient costs

HAQ related annual inpatient costs are applied, based upon the values of TA375[31] inflated to 2018 prices using the HCHS index (Table 55).

Table 55. Inpatient costs as a function of HAQ

HAQ	Cost		HAQ	Cost
0.000	£263		1.625	£491
0.125	£194		1.750	£532
0.250	£167		1.875	£718
0.375	£149		2.000	£905
0.500	£131		2.125	£1,087
0.625	£112		2.250	£1,275
0.750	£96		2.375	£1,643
0.875	£163		2.500	£2,005
1.000	£231		2.625	£2,380
1.125	£302		2.750	£2,747
1.250	£371		2.875	£3,456
1.375	£411		3.000	£4,155
1.500	£452			

Abbreviations: HAQ health assessment questionnaire

5.2.8.3 Ongoing monitoring costs

Ongoing monitoring costs, based upon Malottki et al[303] inflated to 2018 prices using the HCHS index, are differentiated by where the patient is in terms of treatment (Table 56). This approach is in line with TA375[31] .

Table 56. Monitoring costs

Period	Cost
Pre-treatment	£175
6 months assessment period	£1,752
Monthly thereafter	£138

BSC has an annual £742 ongoing cost, based upon the value of TA375 inflated to 2018 prices using the HCHS index. This appears to be in addition to the HAQ-related inpatient costs summarised in Section 5.2.8.2 above.

NICE CG100[8] recommended monthly monitoring while treatment is being established, with an annual review once the patient is stabilised.

5.2.8.4 Adverse event costs

Adverse event costs of a little over £1,500 per event are taken from the same source as TA375, Oppong et al[304], inflated to 2018 costs using the HCHS.

5.2.9 Cost effectiveness results

The company presents a large number of tables of results. For reasons that are not clear the company chooses to separate the cost effectiveness estimates for UPA from those of UPA+MTX despite these being within the same patient group and against the same set of comparator treatments and sequences. For reasons of space and consistency the ERG consolidates these and presents:

- A fully incremental analysis, with the treatment sequences that are compared ranked in order of increasing cost.
- The pairwise cost effectiveness estimates of UPA containing sequence against the other treatment sequences that are compared.
- The pairwise cost effectiveness estimates of UPA+MTX containing sequence against the other treatment sequences that are compared.

The ERG presentation of results adopts a common format for all positions sought in order to ease scanning of results, despite some elements being redundant for some comparisons; e.g. for the MTX intolerant UPA+MTX does not feature as a comparator.

Due to the staggered submission process and ongoing issues with the company submitted model, the company results reported in section 5.2.9 are based upon the word document addendum received by the ERG on the 27th August 2019. As a consequence, the ERG reported pairwise ICERs are subject to rounding errors.

The ERG has cross checked the results reported in Section 5.2.9 with those generated by the final company model received on the 29 August. There are reasonable differences between these and those of the original CS, with the revised ICERs typically being somewhat better than those produced by the originally submitted model even when the modelling using the original model with the updates UPA PAS of [redacted]. These improvements arise from two sources:

- The company revising the visual basic of the model so that those modelled as transitioning from moderate RA to severe RA do not see their HAQ rebound to their original baseline when they were with moderate RA, but rebound to the HAQ score that is modelled when they transition to severe RA.
- The revised time to treatment discontinuation functions, as outlined in section 5.2.6.3.

The results of Section 5.4 and of the cPAS appendix use the company model receives on the 29 August.

5.2.9.1 Position 1a: Moderate RA, MTX intolerant, RTX tolerant, failed one csDMARD

The company estimates of the cost effectiveness of UPA among moderate RA patients who are MTX intolerant, RTX tolerant and have failed to respond to a single csDMARD are provided in Table 57.

Table 57. Position 1a: Moderate RA, MTX intolerant, RTX tolerant, failed one csDMARD

					ICERs		
	Costs	**QALYs**	**Costs**	**QALYs**	**Increm.**	**UPA**	**UPA+MTX**
Int csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	..	£16,554	..
UPA	[redacted]	[redacted]	[redacted]	[redacted]	£16,554	..	..

Abbreviations: csDMARDs, conventional synthetic disease modifying antirheumatic drugs; ICER, incremental cost-effectiveness ratio; increm., incremental; int., intolerant; MTX, methotrexate; QALYs, quality adjusted life years; UPA, upadacitinib

The cost effectiveness of UPA relative to intensified csDMARDs is estimated to be comfortably below the £20k/QALY threshold.

The probabilistic modelling results in an ICER of £16,248 per QALY and probabilities of UPA being cost effective at thresholds of £20k per QALY and £30k per QALY of 68% and 94% respectively.

5.2.9.2 Position 1b: Moderate RA, MTX tolerant, RTX tolerant, failed one csDMARD

The company estimates of the cost effectiveness of UPA among moderate RA patients who are MTX tolerant, RTX tolerant and have failed to respond to a single csDMARD are provided in Table 58.

Table 58. Position 1b: Moderate RA, MTX tolerant, RTX tolerant, failed one csDMARD

					ICERs		
	Costs	**QALYs**	**Costs**	**QALYs**	**Increm.**	**UPA**	**UPA+MTX**
Int csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	..	£22,659	£21,631
UPA	[redacted]	[redacted]	[redacted]	[redacted]	Ext.Dom.	..	£7,183
UPA+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£21,631	..	..

Abbreviations: csDMARDs, conventional synthetic disease modifying antirheumatic drugs; ext.dom., extended dominated; ICER, incremental cost-effectiveness ratio; increm., incremental; int., intolerant; MTX, methotrexate; QALYs, quality adjusted life years; UPA, upadacitinib

Both UPA and UPA+MTX are estimated to have a cost effectiveness above the £20k/QALY threshold but below the £30k/QALY threshold in pairwise comparisons with intensified cDMARDs. But UPA is extendedly dominated by UPA+MTX.

For the pairwise comparison of UPA with intensified csDMARDs the probabilistic modelling results in an ICER of £23,145 per QALY and probabilities of UPA being cost effective at thresholds £20k per QALY and £30k per QALY of 36% and 75% respectively.

For the pairwise comparison of UPA+MTX with intensified csDMARDs the probabilistic modelling results in an ICER of £23,428 per QALY and probabilities of UPA+MTX being cost effective at thresholds £20k per QALY and £30k per QALY of 32% and 77% respectively.

5.2.9.3 Position 2a: Moderate RA, MTX intolerant, RTX tolerant, failed ≥2 csDMARDs

The company estimates of the cost effectiveness of UPA among moderate RA patients who are MTX intolerant, RTX tolerant and have failed to respond to at least two csDMARDs are provided in Table 59.

Table 59. Position 2a: Moderate RA, MTX intolerant, RTX tolerant, failed ≥2 csDMARDs

					ICERs		
	Costs	**QALYs**	**Costs**	**QALYs**	**Increm.**	**UPA**	**UPA+MTX**
BSC	[redacted]	[redacted]	[redacted]	[redacted]	..	£8,885	..
UPA	[redacted]	[redacted]	[redacted]	[redacted]	£8,885	..	..

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; increm., incremental; MTX, methotrexate; QALYs, quality adjusted life years; UPA, upadacitinib

UPA is estimated to have a very good cost effectiveness compared to BSC of £8,885 per QALY.

The probabilistic modelling results in an ICER of £9,560 per QALY and probabilities of UPA being cost effective at both thresholds of £20k per QALY and £30k per QALY of 100%.

5.2.9.4 Position 2b: Moderate RA, MTX tolerant, RTX tolerant, failed ≥2 csDMARDs

The company estimates of the cost effectiveness of UPA among moderate RA patients who are MTX tolerant, RTX tolerant and have failed to respond to at least two csDMARDs are provided in Table 60.

Table 60. Position 2b: Moderate RA, MTX tolerant, RTX tolerant, failed ≥2 csDMARDs

					ICERs		
	Costs	QALYs	Costs	QALYs	Increm.	UPA	UPA+MTX
MTX	[redacted]	[redacted]	[redacted]	[redacted]	..	£13,568	£13,434
UPA	[redacted]	[redacted]	[redacted]	[redacted]	Ext.Dom.	..	£12,261
UPA+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£13,434	..	..

Abbreviations: ICER, incremental cost-effectiveness ratio; increm., incremental; MTX, methotrexate; QALYs, quality adjusted life years; UPA, upadacitinib

In the pairwise comparisons both UPA and UPA+MTX have a cost effectiveness estimate compared to MTX that is comfortably below the £20k/QALY threshold. The cost effectiveness of UPA+MTX compared to UPA is also well below £20k/QALY.

For the pairwise comparison of UPA with intensified MTX the probabilistic modelling results in an ICER of £14,867 per QALY and probabilities of UPA being cost effective at thresholds £20k per QALY and £30k per QALY of 76% and 97% respectively.

For the pairwise comparison of UPA+MTX with intensified MTX the probabilistic modelling results in an ICER of £15,323 per QALY and probabilities of UPA+MTX being cost effective at thresholds £20k per QALY and £30k per QALY of 75% and 75% respectively.

5.2.9.5 Position 3a: Severe RA, MTX intolerant, RTX tolerant, failed ≥2 csDMARDs

The company estimates of the cost effectiveness of UPA among severe RA patients who are MTX intolerant, RTX tolerant and have failed to respond to at least two csDMARDs are provided in Table 61.

Table 61. Position 3a: Severe RA, MTX intolerant, RTX tolerant, failed ≥2 csDMARDs

					ICERs		
	Costs	QALYs	Costs	QALYs	Increm.	UPA	UPA+MTX
UPA	[redacted]	[redacted]	[redacted]	[redacted]	Reference	..	..
ADA	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant	..
ETN	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant	..
CTZ	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant	..
TFC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant	..
BRC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant	..
SRL	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant	..

					ICERs		
	Costs	QALYs	Costs	QALYs	Increm.	UPA	UPA+MTX
TCZ_{SC}	[redacted]	[redacted]	[redacted]	[redacted]	£502k	£502k SW	..
TCZ_{IV}	[redacted]	[redacted]	[redacted]	[redacted]	Ext.Dom	£506k SW	..

Abbreviations: ADA, adalimumab; BRC, baricitinib; csDMARDs, conventional synthetic disease modifying antirheumatic drugs; CTZ, certolizumab pegol; ETN, etanercept; ext. dom., extended dominated; ICER, incremental cost-effectiveness ratio; increm., incremental; IV, intravenous; MTX, methotrexate; QALYs, quality adjusted life years; SC, subcutaneous; SRL, sarilumab; TCZ, tocilizumab; TFC, tofacitinib; UPA, upadacitinib

UPA is estimated to dominate all the other comparators with the exception of TCZ_{SC}, but the cost effectiveness of TCZ_{SC} relative to UPA is extremely poor due to only minor QALY gains and quite large additional costs resulting in a cost effectiveness estimate for TCZ_{SC} of £502k per QALY.

The probabilistic modelling estimates a cost effectiveness for UPA against TCZ_{SC} of £512k per QALY, and probabilities UPA+MTX being cost effective at thresholds of both £20k per QALY and £30k per QALY of 100%.

5.2.9.6 Position 3b: Severe RA, MTX tolerant, RTX tolerant, failed ≥2 csDMARDs

The company estimates of the cost effectiveness of UPA among severe RA patients who are MTX tolerant, RTX tolerant and have failed to respond to at least two csDMARDs are provided in Table 62.

Table 62. Position 3b: Severe RA, MTX tolerant, RTX tolerant, failed ≥2 csDMARDs

					ICERs		
	Costs	QALYs	ΔCost	ΔQALY	Increm.	UPA	UPA+MTX
UPA	[redacted]	[redacted]				..	£526
UPA+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£526	..	..
IFX+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant	Dominant
ADA+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant	Dominant
ETN+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	£3.7mn SW	Dominant
TFC+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant	Dominant
GOL+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	£1.1mn SW	Dominant
CTZ+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£828,052	£354k SW	£828k SW
BRC+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant	Dominant
TCZ_{SC}+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	£13mn SW	Dominant

					ICERs		
	Costs	QALYs	∆Cost	∆QALY	Increm.	UPA	UPA+MTX
SRL+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	£1.8mn SW	Dominant
TCZ_{IV}+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	£1.2mn SW	Dominant
ABT_{IV}+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	7.3mn SW	Dominant
ABT_{SC}+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant	Dominant

Abbreviations: ABT, abatacept; ADA, adalimumab; BRC, baricitinib; csDMARDs, conventional synthetic disease modifying antirheumatic drugs; CTZ, certolizumab pegol; ETN, etanercept; GOL, golimumab; ICER, incremental cost-effectiveness ratio; IFX, infliximab; increm., incremental; IV, intravenous; MTX, methotrexate; QALYs, quality adjusted life years; SC, subcutaneous; SRL, sarilumab; TCZ, tocilizumab; TFC, tofacitinib; UPA, upadacitinib

UPA is estimated to be somewhat cheaper than all the other comparators, though only slightly cheaper than UPA+MTX. Any comparator patient benefits over UPA involve such an increase in costs as to be clearly outside usual cost effectiveness thresholds. This is with the exception of UPA+MTX which is estimated to have an excellent cost effectiveness estimate of £526 per QALY compared to UPA.

The probabilistic modelling estimates pairwise ICERs for UPA and UPA+MTX against CTZ+MTX of £481k per QALY in the SW quadrant and £1.6mn per QALY in the SW quadrant respectively, with both being estimated to have a 100% probability of cost effectiveness at thresholds of £20k per QALY and £30k per QALY.

5.2.9.7 Position 4a: Severe RA, MTX intolerant, RTX tolerant, failed one bDMARD

The company estimates of the cost effectiveness of UPA among severe RA patients who are MTX intolerant, RTX tolerant and have failed to respond to one bDMARD are provided in Table 63.

Table 63. Position 4a: Severe RA, MTX intolerant, RTX tolerant, failed one bDMARD

					ICERs		
	Costs	QALYs	Costs	QALYs	Increm.	UPA	UPA+MTX
UPA	[redacted]	[redacted]	[redacted]	[redacted]	..	..	..
ADA	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant	..
ETN	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant	..
CTZ	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant	..
TFC	[redacted]	[redacted]	[redacted]	[redacted]	Ext.Dom.	Dominant	..
BRC	[redacted]	[redacted]	[redacted]	[redacted]	Ext.Dom	Dominant	..
SRL	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant	..

					ICERs		
	Costs	QALYs	Costs	QALYs	Increm.	UPA	UPA+MTX
TCZ_{SC}	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant	..
TCZ_{IV}	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant	..

Abbreviations: ADA, adalimumab; BRC, baricitinib; bDMARD, biologic disease modifying antirheumatic drugs; CTZ, certolizumab pegol; ETN, etanercept; ICER, incremental cost-effectiveness ratio; increm., incremental; IV, intravenous; MTX, methotrexate; QALYs, quality adjusted life years; SC, subcutaneous; SRL, sarilumab; TCZ, tocilizumab; UPA, upadacitinib

UPA is estimated to dominate all the other comparators, essentially being estimated to be as effective as all the other treatments but cheaper. This is not due any clinical evidence, but due to the company assuming clinical equivalence which renders the above of questionable relevance.

The probabilistic modelling estimates that UPA no longer dominates TCZ_{SC}, but has a reasonable cost effectiveness estimate of £45,253 per QALY in the SW quadrant. It is also estimated to have a 100% probability of cost effectiveness at thresholds of £20k per QALY and £30k per QALY.

Given the lack of clinical effectiveness evidence for this position the ERG does not further consider it, with the exception of providing the cPAS inclusive results for it in the cPAS appendix.

5.2.9.8 Position 4b: Severe RA, MTX tolerant, RTX intolerant, failed one bDMARD

The company estimates of the cost effectiveness of UPA among severe RA patients who are MTX tolerant, RTX intolerant and have failed to respond to one bDMARD are provided in Table 64.

Table 64. Position 4b: Severe RA, MTX tolerant, RTX intolerant, failed one bDMARD

					ICERs		
	Costs	QALYs	ΔCost	ΔQALY	Increm.	UPA	UPA+MTX
UPA+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Reference		
UPA	[redacted]	[redacted]	[redacted]	[redacted]	Dominated		Dominant
ADA+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant	Dominant
IFX+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant	Dominant
ETN+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant	Dominant
CTZ+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant	Dominant
GOL+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant	Dominant
TFC+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant	Dominant
BRC+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant	Dominant

					ICERs		
	Costs	QALYs	∆Cost	∆QALY	Increm.	UPA	UPA+MTX
TCZ_{SC}+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	£5.3mn SW	Dominant
SRL+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	£1.5mn SW	Dominant
TCZ_{IV}+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£2,155,336	£686k SW	£2.1mn SW
ABT_{IV}+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	£1.2mn SW	Dominant
ABT_{SC}+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	£1.5mn SW	Dominant

Abbreviations: ABT, abatacept; ADA, adalimumab; BRC, baricitinib; csDMARDs, conventional synthetic disease modifying antirheumatic drugs; CTZ, certolizumab pegol; ETN, etanercept; GOL, golimumab; ICER, incremental cost-effectiveness ratio; IFX, infliximab; increm., incremental; IV, intravenous; MTX, methotrexate; QALYs, quality adjusted life years; SC, subcutaneous; SRL, sarilumab; TCZ, tocilizumab; TFC, tofacitinib; UPA, upadacitinib

Unusually, given the results of the original company analyses at the previous UPA PAS, the revised UPA PAS and revised model causes UPA+MTX to be estimated to be both cheaper and more effective than UPA and so to dominate it. UPA+MTX is also estimated to dominate or have an extremely good cost effectiveness against all the other comparators.

The probabilistic model estimates that UPA has a good cost effectiveness relative to TCZ_{IV}+MTX of £2mn per QALY in the SW quadrant, while UPA+MTX dominates TCZ_{IV}+MTX. Both are estimates to have a 100% probability of cost effectiveness at thresholds of £20k per QALY and £30k per QALY.

5.2.9.9 Position 5: Severe RA, MTX tolerant, RTX tolerant, failed one bDMARD

The company estimates of the cost effectiveness of UPA among severe RA patients who are MTX tolerant, RTX tolerant and have failed to respond to one bDMARD are provided in Table 65.

Table 65. Position 5: Severe RA, MTX tolerant, RTX tolerant, failed one bDMARD

					ICERs		
	Costs	QALYs	∆Cost	∆QALY	Increm.	UPA	UPA+MTX
RTX+MTX	[redacted]	[redacted]	[redacted]	[redacted]	..	Dominated	Dominated
UPA	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated	£461k
UPA+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	..	..

Abbreviations: ICERs, incremental cost-effectiveness ratio; increm., incremental; MTX, methotrexate; QALYs, quality-adjusted life years; RTX, rituximab; UPA, upadacitinib

Despite the increase in the UPA PAS, RTX+MTX is estimated to dominate both UPA and UPA+MTX. UPA+MTX has a poor cost effectiveness compared to UPA.

The probabilistic modelling estimates that at central estimates RTX+MTX dominates both UPA and UPA+MTX. Perhaps surprisingly in the light of this, it still estimates probabilities of UPA being cost effective at thresholds of £20k per QALY and £30k per QALY of 43% and 40%, while the corresponding probabilities for UPA+MTX are reported as 45% and 45%.

5.2.9.10 Position 6: Severe RA, MTX tolerant, RTX tolerant, failed RTX

The company estimates of the cost effectiveness of UPA among severe RA patients who are MTX tolerant, RTX tolerant and have failed to respond to RTX are provided in Table 66.

Table 66. Position 6: Severe RA, MTX tolerant, RTX tolerant, failed RTX

					ICERs		
	Cost	**QALY**	**∆Cost**	**∆QALY**	**Increm.**	**UPA**	**UPA+MTX**
UPA	[redacted]	[redacted]	[redacted]	[redacted]		..	£10,000
UPA+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£10,000	..	..
SRL+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	£988kSW	Dominant
TCZ_{IV}+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£420k	£298kSW	£420kSW

Abbreviations: ICERs, incremental cost-effectiveness ratio; increm., incremental; IV, intravenous; MTX, methotrexate; QALYs, quality-adjusted life years; SRL, sarilumab; TCZ, tocilizumab; UPA, upadacitinib

The cost effectiveness of UPA+MTX against UPA is good at £10,000 per QALY. Nut the clinical effectiveness for UPA is based upon an assumed equivalence with BRC+MTX so should probably be disregarded for this comparison. SRL+MTX is dominated by UPA+MTX, while the cost effectiveness of TCZ_{IV}+MTX is very poor.

The probabilistic modelling estimates pairwise ICERs for UPA and UPA+MTX against TCZ_{IV}+MTX of £304k per QALY in the SW quadrant and £445k per QALY in the SW quadrant respectively, with both being estimated to have a 100% probability of cost effectiveness at thresholds of £20k per QALY and £30k per QALY.

5.2.10 Sensitivity analyses

The company scenario analyses for the modelling among moderate RA patients suggests results are reasonably stable for most of the scenario analyses, but are sensitive to:

- The UPA drug costs (±25%)
- Whether the HAQ progression for csDMARDs is linear
- The comparator drug costs (±25%)
- Mapped pain scores (±25%)

The company scenario analyses for the modelling among severe RA patients for the pairwise comparison with CTZ+MTX suggests results are reasonably stable for most of the scenario analyses, but are sensitive to:

- The UPA proportion with a moderate response (95% CI)
- The comparator proportion with a moderate response (95% CI)

- The UPA proportion with a good response (95% CI)
- The comparator proportion with a good response (95% CI)
- Patients' HAQ scores, presumably at baseline
- The HAQ effect upon the hazard ratio for mortality

But these sensitivities are in the context of UPA+MTX dominating CTZ+MTX. It is unclear whether the values reported in figures A.3 and A.4 of the company addendum sent to NICE on 23rd August are bounded by £0 or if this is an error of reporting. It seems likely that the sensitivity to the HAQ HR for mortality is due to extremely small QALY differences being simulated.

5.2.11 Model validation and face validity check

The model is programmed within Visual Basic for Applications (VBA), with an Excel front end that acts as a database store of values. VBA is not on the list of NICE approved software.

NICE has instructed the ERG that the elements of the model which are programmed in VBA should be treated as a "black box" and that the ERG is not required to parse the programming accuracy of these elements of the electronic model.

The ERG provided a range of validation exercises for the company model:

- Black box testing: The model inputs were changed and the output was checked to assess whether in line with expectations. This also sought to replicate the TA375 model structure to the extent possible as presented in Section 5.2.11.1.
- Comparison with TA375 model: The company has provided estimates of its model attempting to replicate the results of the TA375 model. These are reported in Section 5.2.11.2 below. NICE agreed an approach whereby the ERG used the TA375 model to help validate the outputs of the company model as presented in Section 5.2.11.3. However, due to time constraints and the staggered nature of the CS this has not been possible before the ERG report submission deadline.
- Model input values were cross-checked, with discrepancies presented in Sections 5.3.2 and 5.3.3.
- Consideration of the stated model structure, how it compared with those of previous NICE assessments and the degree to which it incorporated the ERG and/or final appraisal determination (FAD) recommended model changes of those

assessments. The innovations of the current model compared to the model of TA375 are reviewed in greater detail in sections 5.3.4.3, 5.3.4.6, 5.3.4.5 and 5.3.4.6 below.

5.2.11.1 Black box testing

A variety of black box testing has been undertaken by the ERG, which has led to some major model revisions by the company. Where particular concerns have arisen these are highlighted in the relevant sections of section 5.3 below

5.2.11.2 Company model outputs compared to TA375 model

The company addendum received by the ERG on the 29 August provides the results of a model validation exercise that compares the ICERs the company model estimates when applying the TA375 HAQ to pain mapping with those of TA375 for severe RA patients (Table 67).

Table 67. Model validation vs TA375 model: severe RA bDMARDs vs MTX ICERs

	Company model	TA375 base case
MTX	Reference	Reference
ADA + MTX	£41,853	£41,567
ETN + MTX	£40,504	£42,494
IFX + MTX	£38,978	£38,503
CTZ + MTX	£41,287	£39,924
GOL + MTX	£42,060	£41,611

Abbreviations: ADA, adalimumab, bDMARD, biologic disease modifying antirheumatic drug; CTZ, certolizumab pegol, ETN, etanercept, GOL, golimumab, ICER, incremental cost-effectiveness ratio; IFX, infliximab, MTX, methotrexate, TCZ, tocilizumab

This provides reassurance for the modelling of severe RA patients when using the company model.

For the validation among moderate RA patients the company provides the following (Table 68).

Table 68. Model validation vs TA375 model: moderate RA ADA+MTX vs MTX ICERs

	Company model	TA375 base case
MTX	Reference	Reference
ADA + MTX	£63,293	£63,513

Abbreviations: ADA, adalimumab, MTX, methotrexate

It should be noted that the main innovation of the company model is in the modelling of moderate RA patients, and how they transition to severe RA. It appears that this aspect of the company model was turned off for the above validation exercise. It would have been helpful if the company had provided an additional comparison with this aspect of the model turned on. As shown in Section 5.3.4.4 below it has a considerable impact upon model results.

5.2.11.3 TA375 model outputs compared to company model

Multiple revisions to the UPA PAS, late delivery (27 August) of company results and late-breaking revisions to the company's economic model (final version received 29 August) have required the revision and re-examination of key aspects of the ERG's work during this appraisal. The ERG has therefore not had sufficient time to run the TA375 model with similar settings to those of the company model as a model validation cross check.

5.3 ERG cross check and critique

5.3.1 Base case results

The ERG has re-run the company model received on the 27 August 2019 and derives results that cross check with those reported in Section 5.2.9 above. The only exception to this is the results for UPA+MTX at Position 5, with the ERG cross check resulting in the following.

Table 69. Position 5: Severe RA, MTX tolerant, RTX tolerant, failed one bDMARD: ERG cross check

					ICERs		
	Costs	**QALYs**	**∆Cost**	**∆QALY**	**Increm.**	**UPA**	**UPA+MTX**
RTX+MTX	[redacted]	[redacted]	[redacted]	[redacted]	..	Dominated	Dominated
UPA+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated	..
UPA	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	..	Dominant

Abbreviations: ICERs, incremental cost-effectiveness ratio; increm., incremental; MTX, methotrexate; QALYs, quality-adjusted life years; RTX, rituximab; UPA, upadacitinib

5.3.2 Data Inputs: Correspondence of written submission with sources cited

The written submission broadly corresponds with the cited sources. The exceptions to this are some of the direct drug and administration costs and the HAQ score related inpatient costs.

The cross-check of the direct drug and administration costs is based upon the information in the *Drug_Costs* worksheet of the model.

5.3.2.1 Upadacitinib list price per packet

The CS in Table 2 of Document B and does not provide a pack price for UPA, and only gives an annual list price of [redacted].

The model applies an annual list price cost for UPA of [redacted]. Within the model there is at times some confusion between calendar months and periods of 28 days.

[redacted] The revised UPA PAS is then applied to this list price.

5.3.2.2 Direct drug and administration costs: RTX

The company calculates a direct drug cost of RTX of £2,096 plus an additional £105 administration cost during the response period. RTX is administered as a course of 2 IV administrations, one at baseline and one at two weeks, each of 1,000 mg. The BNF list price of a 500 mg vial of Rixathon® is £785.84 which implies a cost of £3,143 for 2,000 mg. The IV administration cost is £159, which given the requirement for two infusions per course implies a cost of £318.

The company £2,096 corresponds to 6/9 of £3,143. The company £106 corresponds to 6/9 of £159 which is half the intended amount.

TA195 does not specify an assessment period for cessation of RTX, but rather specifies that treatment should only be continued if an adequate response is maintained following retreatment with a dosing interval of at least six months. The costing of RTX in NICE assessments has typically assumed nine-monthly dosing.

Despite the cost of a course of RTX being incurred during the first two weeks the company assumes that this cost extends to nine months. Thereafter it appears that the long term nine-monthly dosing cost is applied pro-rata either as a monthly amount or as a continuous amount; i.e. a patient discontinuing at 12 months would have the initial six-month cost applied and then six months of the long term nine-monthly dosing cost.

Given non-responder rates of 35% in the csDMARD-IR NMA and 39% for RTX in the bDMARD-IR NMA, the RTX costs for these non-responders is too low. But for the majority of patients who respond and remain on treatment given the model structure and assessment of response at six months, the ERG agrees with the company approach provided that the subsequent monthly costing of RTX is similarly applied on a pro-rata basis until treatment discontinuation, as appears to be the case. This will also underestimate the longer-term RTX direct drug costs as some will cease treatment some time before the nine-month re-administration periods, though again this is complicated by

the nine month being an average with actual re-administrations differing between patients.

During both the initial six-month period and the subsequent longer term costing the administration costs are half what they should be.

5.3.2.3 Direct drug and administration costs: ABT_{IV}

The SmPC specifies three loading doses two weeks apart then extending the dosing frequency to four weekly: "Following the initial administration, ORENCIA should be given two and four weeks after the first infusion, then every four weeks thereafter".[305] The company starts the routine dosing frequency on Day 42 whereas the ERG thinks Day 56 is more appropriate. It appears that the company costing includes an additional two weeks ABT_{IV} during the initial six-month assessment period, which at list prices is an additional £454 cost.

5.3.2.4 Direct drug and administration costs: GOL

The GOL SmPC specifies monthly dosing on the same date each month.[306] The company takes this to mean four-weekly dosing. This inflates the GOL cost by 9%.

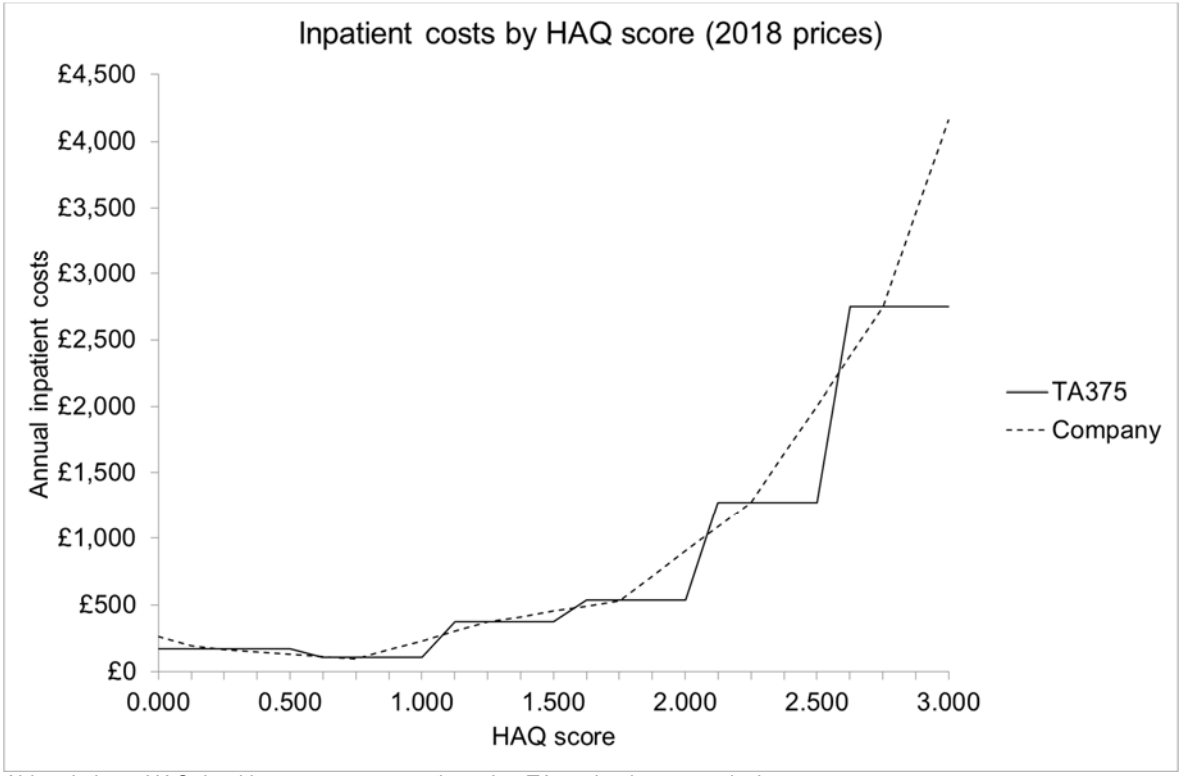
5.3.2.5 Direct drug and administration costs: IFX

The SmPC specifies three loading doses then extending the dosing frequency to eight weekly: "3 mg/kg given as an intravenous infusion followed by additional 3 mg/kg infusion doses at two and six weeks after the first infusion, then every eight weeks thereafter".[307] The company starts the routine dosing frequency on Day 42 whereas the ERG thinks Day 98 is more appropriate. The company costing inflates the IFX costs during the initial six-month assessment period by around 22%.

5.3.2.6 HAQ related inpatient costs: Minor Issue

The company derives HAQ score related inpatient costs from TA375[31]. TA375 provides HAQ related inpatient costs by banded HAQ. The company interpolates reasonable values based upon the TA375 data, though its HAQ cost function has a tendency to lie above that of TA375 for higher HAQ scores. What is more questionable is the extrapolation of the costs for the TA375 banded category of HAQ scores greater than or equal to 2.6. Uprated to 2018 prices using the HCHS as per the company suggests a TA375 cost of £2,747. The company extrapolates from this to estimate costs of £3,456 for a HAQ score of 2.875 and £4,155 for a HAQ score of 3.000.

Figure 11. TA375 and company HAQ score related inpatient costs (2018 prices)



Abbreviations: HAQ, health assessment questionnaire; TA, technology appraisal

In the light of the above the ERG will apply the TA375 HAQ score cost function, updated to 2018 prices. This seems unlikely to much affect results as few patients will be simulated as worsening to these HAQ scores. For instance, the ICER for UPA+MTX versus MTX at position 2b only worsens from £13,434 per QALY to £13,365 per QALY.

5.3.3 Data Inputs: Correspondence of written submission with electronic model

While the written submission generally corresponds with the electronic model it does not fully itemise the model structure and inputs to it. The ERG has tried to address this in Section 5.2.

There appear to be some discrepancies in the equivalence assumptions as reviewed below in Section 5.3.3.1.

5.3.3.1 Clinical equivalence assumptions for treatments with no NMA estimates.

At both position 1a and position 2a, for those transitioning to severe RA first-line BRC in the intensified csDMARDs arm is not assumed to have the same efficacy as BRC+MTX, moderate and good EULAR response rates of 30% and 39% but is rather assumed to have the same efficacy as ADA, moderate and good EULAR response rates of 26% and 28%. This seems likely to bias the analysis in favour of UPA.

5.3.4 ERG commentary on model structure, assumptions and data inputs

5.3.4.1 Model cPAS implementation

An issue arose during the course of the assessment, with the model giving incorrect results for the cPAS analyses. The company submitted a revised model. The ERG has cross checked this through black box testing using the cPAS percentages of the comparator treatments and running the model for moderate RA patients.

As a further cross check the ERG applied a 50% PAS for all the other treatments[1], further halved the cost of UPA[2] and halved the administration costs[3]. The model run that resulted in a cost effectiveness estimate for UPA+MTX versus intensified csDMARDs among moderate RA patients of £21,631 per QALY was then re-run. The direct drug and administration costs in the UPA+MTX arm were 54% of the previous model run while the direct drug and administration costs in the intensified csDMARDs arm were 60% of the previous model run. Further halving the annual BSC costs[4] resulted in the reported drug and administration costs in both arms being 50% of the original model run. This suggests that the model correctly implements the cPAS percentages.

5.3.4.2 Model implementation of upadacitinib PAS

When providing the final 29 August model the company outlined that the comparator treatments should have their cPAS percentages applied in a given column of the Drug Costs worksheet. But the UPA PAS should not be applied in this column. Rather the UPA price inclusive of its PAS should be entered directly into a different column of the Drug Costs worksheet. The ERG has cross checked that using TFC as a proxy, applying a cPAS percentage to equalise its costs with the UPA PAS inclusive price and assuming it has the same response rates as UPA results in the same model outputs when TFC replaces UPA in the moderate RA treatment sequence. This suggests that the model correctly implements the UPA PAS.

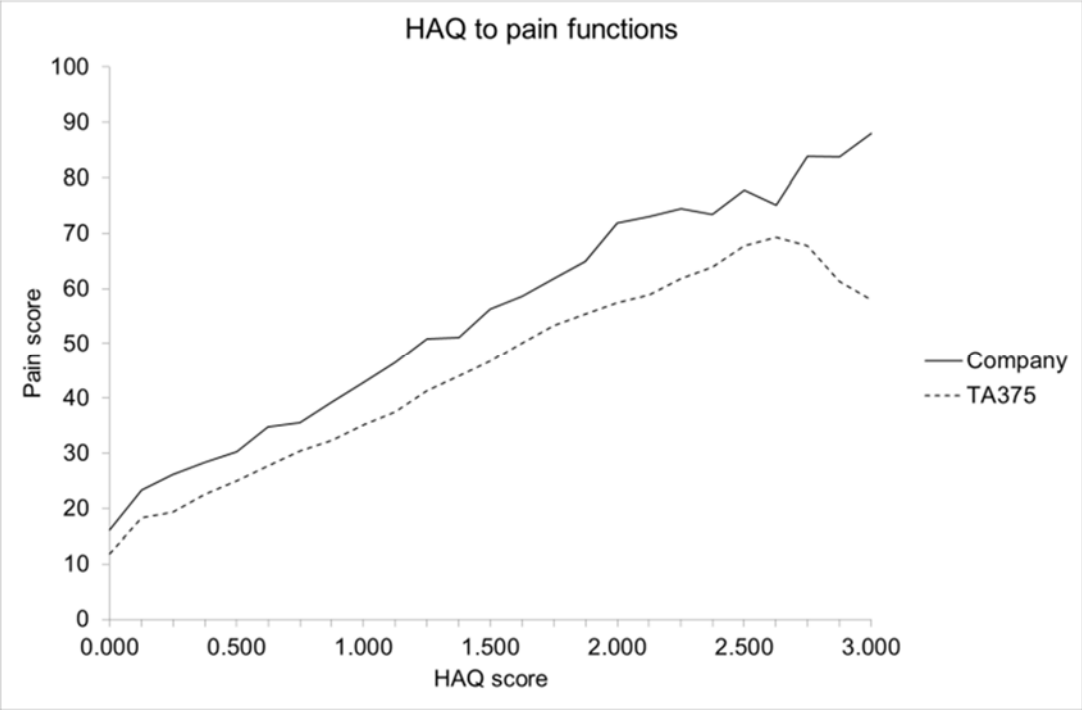
5.3.4.3 Non-TA375: HAQ to pain mapping and QoL

The company estimates a function mapping HAQ to pain from pooled SELECT trial data. TA375[31] estimated a mapping function from National Databank for Rheumatic Diseases (NDB) data. The company uses its HAQ to pain mapping function to simulate pain

[1] Implemented by setting Drug costs cells Y11:Y13, Y19, Y23, Y25, Y32, Y35, Y41, Y43, Y45, Y47, Y48, Y52, Y54, Y56, Y60 equal to 50%. Note that this does not affect the price of CTZ, but CTZ is not in any of the treatment sequences that are modelled for this comparison.
[2] Implemented by multiplying Drug costs cell Z67 by 50%.
[3] Implemented by multiplying Admin costs cells E5:E7 by 50%.
[4] Implemented by multiplying Raw – drug acquisition cost cell D27 by 50%.

scores, with these HAQ and pain scores then being fed into the same functional form as TA375 to estimate patients' QoL. The mapping of HAQ to pain of the company and of TA375 is provided in Figure 12.

Figure 12. Company HAQ to pain function and TA375 HAQ to pain data



Abbreviations: HAQ, health assessment questionnaire; TA, technology appraisal

The two curves appear to reasonably similar in slope but the company mapping lies everywhere above the TA375 curve. The curves clearly diverge towards the upper end of the HAQ scale.

Results are reasonably sensitive to whether the company HAQ to pain function or the TA375 derived HAQ to pain function is applied, the latter having more of a concave shape than the former. The net QALYs of the company base case modelling for Sequence 1b: moderate RA patients who are MTX and RTX tolerant and have failed on one csDMARD fall by around 13% when the mapping of TA375 is applied.

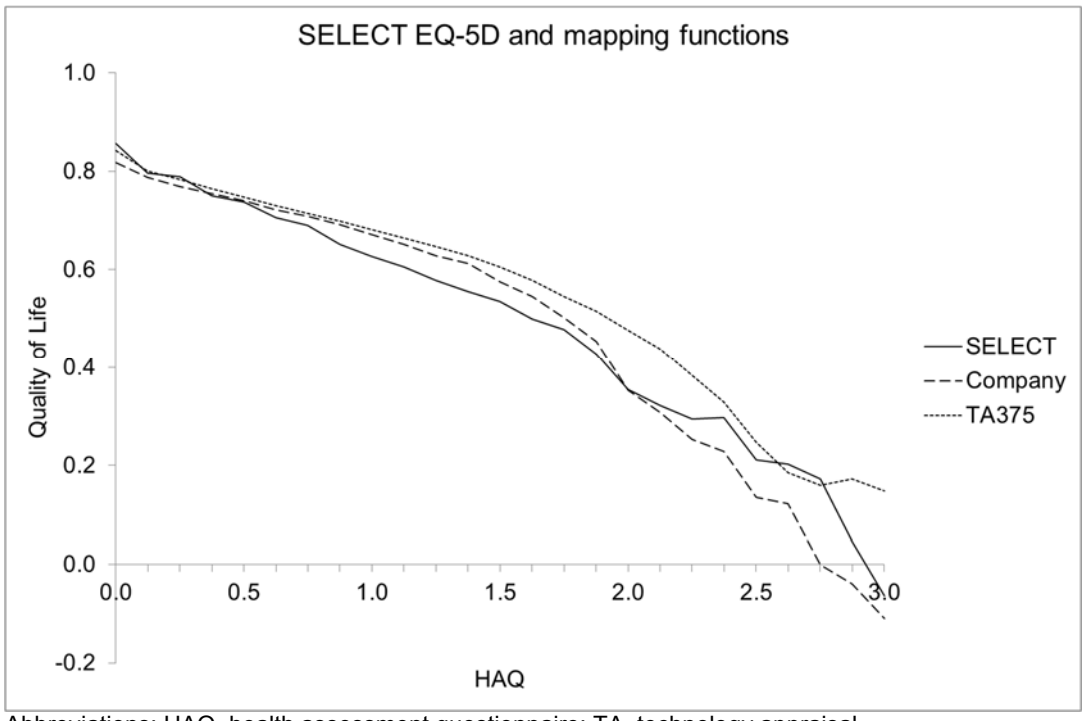
The HTA monograph of TA375[299] (page 260) notes that for simulating the expected pain score associate with the HAQ:

> *"Health Assessment Questionnaire and pain are not related in a simple linear fashion as shown in data from the NDB and data from ERAS, which incorporate 100,398 observations for the NDB and 13,357 from ERAS. Data from the NDB are used to*

populate the mathematical model, with the mean pain score (and its variance) being estimated for each feasible HAQ score."

The quality of life values that result from each approach can be compared with those observed within the SELECT trials.

Figure 13. Company and TA375 HAQ to QoL functions



Abbreviations: HAQ, health assessment questionnaire; TA, technology appraisal

Unfortunately, the company has only supplied the mean SELECT quality of life values by HAQ. There are no measures of dispersion and the number of observations contributing to each data point is unknown. But it seems likely that somewhat fewer observations will underlie the mean values for the very high HAQ values.

Both the company and the TA375 QoL functions are a bit flatter than the SELECT trials' EQ-5D data up to a HAQ of around 1.375. They then both steepen to become steeper than the SELECT trials' EQ-5D data, with the company QoL function steepening somewhat more than that of TA375. This is to the extent that the company QoL function drops below the values of the SELECT trials' EQ-5D data from a HAQ of 2.000. The steepening of the TA375 QoL modelling is less severe and its values converges with the SELECT trials' EQ-5D data towards the upper range of the HAQ, and only lie above the SELECT trials' EQ-5D data for the highest HAQ values of 2.875 and 3.000. Given that the slope of the QoL function is what determines the net QALY gains, when compared

with the SELECT trials' EQ-5D data the ERG has a preference for the TA375 QoL function.

It cannot be definitively determined whether the company mapping based upon SELECT trial data or the TA375 Assessment Group mapping based upon NDB data is superior. But the very large number of observations contributing to the TA375 mapping is a strong argument in its favour, and the ERG preference for the TA375 mapping as a fit for the SELECT trial EQ-5D data further pulls in this direction.

In the light of that above the ERG will apply the TA375 HAQ to pain mapping in its revised base case. It will apply the company HAQ to pain mapping as a sensitivity analysis.

5.3.4.4 Non-TA375: Moderate RA patients worsening to severe RA

It appears that a key model difference from the TA375[31] model is that moderate RA patients can see their DAS-28 worsen to >5.1 and so become severe RA patients. These patients then receive a treatment sequence of bDMARDs.

The model has the facility to turn off this aspect of the model. As an example, for the moderate having failed at least two csDMARDs, among the MTX eligible the cost effectiveness estimates worsen as below (Table 70).

Table 70. Position 2b: Moderate RA, MTX eligible, failed ≥2 csDMARDs: Effect of transfer to severe RA

	ICERs incl. transfer to severe			ICERs excl. transfer to severe		
	Increm.	**UPA**	**UPA+MTX**	**Increm.**	**UPA**	**UPA+MTX**
MTX	..	£13,568	£13,434	..	£22,742	£22,220
UPA	Ext.Dom.	..	£12,261	Ext.Dom.	..	£16,316
UPA+MTX	£13,434	..	..	£22,220	..	..

Abbreviations: csDMARDs, conventional synthetic disease modifying antirheumatic drugs; excl, excluding; ICERs, incremental cost-effectiveness ratio; increm., incremental; MTX, methotrexate; RA, rheumatoid arthritis; UPA, upadacitinib

The modelling of moderate RA patients worsening to have severe RA is a key determinant of the estimated cost effectiveness of UPA among moderate RA patients.

The written submission contains no detail of how this aspect of the model works, what the parameter inputs are or how these parameters were estimated. A brief account of this has been supplied at clarification, with it being determined by the modelling of the change in patients' DAS-28 as reviewed in Section 5.3.4.5 below.

5.3.4.5 Extrapolation: Change in DAS-28 and from moderate RA to severe RA

As outlined in the summary of the model structure, the company ran a repeated measures linear mixed effects model on the SELECT trials' three and six month data to estimate the change in DAS-28 between baseline and timepoint T as a function of the change in HAQ between baseline and timepoint T. Within a hidden worksheet the original company model contained the following function.

$$(\text{DAS-28}_T\text{-DAS-28}_{BASELINE}) = -1.16 + 0.91\ (\text{HAQ}_T\text{-HAQ}_{BASELINE})$$

Both the intercept and the Δ HAQ coefficient were significant with p-values < 0.0001.

The original model did not apply the intercept. The company response to ERG clarifications questions mentions the Δ HAQ coefficient but not the intercept. The company worked example supplied at clarification also only applies the Δ HAQ coefficient and there is no mention of the intercept. The models submitted at clarification and subsequent to clarification have deleted all the references to the intercept term.

Within the front end Excel database to the VBA model it is possible to apply the intercept term. Doing so[5] changes the cost-effectiveness estimates for Position 2b as follows.

Table 71. Position 2b: Moderate RA, MTX eligible, failed ≥2 csDMARDs: Effect of including the intercept term of the Δ HAQ to Δ DAS analysis

	ICERs incl. intercept			ICERs excl. intercept		
	Increm.	**UPA**	**UPA+MTX**	**Increm.**	**UPA**	**UPA+MTX**
MTX	..	£13,568	£13,434	..	£22,742	£22,220
UPA	Ext.Dom.	..	£12,261	Ext.Dom.	..	£16,316
UPA+MTX	£13,434	..	..	£22,220	..	..

Abbreviations: csDMARDs, conventional synthetic disease modifying antirheumatic drugs; excl, excluding; ICERs, incremental cost-effectiveness ratio; increm., incremental; MTX, methotrexate; RA, rheumatoid arthritis; UPA, upadacitinib

The ERG cannot state unequivocally that it has correctly applied the intercept terms as it is unclear how the VBA handles the data stored in the Excel front end, and indeed quite how the intercept term should be interpreted. But it appears that applying the intercept results in the model not simulating any patients worsening to severe RA, as the ICERs that result are the same as those that result from turning off consideration of transitioning from moderate RA to severe RA.

[5] Implemented in the Mod to sev transition worksheet by subtracting 1.16 from cells D5:D57

More generally, a point to note is that within the pooled three and six month data of the SELECT trials not only was the mean change in HAQ an improvement, but it was an improvement for the three subgroups with EULAR responses of none, moderate and good. As a consequence, it appears that much of the data within the regression will relate to HAQ improvements at three and six months.

By definition, those on bDMARDs are assumed to have an unchanging HAQ after the initial treatment effect so the regression is in effect not applied until these patients cease all bDMARD treatment and move onto either cDMARDs or BSC.

It appears that the regression is only really applied among those on cDMARDs and on BSC. But here it is also being applied during extrapolation beyond six months out to as much as 45 years, and in the context of the HAQ worsening. It is not obvious that a regression estimated during the first six months of treatment when the HAQ is generally improving can simply be reversed to apply to situations where the HAQ is worsening during the subsequent 45 years.

The regression appears to imply that for moderate RA patients there is a general improvement in the DAS-28, independent of the changes in the HAQ. The company avoids this by simply not applying the regression intercept. This seems invalid, and suggests that the model overestimates patients' DAS-28 by 1.16. As a consequence, the model will estimate that moderate RA patients on csDMARDs and BSC develop severe RA somewhat sooner than that implied by the company regression. This appears to apply to two circumstances:

- The HAQ of those on csDMARDs worsening while they remain on csDMARDs due to natural progression.
- The HAQ of those on csDMARDs rebounding, by assumption, to baseline when they cease treatment.

In the opinion of the ERG given the company regression, among moderate RA patients the model should estimate an improvement in the DAS-28 independent of the change in HAQ. The model may simulate moderate RA patients developing severe RA too quickly.

Assuming that a regression based upon six-month data during which HAQ improvements were the norm can be reversed to apply over the 45 year time horizon of the model when the HAQ is modelled as worsening is a concern.

5.3.4.6 Difference from TA375: Treatment sequences

The treatment sequences explored naturally show some differences from those of TA375[31], given the greater range of advanced DMARDs which are now available. Rather than review the TA375 treatment sequences, the ERG relies upon expert opinion to determine the probable sequences of treatments. As reviewed in greater detail later, for patients ceasing one type of treatment due to a lack of response the choice of the next in line is guided by:

- Trying a treatment with a different method of action; e.g. a JAK is unlikely to be followed by a JAK.
- Clinical effectiveness among treatments with a given method of action.
- Cost.

The first bullet would apply with less force among those ceasing one type of therapy due to an AE, but this cannot be incorporated in the modelling. The ERG presents its preferred set of treatment sequences later in section 5.4 due to the intervening sections having a bearing upon this.

5.3.4.7 Difference from TA375: Revised treatment cessation curves: Minor issue

The company revised the company model during the course of the assessment, a reasonably major revision being made to the treatment cessation curves as presented in Section 5.2.6.3 above.

The originally presented treatment cessation curves do lie unreasonably above the company digitised IPD data derived from the Kaplan Meier figures in TA375[31]. But the revised curve for the moderate may also not be reasonable. It appears that the company may have simply fitted a generalised gamma to the start and end points of company pseudo Kaplan Meier curves.

The generalised gamma fit to the pseudo Kaplan Meier curve for the severe is reasonable. But the generalised gamma fit to the pseudo Kaplan Meier curve for the moderate appears poor. It seems to tend to lie somewhat below the pseudo Kaplan Meier curve.

If the original generalised gamma is applied for moderate RA patients, at Position 2b the ICER worsens from £13,434 per QALY to £13,601 per QALY. The ERG does not explore this aspect further.

5.3.4.8 Constant EULAR response rates by line of treatment

A key assumption of the modelling is that when applying the results of; e.g., the bDMARD-IR NMA, the EULAR response rates of a treatment does not decline as patients move through lines of treatment; i.e. using TFC as a third-line treatment has exactly the same EULAR response rates among the patients being treated at third-line as using TFC as a first-line treatment among patients being treated at first-line.

It is generally the case that the EULAR response rates of the bDMARD-IR NMA are worse than those of the csDMARD-IR NMA. To the ERG this suggests that there is a tendency for the EULAR response rates of a treatment to decline as patients move through lines of treatment. This may simply be due to those progressing through lines of being a subgroup of patients who tend not to respond and are harder to treat for whatever reason.

If EULAR response rates do decline by line of treatment, it can be argued that there are no estimates for how much it declines among the advanced DMARD experienced population. A simplifying assumption is required. Assuming the same EULAR responses regardless of treatment line may be the most reasonable, and it may not be too serious when treatment sequences of equal length are being compared.

But if EULAR response rates do decline by line of treatment and the treatment sequences that are being compared are not of equal length, it seems likely that this assumption will bias the analysis in favour of the longer treatment sequence. This should be considered if it is felt that UPA will lengthen the treatment sequences patients may receive.

The assumption of constant EULAR response rates by line of treatment may be particularly questionable when assessing UPA later in the treatment pathway. This may apply with particular force to the assessment of UPA among those who have failed to respond to RTX therapy, and it can be noted that in SELECT-BEYOND prior exposure to RTX was only 14%[6].

5.3.4.9 Treatment effect estimates at first-line and at subsequent lines of treatment

The company modelling of UPA among moderate RA patients applies the response rates for the first-line treatment in both the UPA treatment sequence and the comparator sequence using the csDMARD-IR NMA results, which is appropriate. But based upon the

[6] CSR Table 14.1_8.1.2

written submission it appears that the model also applies response rates taken from the csDMARD-IR NMA results for treatment of moderate RA patients at second-line, third-line etc., which seems incorrect. This should be differentiated by arm.

- Those who have failed to respond to UPA should have response rates at second-line, third-line etc. drawn from the bDMARD-IR NMA.
- Those in the comparator arm who have only failed to respond to csDMARDs should have response rates at second-line, third-line etc. drawn from the csDMARD-IR NMA.

When modelling moderate RA patients, patients can worsen to severe RA and so be treated with a sequence of bDMARDs. Again, based upon the written submission, it appears that the company modelling uses the same NMA to estimates the effectiveness of the first-line bDMARD among those moving into severe RA. The same point applies, in that these should be differentiated by arm.

- Those who received UPA when in moderate RA and have since worsened to severe RA should have clinical effectiveness estimates for the first-line bDMARD when severe drawn from the bDMARD-IR NMA.
- Those in the comparator arm who only received csDMARDs when in moderate RA and have since worsened to severe RA should have clinical effectiveness estimates for the first-line bDMARD when severe drawn from the csDMARD-IR NMA.

The EULAR response rates within the cDMARD-IR NMA are better than those of the bDMARD-IR NMA. The company approach biases the clinical effect estimates in favour of UPA.

When modelling severe RA patients on their first bDMARD it appears that the model applies EULAR response rates of the csDMARD-IR NMA to all treatments regardless of whether they are first-line or a subsequent line of treatment. It seems more appropriate to apply the EULAR response rates of the bDMARD-IR NMA to lines of treatment subsequent to the first-line of treatment. It seems likely that the company approach will bias the clinical effect estimates in favour of the less effective treatment.

This can be illustrated by revising the modelling at position 1b of moderate RA patients who are eligible for MTX and RTX. In the light of ERG comments, to abstract from the effects of unequal treatment sequences and the questionable application of MTX

response rates for moderate RA patients UPA+MTX can be compared directly with intensive csDMARDs, with only BSC among non-responders. Those progressing to severe RA can be assumed to have a common treatment sequence of ADA+MTX, followed by RTX+MTX, followed by TCZ_{IV}+MTX followed by BSC. The company approach of applying the response rates of the csDMARD-IR NMA results in the following cost effectiveness estimates.

Table 72. Not differentiating responses by bDMARD experience

	Costs	QALYs	∆Cost	∆QALY	ICER
Int.csDMARDs	[redacted]	[redacted]	[redacted]	[redacted]	
UPA+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£47,649

Abbreviations: bDMARD, biologic disease-modifying antirheumatic drugs; csDMARDs, conventional synthetic disease modifying antirheumatic drugs; ICERs, incremental cost-effectiveness ratio; MTX, methotrexate; QALYS, quality-adjusted life years; RA, rheumatoid arthritis; UPA, upadacitinib

The ERG approach[7] of applying the csDMARD-IR NMA response estimates for those failing to respond to csDMARDs and the bDMARD-IR NMA response estimates for those failing to respond to bDMARDs results in the following cost effectiveness estimates.

Table 73. Differentiating responses by bDMARD experience

	Costs	QALYs	∆Cost	∆QALY	ICER
Int.csDMARDs	[redacted]	[redacted]	[redacted]	[redacted]	
UPA+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£50,159

Abbreviations: bDMARD, biologic disease-modifying antirheumatic drugs; csDMARDs, conventional synthetic disease modifying antirheumatic drugs; ICERs, incremental cost-effectiveness ratio; MTX, methotrexate; QALYS, quality-adjusted life years; RA, rheumatoid arthritis; UPA, upadacitinib

It should be borne in mind that the costs in the above do not take into account the comparator cPAS prices. The main effect of differentiating response rates between the bDMARD naïve and the bDMARD experienced is to reduce the net QALY gains by around 7-8%. Total costs do change slightly and the change in the list prices ICER is less; it worsens by around 5%.

[7] This requires the model to be run twice, the run estimating costs and QALYs for the upadacitinib arm applying the bDMARD-IR NMA response rates for ADA+MTX, RTX+MTX and TCZ_{IV}+MTX and the run estimating the costs and QALYs for the intensive csDMARDs arm applying the cDMARD-IR NMA response rates for ADA+MTX and the bDMARD-IR NMA response rates for RTX+MTX and TCZ_{IV}+MTX.

The ERG will differentiate the source of effectiveness estimates based upon whether patients have only failed to respond to csDMARDs or have failed to respond to at least 1 bDMARD.

5.3.4.10 Natural recovery and the placebo effect

Within the SELECT trials the control arms showed reasonably high ACR20 and ACR50 response rates, and non-negligible ACR70 response rates (Table 74).

Table 74. SELECT trials: Control arm ACR response rates

		PBO/control arm			UPA arm		
SELECT	**Cont.**	**ACR20**	**ACR50**	**ACR70**	**ACR20**	**ACR50**	**ACR70**
COMPARE (Wk 12)	PBO	36%	15%	5%	71%	45%	25%
COMPARE (Wk 26)	PBO	36%	21%	10%	67%	54%	35%
NEXT	PBO	36%	15%	6%	64%	38%	21%
MONOTHERAPY	MTX	41%	15%	3%	68%	42%	23%
BEYOND	PBO	28%	12%	7%	65%	34%	12%

Abbreviations: ACR 20/50/70, American College of Rheumatology 20%/50%/70% response; Cont., control; MTX, methotrexate; PBO, placebo; UPA, upadacitinib

ERG expert opinion notes that this is generally the case within RA trials. The company csDMARD-IR also estimates non-negligible response rates for the pooled PBO control arms: ACR20, ACR50 and ACR70. The degree to which this is due to natural recovery and to which it is a pure PBO effect is unclear. The scope suggests that natural recovery occurs among some patients[11]:

> *"Rheumatoid arthritis is usually a chronic relapsing condition which has a pattern of flare-ups followed by periods of lower disease activity; however, for some people, the disease is constantly progressive."*

To the ERG this suggested that the company model should seek to estimate the cost effectiveness of UPA relative to an active comparator or relative to PBO. But among moderate RA patients the company modelling approach assumes 0% ACR20, 0% ACR50 and 0% ACR70 response rates in the comparator arm. This is most easily seen in the modelling of Sequence 2a, Table 40 being reproduced below for ease of reference.

Table 75. Sequence: 2a: Moderate RA: MTX intolerant, RTX tolerant, failed ≥2 csDMARD: Among moderate patients

Sequence	**First-line**	**Second-line**

1.	UPA	BSC
2.	BSC	..

Abbreviations: BSC, best supportive care; UPA, upadacitinib

Based upon the CS csDMARD-IR NMA, in Sequence 1 first-line UPA has [redacted], and response rates, with these being both the absolute response rates for UPA and the net response rates relative to BSC. This compares to Week 14 net effects during SELECT-MONOTHERAPY, the trial linking UPA monotherapy into the csDMARD-IR NMA, for UPA monotherapy compared to MTX of [redacted] UPA and MTX.

The company clarification response reported 26 week EULAR response rates for SELECT-COMPARE, calculated based upon NRI and LOCF.

Table 76. EULAR response rates: SELECT-COMPARE vs model

			EULAR response rates					
			Cont.		UPA		Net	
SELECT-COMPARE	**Wk**	**Cont**	**Mod.**	**Good**	**Mod.**	**Good**	**Mod.**	**Good**
NRI	26	PBO	24%	17%	19%	54%	-5%	37%
LOCF	26	PBO	36%	18%	31%	59%	-5%	41%
Modelling UPA+csDMARD	..	BSC	0%	0%	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Cont, control; csDMARDs, conventional synthetic disease-modiyfing antirheumatic drugs; EULAR, European League Against Rheumatism; LOCF, last observation carried forward; Mod, moderate; NRI, non-responder imputation; PBO, placebo; UPA, upadacitinib; vs, versus

While the net proportions with a good EULAR response are reasonably aligned between SLEECT-COMPARE and the model inputs, the net proportions with a moderate EULAR response are not aligned with the model inputs somewhat favouring UPA. Note that these values have only been supplied at clarification, there is no ready means of cross checking them.

It is unclear whether the above EULAR response estimates are mapped from ACR rates or are directly reported in the SELECT-COMPARE trial. It should be borne in mind that EULAR response rates are not reported for any of the trials in the clinical effectiveness sections of the CSs. A free text search for “EULAR” in the SELECT-COMPARE CSR only seems to return Boolean EULAR remission, i.e. Yes/No, and does not appear to consider rates of EULAR moderate response and EULAR good response. As a consequence, it is not clear to the ERG quite what is being reported in the above, why

the above was not reported in the clinical effectiveness sections of the CSs and why this has not been reported for the other SELECT trials.

Applying the company ACR response to EULAR response mapping to the central ACR response estimates[8] of the SELECT trials included in the company cDMARD-IR NMA, ignoring the Japanese SELECT-SUNRISE results in the following (Table 77) which can be compared with the modelling for UPA monotherapy and UPA+csDMARDs when compared to BSC.

Table 77. EULAR response rates: SELECT csDMARD-IR trials mapping vs model

			EULAR response rates					
			Control		UPA		Net	
SELECT	**Wk**	**Cont**	**Mod.**	**Good**	**Mod.**	**Good**	**Mod.**	**Good**
For comparison with UPA+csDMARDs modelling								
COMPARE	12	PBO	24%	22%	31%	40%	7%	18%
COMPARE	26	PBO	23%	23%	30%	40%	7%	17%
NEXT	12	PBO	24%	22%	31%	36%	6%	14%
Modelling UPA+csDMARD	..	BSC	0%	0%	[redacted]	[redacted]	[redacted]	[redacted]
For comparison with UPA monotherapy modelling								
MONOTHERAPY	14	MTX	25%	25%	31%	38%	6%	14%
Modelling UPA	..	BSC	0%	0%	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Cont: Control, csDMARDs, conventional synthetic disease modifying antirheumatic drugs; IR, inadequate response; Mod., moderate; vs., versus

The SELECT trials' control arms' mapped response rates are very similar across the three trials reported above. This is perhaps unsurprising In SELECT-COMPARE patients had previously failed to respond adequately to MTX, and while the control arm is PBO patients in all arms remained on background MTX. Similarly, in SELECT-NEXT patients had previously failed to respond adequately to csDMARDs, and while the control arm is PBO patients in all arms remained on background csDMARDs. SELECT-MONOTHERAPY is a little different in that patients had previously failed to respond adequately to MTX and the control arm was MTX, but across all three trials it seems patients in the control arm received either MTX or csDMARDs.

The modelling assumes a much larger net treatment effect over the control arm than was observed during the SELECT trials, due to significant and clinically meaningful response rates in the SELECT trials' control arms being ignored in the modelling. It is not clear

[8] It would be formally more correct to undertake this mapping probabilistically as outlined in section 4.4.1.

whether the response rates in the SELECT trials' control arms arose from natural recovery, a pure PBO effect or some combination of the two but it seems incorrect to entirely ignore it.

If the response rates in the control arms arose from natural recovery or a delayed treatment effect it is definitely incorrect to ignore them.

If the there is no degree of natural recovery or delayed treatment effect among patients and the response rates in the control arms are pure PBO effect, it can be argued that this effect would not apply in day-to-day clinical practice. But in the opinion of the ERG the cost effectiveness estimates should not include the PBO effect in only one arm. To argue otherwise is, in extremis, to suggest that an active treatment which during its RCT showed a minimal but statistically significant benefit over the control arm is still cost effective due to it realising the PBO effect; i.e. a treatment with a statistically significant 5% improvement over a PBO control arm with a 50% response rate should be granted the full 55% response rate, but the comparator arm nothing. Homeopathic remedies, even those with a high price, would be estimated to be very cost effective under this approach.

In the light of this, where the length of treatment sequences differs the ERG will apply a control arm treatment effect for BSC at the line of treatment where it is being compared with an active comparator. When considering the trials' data for comparisons with UPA+MTX, the ERG will apply SELECT-COMPARE data supplied by the company at clarification. The company has only supplied the week 26 SELECT-COMPARE EULAR response rates, as reported in Table 76 above so the ERG does not have the values before rescue therapy. The ERG selects the LOCF values on the basis of LOCF being the default method for analysing secondary variables in the SELECT-COMPARE CSR.

The less optimistic SELECT-NEXT response rates are provided as a scenario analysis. When considering the trials' data for comparisons with UPA, the ERG will apply the Week 12 response rates of SELECT-MONOTHERAPY.

While less immediately obvious, the consideration of natural recovery and the PBO effect in the SELECT trials also applies in all the comparisons where UPA lengthens the treatment sequence such that at some point in the treatment sequences, the n^{th} line of treatment, there is an active treatment in the UPA containing sequence but only BSC in the comparator sequence.

Note that these considerations do not apply when comparing active treatment sequences of the same length. It also seems likely that they will not matter for decision making purposes when comparing sequences of differing lengths if the longer sequence is

estimated to not be cost effective. Including the control arm treatment effect would probably just further worsen the cost effectiveness estimate, and so not affect the decision. They only matter when comparing sequences of differing lengths if the longer sequence is estimated to be cost effective.

5.3.4.11 Possible evidence of ongoing natural recovery

There may be some evidence to support the possibility of natural improvement over time from the SELECT trial data, ACR response rates being reported at Week 1 and Week 12 for SELECT-BEYOND and at Week 12 and Week 26 for SELECT-COMPARE (Table 78).

Table 78. SELECT trials: Control arm ACR responses over time

SELECT	Week	ACR20	ACR50	ACR70
BEYOND	1	10.7%	NA	NA
	12	28.4%	11.8%	6.5%
COMPARE	12	36.4%	14.9%	4.9%
	26	35.6%	20.9%	9.5%

Abbreviations: ACR 20/50/70, American College of Rheumatology 20%/50%/70% response; NA, not applicable

Within SELECT-BEYOND the initial ACR20 response of 10.7% at Week 1 increase to 28.4% by Week 12. Within SELECT-COMPARE the proportion of patients with an ACR20 response remained largely unchanged between Week 12 and Week 26. But among those with an ACR20 response there is evidence of further improvements between Week 12 and Week 26, with the ACR70 response rate roughly doubling from 4.9% to 9.5%. While it cannot be stated unequivocally, this can be interpreted as roughly 5% of the ACR20 but not ACR50 at Week 12 improving to an ACR50 by Week 26, and similarly roughly 5% of the ACR50 but not ACR70 at Week 12 improving to an ACR70 by Week 26.

But within SELECT-COMPARE rescue treatment was permitted in all arms at weeks 14, 18 and 22. Those not achieving at least a 20% improvement in their TJC were permitted to switch treatment, with the PBO arm and ADA arm patients receiving rescue UPA and the UPA arm patients receiving rescue ADA. Rates of rescue were highest in the PBO arm, with the UPA arm having the lowest rates of rescue as per the CSR report table 14.1_1.4.

Table 79. SELECT-COMPARE rescue treatment by arm

Week	PBO	ADA	UPA
14	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]
22	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; PBO, placebo; UPA, upadacitinib

Despite the higher rates of rescue in the PBO arm, the PBO arm ACR20 response rate remains reasonably constant between Week 12 and Week 26. This appears to be due to patients receiving rescue therapy being analysed for secondary variables (i.e. beyond the primary endpoints of ACR20 at 12 weeks and DAS28-CRP clinical remission) on the basis of LOCF from the point of rescue. The ongoing improvement in the distribution across the ACR20, ACR50 and ACR70 response rates in the PBO arm among those remaining on PBO and not receiving rescue therapy may suggest ongoing natural recovery between Week 12 and Week 26.

If there is ongoing natural recovery or some treatment effect among those who receive rescue treatment, the differential rates of rescue therapy between the arms and so differential rates of LOCF being applied may give rise to some concerns about the net effects estimated at Week 26. But any consideration of this may complicated if there might be a treatment effect in addition to natural recovery in the active treatment arms. Perhaps the most that can be said is that rescue therapy and LOCF makes interpretation of the SELECT-COMPARE week 26 ACR response rates more difficult than interpretation of the week 12 ACR response rates. Indeed, NMA estimates of UPA effectiveness at six months rely on meta-regression estimates (see Section 4.4.1).

5.3.4.12 Moderate RA: lines of treatment

As an illustration, for Position 1b (Section 5.2.4.2), the following treatment sequences apply for patients who remain with moderate RA (Table 80).

Table 80. Sequence 1b: Moderate RA, one csDMARD fail, MTX tolerant

Sequence	First-line	Second-line	Third-line	Fourth-line
1	UPA+MTX	Int csDMARDs	MTX	BSC
2	UPA	Int csDMARDs	MTX	BSC
3	Int csDMARDs	MTX	BSC	..

Abbreviations: BSC, best supportive care; cDMARDs, conventional synthetic disease modifying antirheumatic drugs; int., intolerant; MTX, methotrexate; RA, rheumatoid arthritis; UPA, upadacitinib

The patients in this comparison will by definition have already tried and failed MTX before trying UPA. It appears that the model structure assumes that in the above MTX will be associated with the EULAR response rates of the csDMARD-IR NMA. ERG expert opinion is that the above treatment sequences make little clinical sense. ERG opinion is that even if the above treatment sequences do make clinical sense, the EULAR response estimates for MTX subsequent to both UPA and intensified csDMARDs are not be relevant to the patient population being modelled.

ERG expert opinion is that moderate RA patients who remain without a EULAR response typically do not have their treatment withdrawn to then be placed upon BSC, unless this is with a view to provoking a flare to severe RA, so making the advanced DMARDs available. In the current context of only csDMARDs being available for moderate RA patients, ERG expert opinion is that patients without a EULAR response to csDMARDs will remain on whichever combination of csDMARDs proved best, possibly with the addition of courses of steroids. In the context of NICE approving UPA for moderate RA it is less clear what would happen, given the cost of UPA. Moderate RA patients without a EULAR response might remain on UPA, but if so given the cost of UPA it might seem perverse not to try a different advanced DMARD. Or UPA might be withdrawn and patients placed back on whichever combination of csDMARDs proved best.

In the context of the modelling this raises two possibilities:

- Assume that those without a EULAR response to first-line treatment remain on their existing first-line treatment and incur its costs, but remain without a EULAR response.
- Assume that those without a EULAR response revert to csDMARDs in both arms and incur a common cost, but remain without a EULAR response.

But this does not address patient benefits. These patients would by definition not have achieved a EULAR response but they would have had some improvement from baseline. The SELECT trials provide some evidence of an improvement in the HAQ of a mean of 0.123 among those without a EULAR response.

Unfortunately, the economic model has not been constructed to permit an exploration of this. As a consequence, the ERG exploration of this is limited to restricting the number of treatments prior to BSC to a single line of treatment so as to avoid modelling patients who have already failed on MTX having a response to subsequent treatment with MTX.

As an example, in the modelling of moderate RA patients the cost effectiveness of UPA+MTX against intensified csDMARDs if both are only followed by BSC is £35,148 per QALY. If both can be followed by MTX before going onto BSC the cost effectiveness worsens to £44,687 per QALY. While in some manner this approximates to patients with a poor response not having treatment entirely withdrawn, at least for a period, in the opinion of the ERG applying the MTX response rates among patients who have previously failed on MTX is unlikely to be reliable.

The preference of the ERG is to leave the question of what happens to patients who do not respond to intensification of treatment as an unquantified uncertainty. This may mean that the ERG modelled ICERs for moderate RA patients are biased in favour of UPA. The extent of this bias is difficult to quantify.

5.3.4.13 Moderate RA: positioning of UPA pre and post intensified csDMARDs

The company model does not consider the optimal positioning of UPA within the moderate treatment sequence. Common sense suggests it may be more cost effective to trial a patient on intensified cDMARDs, which are very cheap, prior to using UPA among treatment failures, compared to trialling the patient on UPA, which is very expensive, and only trying intensified cDMARDs among treatment failures. As an example, and in the light of previous comments on the inappropriateness of modelling a second response to MTX, among those with moderate RA who have failed one csDMARD this suggests exploring the following possibilities[9].

Table 81. Modified sequence 1b: Moderate RA, one csDMARD fail, MTX tolerant

Sequence	First-line	Second-line	Third-line
1	UPA+MTX	Int csDMARDs	BSC
2	Int csDMARDs	UPA+MTX	BSC
3	UPA	Int csDMARDs	BSC
4	Int csDMARDs	UPA	BSC

Abbreviations: BSC, best supportive care; csDMARDs, conventional synthetic disease modifying antirheumatic drugs; int., intolerant; MTX, methotrexate; RA, rheumatoid arthritis; UPA, upadacitinib

Sequence 1 compared to Sequence 2 involves an additional [redacted] cost and results in an additional [redacted] QALYs, which suggests an ICER of £49,715 per QALY. This result is also robust if the same treatment sequence for those progressing to severe RA is assumed,

[9] The ERG modelling of this sets the treatment sequence for those developing severe RA to be equal across Sequences 1 to 4, and to be equal to the severe RA treatment sequence of Sequence 1 of Table 35 of the CS.

which in the opinion of the ERG is the more reasonable comparison, this yielding and ICER of £77,658 per QALY.

Similarly, Sequence 3 compared to Sequence 4 involves an additional [redacted] cost and results in an additional [redacted] QALYs, which suggests an ICER of £73,369 per QALY. The more reasonable comparison with a common treatment sequence for those progressing to severe RA yields an ICER of £76,793 per QALY.

At conventional willingness to pay thresholds for moderate RA patients the model estimates that it is substantially more cost effective to trial intensified csDMARDs before trialling the somewhat more expensive UPA, much as intuition would suggest. While the cPAS inclusive ICERs cannot be reported here, they do not affect this conclusion.

This suggests that among moderate RA patients, UPA should only be considered towards the end of the line after at least some of the cheaper intensified cDMARDs have been tried. As a consequence, the ERG does not further consider UPA at Position 1 and only considers it at Position 2 for treatment of moderate RA patients.

5.3.4.14 Severe RA: positioning of UPA vs cheaper bDMARDs

A similar argument to Section 5.3.4.13 applies among severe RA patients. For instance, at Position 3a the following comparison is possible.

Table 82. Modified sequence 3a: Severe RA, ≥2 csDMARD fail, MTX intolerant

Sequence	First-line	Second-line	Third-line
1	UPA	ADA	BSC
2	ADA	UPA	BSC

Abbreviations: ADA, adalimumab; BSC, best supportive care; csDMARD, conventional synthetic disease-modifying antirheumatic drug; MTX, methotrexate; RA, rheumatoid arthritis; UPA, upadacitinib

The costs effectiveness of sequence 1 compared to sequence 2 is for it to be cost saving in terms of the drug and administration costs by [redacted], but net costs everywhere else to be roughly the same between the arms. Sequence 1 only confers an additional [redacted] QALYs compared to sequence 2. This does apply the revised [redacted] UPA PAS but does not take into account the substantially lower confidential prices of ADA and its biosimilars.

The cPAS inclusive ICER cannot be reported here, but applying the cPAS price discounts results in Sequence 1 involving reasonably substantial additional direct drug and administration costs compared to Sequence 2. Given the minimal QALY gains that

are modelled, the resulting ICER for Sequence 1 compared to Sequence 2 is in the millions of pounds per QALY.

For the modelling of moderate RA patients who progress to severe RA, to the ERG this suggests that the company Sequence 2 should be revised to move JAK usage from before ADA to after ADA, and for the JAK to be UPA rather than BRC.

But the situation is more complicated for the modelling of severe RA patients due the number of bDMARDs that have been approved by NICE. Some may be more expensive than UPA and some cheaper. It may be less reasonable for UPA to be singled out for the above comparison and the other bDMARDs not considered similarly. As a consequence, the ERG will not particularly seek to take this into account other than noting that TA375 recommended “Start treatment with the least expensive drug (taking into account administration costs, dose needed and product price per dose). This may need to be varied for some people because of differences in the mode of administration and treatment schedules.”

5.3.4.15 Severe RA: multiple advanced DMARDs before RTX

ERG expert opinion is that clinicians will recommend RTX among severe RA patients who have failed to respond to one advanced DMARD. But ERG expert opinion also noted that patients can be well informed and demanding, and that some have a strong preference for oral and SC administration over IV infusion. A proportion of patients may consequently receive more than one advanced DMARD before being treated with RTX. ERG expert opinion is that RTX is tending to fall more into the box of advanced DMARDs rather than being in a box of its own as in the company treatment diagram and necessarily the second-line bDMARD where tolerated.

5.3.4.16 Severe RA: RTX monotherapy

In contrast to IFX which is apparently always administered as IFX+MTX and so cannot be administered to patients who are MTX intolerant, ERG expert opinion is that it is relatively common practice for RTX to be administered as monotherapy among the MTX intolerant and that there is a relatively good evidence base for this.

5.3.4.17 Tociluzumab IV vs tociluzumab SC vs sarilumab SC

The company sequences suggest that the preferred interleukin is TCZ_{IV}. The preference for IV administration obviates consideration of SRL which is only available as SC administration.

ERG expert opinion notes that there is a strong patient preference for SC over IV, and among his patients receiving TCZ only three are receiving TCZ_{IV} compared to 40–50 who are receiving TCZ_{SC}. ERG expert opinion also indicates that if SRL_{SC} were locally cheaper than TCZ_{SC}, SRL_{SC} would be used.

In the light of this the ERG will assume interleukin administration to be SC and will base the treatment sequence on the least costly interleukin.

5.3.4.18 Palliative care costs for moderate RA patients

An annual £742 palliative care cost is applied, which the ERG assumes applies to BSC. This is based upon a palliative care / rescue therapy cost of £720 in TA375[31]. This cost is in addition to the HAQ based inpatient costs.

In the light of this cost being additional to inpatient costs, it may be questionable for the same palliative care costs to be applied to those with moderate RA as to those with severe RA, or indeed for there to be any palliative care costs among those with moderate RA given that patient monitoring is accounted for elsewhere. As an example, setting the BSC cost to zero worsens the company ICER of position 2b from £13,434 per QALY to £16,755 per QALY. But it should be recognised that setting the BSC to zero applied this not only among moderate RA patients who go on to receive BSC, but also among severe RA patients who go on to receive BSC. This scenario analysis consequently exaggerates the effect of setting the BSC among moderate RA patients to zero. It remains an unquantifiable uncertainty and possible model bias in favour of UPA among moderate RA patients.

5.3.4.19 Monitoring frequency

In newly diagnosed RA, NICE CG100[8] recommends monthly monitoring when initiating treatment until disease is stabilised, a review at six months after achieving stability and an annual review thereafter. Longer term monitoring of resource use may consequently be too high. But since no survival gains are modelled the ERG thinks that this is likely to net out between the arms and not particularly affect results.

5.4 Exploratory and sensitivity analyses undertaken by the ERG

5.4.1 ERG preferred treatment sequences: UPA+MTX vs UPA

In general the company finds UPA+MTX to be cost effective relative to UPA where both can be used. As a consequence, for patients tolerant of MTX the ERG only considers UPA+MTX and for patients intolerant of MTX the ERG only considers UPA.

5.4.2 ERG treatment sequences for modelling moderate RA patients

The discussion of Section 5.3.4.13 highlights that for moderate RA patients it is unlikely to be cost effective to trial UPA or UPA+MTX prior to intensifying the much cheaper csDMARDs. The ERG does not consider Position 1 any further.

As a consequence, when modelling moderate RA patients the ERG only compares UPA with intensified csDMARDs and BSC. It should be noted that the ERG also applies the effectiveness estimates of the SELECT trial control arms for BSC at the position where BSC[10] is at the same line of therapy as UPA among moderate RA patients.

ERG expert opinion is that among those progressing from moderate RA to severe RA most will be treated with the cheapest advanced DMARD, ADA. Those tolerant of RTX will tend to receive it next, even if they are intolerant of MTX. Third-line treatment may be an interleukin. But since JAKs and interleukins act through similar pathways, those who received UPA when in moderate RA might tend instead to receive a treatment with a different method of action such as ABT. This will be presented as a scenario analysis by the ERG, and again due to patient preference it will be assumed to be ABT_{SC} rather than ABT_{IV} (Scenario 01). Patients also often have a preference for oral over subcutaneous administration and as a consequence UPA might be used for those with severe disease who did not receive UPA when in moderate RA (Scenario 02). The changes of Scenario 01, ABT_{SC} for severe RA in the UPA arm, and of Scenario 02, UPA for severe RA in the comparator arm, can be combined to yield Scenario 3. Finally, Scenario 4 mirroring the company treatment sequences but also reflecting the considerations of Section 5.3.4.14 can be defined as the sequences of the ERG base case but with the additional insertion of UPA after ADA into the treatment sequence for severe RA in the comparator arm.

5.4.2.1 ERG Position: 2a: Moderate MTX intolerant RTX tolerant failed ≥2 csDMARDs

This results in the following treatment sequences for those with moderate RA who are tolerant of RTX but intolerant of MTX. Note that within this, due to the discussion in sections 5.3.4.9 and 5.3.4.12, UPA is compared on a pairwise basis with Sequences 2a and 2b.

[10] This requires that a placeholder in the model be used for control or placebo BSC to avoid it becoming confused with BSC when all treatment has been ceased and it is assumed no patients have a EULAR response. The ERG has selected TCZ_{IV} for this due to TCZ_{SC} being available and much preferred by patients. This means that in the model implementation TCZ_{IV} is assumed to have zero drug and administration costs, the latter by assuming it to be oral. It is then assumed to have the relevant SELECT trial control arm treatment effectiveness. It can be further argued that the 6 month treatment establishment monitoring costs of £1,752 should be roughly halved to the £828 cost of routing ongoing monitoring.

Table 83. ERG Position: 2a: Moderate RA: MTX intolerant, RTX tolerant, failed ≥2 csDMARDs: Among moderate RA patients

Sequence	Firstine	Second-line
1.	UPA	BSC
2a.	Int.csDMARD	BSC
2b.	PBO / BSC	BSC

Abbreviations: BSC, best supportive care; csDMARD, conventional synthetic disease-modifying antirheumatic drug; PBO, placebo; RA, rheumatoid arthritis; UPA, upadacitinib

The treatment sequences for those worsening to severe RA depend upon which treatment sequence was received when with moderate RA (Table 43).

Table 84. ERG Position: 2a: Moderate RA: MTX intolerant, RTX tolerant, failed ≥2 csDMARDs: Among patients who have progressed to severe

Sequence	First-line	Second-line	Third-line	Fourth-line
1.	ADA	RTX	SRL	BSC
2a.& 2b	ADA	RTX	SRL	BSC

Abbreviations: ADA, adalimumab; BSC, best supportive care; csDMARD, conventional synthetic disease-modifying antirheumatic drug; MTX, methotrexate; RA, rheumatoid arthritis; RTX, rituximab; SRL, sarilumab; UPA, upadacitinib

The bDMARD-IR NMA does not provide estimates for RTX and the ERG has applied those of RTX+MTX. This may be too optimistic.

And the following scenario analyses for those progressing to severe RA.

Table 85. ERG Position: 2a: Moderate RA: MTX intolerant, RTX tolerant, failed ≥2 csDMARDs: Among patients who have progressed to severe: Scenario 01

Sequence	First-line	Second-line	Third-line	Fourth-line
1.	ADA	RTX	ABT_{SC}	BSC
2a.& 2b	ADA	RTX	SRL	BSC

Abbreviations: ADA, adalimumab; ABT, abatacept; BSC, best supportive care; csDMARD, conventional synthetic disease-modifying antirheumatic drug; MTX, methotrexate; RA, rheumatoid arthritis; RTX, rituximab; SC, subcutaneous; SRL, sarilumab; UPA, upadacitinib

The bDMARD-IR NMA does not provide estimates for ABT_{SC} and the ERG has applied those of TCZ_{SC}.

Table 86. ERG Position: 2a: Moderate RA: MTX intolerant, RTX tolerant, failed ≥2 csDMARDs: Among patients who have progressed to severe: Scenario 02

Sequence	First-line	Second-line	Third-line	Fourth-line
1.	ADA	RTX	SRL	BSC
2a.& 2b	ADA	RTX	UPA	BSC

Abbreviations: ADA, adalimumab; ABT, abatacept; BSC, best supportive care; csDMARD, conventional synthetic disease-modifying antirheumatic drug; MTX, methotrexate; RA, rheumatoid arthritis; RTX, rituximab; SC, subcutaneous; SRL, sarilumab; UPA, upadacitinib

The above also suggests a Scenario 03 of third-line treatment of severe RA patients with ABT_{SC} following treatment with UPA when in moderate RA and with UPA following treatment with intensified csDMARD or PBO/BSC when in moderate RA.

The ERG will also model treatment sequences for those who have progressed to severe that mirror the assumptions of the company but also reflect the considerations of Section 5.3.4.14.

Table 87. ERG Position: 2a: Moderate RA: MTX intolerant, RTX tolerant, failed ≥2 csDMARDs: Among patients who have progressed to severe RA: Scenario 04

Sequence	First-line	Second-line	Third-line	Fourth-line	Fifth-line
1.	ADA	RTX	SRL	BSC	..
2a.& 2b	ADA	UPA	RTX	SRL	BSC

Abbreviations: ADA, adalimumab; ABT, abatacept; BSC, best supportive care; csDMARD, conventional synthetic disease-modifying antirheumatic drug; MTX, methotrexate; RA, rheumatoid arthritis; RTX, rituximab; SC, subcutaneous; SRL, sarilumab; UPA, upadacitinib

Scenario 4 is subject to the concerns around possible biases that may arise from modelling sequences of differing lengths when combined with the working assumption of there being no decline in EULAR response rates by line of treatment.

5.4.2.2 ERG Position: 2b: Moderate MTX tolerant RTX tolerant failed ≥2 csDMARDs

This results in the following treatment sequences for those with moderate RA who are tolerant of RTX and tolerant of MTX. Note that within this, due to the discussion of Sections 5.3.4.12 and 5.3.4.13 UPA+MTX is compared on a pairwise basis with Sequences 2a and 2b.

Table 88. ERG Position: 2b: Moderate RA: MTX tolerant, RTX tolerant, failed ≥2 csDMARDs: Among moderate patients

Sequence	First-line	Second-line
1.	UPA+MTX	BSC
2a.	Int.csDMARD	BSC
2b.	PBO / BSC	BSC

Abbreviations: BSC, best supportive care; csDMARD, conventional synthetic disease-modifying antirheumatic drug; MTX, methotrexate; PBO, placebo; RA, rheumatoid arthritis; RTX, rituximab; UPA, upadacitinib

The ERG also explores MTX at second-line followed by BSC at third-line as Scenario 00.

The treatment sequences for those worsening to severe RA depend upon which treatment sequence was received when with moderate RA (Table 43).

Table 89. ERG Position: 2b: Moderate RA: MTX tolerant, RTX tolerant, failed ≥2 csDMARDs: Among patients who have progressed to severe RA

Sequence	First-line	Second-line	Third-line	Fourth-line
1.	ADA+MTX	RTX+MTX	SRL+MTX	BSC
2a.& 2b	ADA+MTX	RTX+MTX	SRL+MTX	BSC

Abbreviations: ADA, adalimumab; BSC, best supportive care; csDMARD, conventional synthetic disease-modifying antirheumatic drug; MTX, methotrexate; RA, rheumatoid arthritis; RTX, rituximab; SRL, sarilumab

And the following scenario analyses for those progressing to severe RA.

Table 90. ERG Position: 2b: Moderate RA: MTX tolerant, RTX tolerant, failed ≥2 csDMARDs: Among patients who have progressed to severe RA: Scenario 01

Sequence	First-line	Second-line	Third-line	Fourth-line
1.	ADA+MTX	RTX+MTX	ABT_{SC}+MTX	BSC
2a.& 2b	ADA+MTX	RTX+MTX	SRL+MTX	BSC

Abbreviations: ABT, abatacept; ADA, adalimumab; BSC, best supportive care; csDMARD, conventional synthetic disease-modifying antirheumatic drug; MTX, methotrexate; RA, rheumatoid arthritis; RTX, rituximab; SC, subcutaneous; SRL, sarilumab; UPA, upadacitinib

The bDMARD-IR NMA does not provide estimates for ABT_{SC}+MTX and the ERG has applied those of TCZ_{SC}+MTX.

Table 91. ERG Position: 2b: Moderate RA: MTX tolerant, RTX tolerant, failed ≥2 csDMARDs: Among patients who have progressed to severe RA: Scenario 02

Sequence	First-line	Second-line	Third-line	Fourth-line
1.	ADA+MTX	RTX+MTX	SRL+MTX	BSC
2a.& 2b	ADA+MTX	RTX+MTX	UPA+MTX	BSC

Abbreviations: ADA, adalimumab; BSC, best supportive care; csDMARD, conventional synthetic disease-modifying antirheumatic drug; MTX, methotrexate; RA, rheumatoid arthritis; RTX, rituximab; SRL, sarilumab; UPA, upadacitinib

The above also suggests a Scenario 03 of third-line treatment of severe RA patients with ABT_{SC}+MTX following treatment with UPA when in moderate RA and with UPA+MTX following treatment with intensified csDMARD or PBO/BSC when in moderate RA.

The ERG will also model treatment sequences for those who have progressed to severe that mirror the assumptions of the company but also reflect the considerations of Section 5.3.4.14.

Table 92. ERG Position: 2b: Moderate RA: MTX tolerant, RTX tolerant, failed ≥2 csDMARDs: Among patients who have progressed to severe RA: Scenario 04

Sequence	First-line	Second-line	Third-line	Fourth-line	Fifth-line
1.	ADA+MTX	RTX+MTX	SRL+MTX	BSC	..
2a.& 2b	ADA+MTX	UPA+MTX	RTX+MTX	SRL+MTX	BSC

Abbreviations: ADA, adalimumab; BSC, best supportive care; csDMARD, conventional synthetic disease-modifying antirheumatic drug; MTX, methotrexate; RA, rheumatoid arthritis; RTX, rituximab; SRL, sarilumab; UPA, upadacitinib

Scenario 4 is subject to the concerns around possible biases that may arise from modelling sequences of differing lengths when combined with the working assumption of there being no decline in EULAR response rates by line of treatment.

5.4.2.3 ERG Seq: 2c: Moderate MTX intolerant RTX intolerant failed ≥2 csDMARDs

This results in the following treatment sequences for those with moderate RA who are intolerant of RTX and intolerant of MTX.

Table 93. ERG Seq: 2c: Moderate RA: MTX intolerant, RTX intolerant, failed ≥2 csDMARDs: Among moderate patients

Sequence	First-line	Second-line
1.	UPA	BSC
2a.	Int.csDMARD	BSC
2b.	PBO / BSC	BSC

Abbreviations: BSC, best supportive care; csDMARD, conventional synthetic disease-modifying antirheumatic drug; MTX, methotrexate; PBO, placebo; RA, rheumatoid arthritis; RTX, rituximab; UPA, upadacitinib

The treatment sequences for those worsening to severe RA depend upon which treatment sequence was received when with moderate RA (Table 43).

Table 94. Sequence: 2c: Moderate RA: MTX intolerant, RTX intolerant, failed ≥2 csDMARDs: Among patients who have progressed to severe RA

Sequence	First-line	Second-line	Third-line
1.	ADA	SRL	BSC
2a.& 2b	ADA	SRL	BSC

Abbreviations: ADA, adalimumab; BSC, best supportive care; csDMARD, conventional synthetic disease-modifying antirheumatic drug; MTX, methotrexate; RA, rheumatoid arthritis; RTX, rituximab; SRL, sarilumab

And the following scenario analyses for those progressing to severe RA.

Table 95. Sequence: 2c: Moderate RA: MTX intolerant, RTX intolerant, failed ≥2 csDMARDs: Among patients who have progressed to severe RA: Scenario 01

Sequence	First-line	Second-line	Third-line
1.	ADA	ABT_{SC}	BSC
2a.& 2b	ADA	SRL	BSC

Abbreviations: ABT, abatacept; ADA, adalimumab; BSC, best supportive care; csDMARD, conventional synthetic disease-modifying antirheumatic drug; MTX, methotrexate; RA, rheumatoid arthritis; RTX, rituximab; SC, subcutaneous; SRL, sarilumab

Table 96. Sequence: 2c: Moderate RA: MTX intolerant, RTX intolerant, failed ≥2 csDMARDs: Among patients who have progressed to severe RA: Scenario 02

Sequence	First-line	Second-line	Third-line
1.	ADA	SRL	BSC
2a.& 2b	ADA	UPA	BSC

Abbreviations: ADA, adalimumab; BSC, best supportive care; csDMARD, conventional synthetic disease-modifying antirheumatic drug; MTX, methotrexate; RA, rheumatoid arthritis; RTX, rituximab; SRL, sarilumab; UPA, upadacitinib

The above also suggests a Scenario 03 of third-line treatment of severe RA patients with ABT_{SC} following treatment with UPA when in moderate RA and with UPA following treatment with intensified csDMARD or PBO/BSC when in moderate RA.

The ERG will also model treatment sequences for those who have progressed to severe that mirror the assumptions of the company but also reflect the considerations of Section 5.3.4.14.

Table 97. ERG Position: 2c: Moderate RA: MTX intolerant, RTX intolerant, failed ≥2 csDMARDs: Among patients who have progressed to severe RA: Scenario 04

Sequence	First-line	Second-line	Third-line	Fourth-line
1.	ADA	SRL	BSC	..
2a.& 2b	ADA	UPA	SRL	BSC

Abbreviations: ADA, adalimumab; BSC, best supportive care; csDMARD, conventional synthetic disease-modifying antirheumatic drug; MTX, methotrexate; RA, rheumatoid arthritis; RTX, rituximab; SRL, sarilumab

Scenario 4 is subject to the concerns around possible biases that may arise from modelling sequences of differing lengths when combined with the working assumption of there being no decline in EULAR response rates by line of treatment.

5.4.3 ERG treatment sequences for modelling severe RA patients

For the modelling of severe RA patients the ERG broadly follows the treatment sequences of the company but with the following changes:

- For patients tolerant of MTX, UPA monotherapy is not considered and only UPA+MTX is modelled.
- The use of TCZ_{IV} and TCZ_{IV}+MTX subsequent to first-line treatment is replaced by SRL and SRL+MTX
- A final treatment line of MTX is not considered.
- Position 4a is not considered due to the company essentially assuming clinical equivalence between the first-line treatments.

5.4.4 ERG model revisions

For its preferred base case the ERG revised the company model of the 29 August along the following lines:

- Correcting the direct drug and administration costs.
- Applying the TA375 HAQ to pain mapping function.

- Applying the TA375 HAQ to inpatient cost mapping function, updated to 2018 prices.
- Applying the csDMARD-IR NMA results for PBO for first-line PBO / BSC for moderate RA patients.
- Applying the csDMARD-IR NMA estimates for bDMARD treatment naïve patients and the bDMARD-IR NMA estimates for bDMARD treatment experienced patients.

Note that the revision of the last bullet mainly affects the treatment efficacy of ADA and ADA+MTX after UPA or UPA+MTX. But for ADA, the company assumptions have the perverse result of applying worse EULAR response rates for the csDMARD-IR NMA than for the bDMARD-IR NMA. For ADA+MTX the company assumptions result in a better EULAR response rates for the csDMARD-IR NMA than for the bDMARD-IR NMA as seems reasonable. As a consequence, in what follows the ICERs for positions 2a and 2c may be too optimistic, while those for Position 2b may be more reliable.

The revision of the last bullet has only been implemented by the ERG for the modelling of moderate RA patients. It is most likely to be a major issue for moderate RA patients because for the first-line treatment of those transitioning to severe RA the bDMARD-IR NMA results are being used in the UPA arm, whereas the csDMARD-IR NMA results are being used in the comparator arms. It also requires that the model be run separately for each arm that it being considered. The modelling of moderate RA patients only considers three arms. The modelling of severe RA patients considers up to 14 arms at times. Time constraints prevented the ERG running this number of analyses.

It should also be noted that the ERG has had to run the company DES model hundreds of times in a very short period of time. It is inevitable that there will be some modelling errors in the results reported below, and the ERG urges the company to cross check these. But unless the ERG has made a major systematic error in its modelling, this seems unlikely to alter the main thrust of the results and the conclusions that flow from them.

5.4.5 ERG Sensitivity analyses

The ERG undertakes the following sensitivity analyses for the modelling of moderate RA patients.

- SA01: Applying the relevant SELECT trials' head-to-head clinical effectiveness estimates for the modelling of moderate RA patients when UPA+MTX or UPA is

being evaluated at the same line of treatment as BSC / PBO. For SELECT-COMPARE the EULAR response rates are applied, with an additional scenario analysis of applying the EULAR response rates mapped from the ACR response rates that were reported in the CS. The EULAR response rates mapped from the ACR response rates that were reported in the CS are applied for SELECT-NEXT and SELECT-MONOTHERAPY.

- SA02: Assuming no natural recovery and no PBO effect for PBO / BSC.
- SA03: Applying the company HAQ to pain mapping function.
- SA04: Applying the company DAS-28 to HAQ intercept term in the modelling of moderate RA patients.

For the modelling of severe RA patients SA01, SA02 and SA04 do not apply. Only SA03 applies. Due to the severe RA modelling comparing UPA with other advanced DMARDs at first-line, and the analyses including the UPA PAS but not the other comparator cPASs, SA03 shows little of interest and so is not reported for the severe for reasons of space.

5.4.6 ERG modelling results: Position 2a: Moderate RA: MTX intolerant, RTX tolerant, failed ≥2 csDMARDs

The ERG base case results for the comparison of UPA with intensified csDMARDs at this position are provided in Table 98.

Table 98. ERG base case: Position 2a vs csDMARDs: Moderate RA: MTX intolerant, RTX tolerant, failed ≥2 csDMARDs

	Costs	QALYs	ΔCost	ΔQALY	ICER
Int. csDMARDs	[redacted]	[redacted]			
UPA	[redacted]	[redacted]	[redacted]	[redacted]	£52,990

Abbreviations: csDMARD, conventional synthetic disease-modifying antirheumatic drug; ICER, incremental cost-effectiveness ratio; MTX, methotrexate; QALYs, quality-adjusted life years; RA, rheumatoid arthritis; RTX, rituximab; UPA, upadacitinib

The ERG base case results for the comparison of UPA with PBO / BSC at this position are provided in Table 99.

Table 99. ERG base case: Position 2a vs PBO / BSC: Moderate RA: MTX intolerant, RTX tolerant, failed ≥2 csDMARDs

	Costs	QALYs	ΔCost	ΔQALY	ICER
PBO / BSC	[redacted]	[redacted]			
UPA	[redacted]	[redacted]	[redacted]	[redacted]	£38,432

Abbreviations: BSC, best supportive care; csDMARD, conventional synthetic disease-modifying antirheumatic drug; ICER, incremental cost-effectiveness ratio; MTX, methotrexate; PBO, placebo; QALYs, quality-adjusted life years; RA, rheumatoid arthritis; RTX, rituximab; UPA, upadacitinib

The scenario and sensitivity analyses for the comparison of UPA with intensified csDMARDs at this position are provided in Table 100.

Table 100. ERG scenario analyses: Position 2a vs csDMARDs: Moderate RA: MTX intolerant, RTX tolerant, failed ≥2 csDMARDs

	ΔCost	ΔQALY	ICER
Base case sequences	[redacted]	[redacted]	£52,990
Scenario 01 sequences	[redacted]	[redacted]	£57,335
Scenario 02 sequences	[redacted]	[redacted]	£63,220
Scenario 03 sequences	[redacted]	[redacted]	£67,565
Scenario 04 sequences	[redacted]	[redacted]	£66,328
SA03: Company HAQ to pain mapping	[redacted]	[redacted]	£47,006
SA04: Company HAQ to DAS-28 intercept	[redacted]	[redacted]	£56,626

Abbreviations: BSC, best supportive care; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAS-28, disease activity score in 28 joints; HAQ, health assessment questionnaire; ICER, incremental cost-effectiveness ratio; MTX, methotrexate; PBO, placebo; QALYs, quality-adjusted life years; RA, rheumatoid arthritis; RTX, rituximab; UPA, upadacitinib

The scenario and sensitivity analyses for the comparison of UPA with PBO / BSC at this position are provided in Table 101.

Table 101. ERG scenario analyses: Position 2a vs PBO / BSC: Moderate RA: MTX intolerant, RTX tolerant, failed ≥2 csDMARDs

	∆Cost	∆QALY	ICER
Base case sequences	[redacted]	[redacted]	£38,432
Scenario 01 sequences	[redacted]	[redacted]	£41,991
Scenario 02 sequences	[redacted]	[redacted]	£47,907
Scenario 03 sequences	[redacted]	[redacted]	£51,466
Scenario 04 sequences	[redacted]	[redacted]	£46,354
SA01a: COMPARE EULAR	[redacted]	[redacted]	n.a.
SA01b: COMPARE EULAR mapped	[redacted]	[redacted]	n.a.
SA01c: NEXT EULAR Mapped	[redacted]	[redacted]	n.a.
SA01d: MONOTHERAPY EULAR mapped	[redacted]	[redacted]	£87,847
SA02: PBO / BSC 0% EULAR responses	[redacted]	[redacted]	£17,506
SA03: Company HAQ to pain mapping	[redacted]	[redacted]	£32,545
SA04: Company HAQ to DAS-28 intercept	[redacted]	[redacted]	£41,400

Abbreviations: BSC, best supportive care; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAS-28, disease activity score in 28 joints; EULAR, European League Against Rheumatism; HAQ, health assessment questionnaire; ICER, incremental cost-effectiveness ratio; MTX, methotrexate; n.a., not applicable; PBO, placebo; QALYs, quality-adjusted life years; RA, rheumatoid arthritis; RTX, rituximab; UPA, upadacitinib

5.4.7 ERG modelling results: Position 2b: Moderate RA: MTX tolerant, RTX tolerant, failed ≥2 csDMARDs

The ERG base case results for the comparison of UPA with intensified csDMARDs at this position are provided in Table 102.

Table 102. ERG base case: Position 2b vs csDMARDs: Moderate RA: MTX tolerant, RTX tolerant, failed ≥2 csDMARDs

	Costs	QALYs	∆Cost	∆QALY	ICER
Int. csDMARDs	[redacted]	[redacted]			
UPA+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£47,466

Abbreviations: csDMARD, conventional synthetic disease-modifying antirheumatic drug; ICER, incremental cost-effectiveness ratio; MTX, methotrexate; PBO, placebo; QALYs, quality-adjusted life years; RA, rheumatoid arthritis; RTX, rituximab; UPA, upadacitinib

The ERG base case results for the comparison of UPA with PBO / BSC at this position are provided in Table 103.

Table 103. ERG base case: Position 2b vs PBO / BSC: Moderate RA: MTX tolerant, RTX tolerant, failed ≥2 csDMARDs

	Costs	QALYs	∆Cost	∆QALY	ICER
PBO / BSC	[redacted]	[redacted]			
UPA+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£35,958

Abbreviations: csDMARD, conventional synthetic disease-modifying antirheumatic drug; ICER, incremental cost-effectiveness ratio; MTX, methotrexate; PBO, placebo; QALYs, quality-adjusted life years; RA, rheumatoid arthritis; RTX, rituximab; UPA, upadacitinib

The scenario and sensitivity analyses for the comparison of UPA with intensified csDMARDs at this position are provided in Table 104.

Table 104. ERG scenario analyses: Position 2b vs csDMARDs: Moderate RA: MTX tolerant, RTX tolerant, failed ≥2 csDMARDs

	∆Cost	∆QALY	ICER
Base case sequences	[redacted]	[redacted]	£47,466
Scenario 01 sequences	[redacted]	[redacted]	£51,130
Scenario 02 sequences	[redacted]	[redacted]	£56,678
Scenario 03 sequences	[redacted]	[redacted]	£60,272
Scenario 04 sequences	[redacted]	[redacted]	£57,703
SA03: Company HAQ to pain mapping	[redacted]	[redacted]	£42,014
SA04: Company HAQ to DAS-28 intercept	[redacted]	[redacted]	£50,874

Abbreviations: BSC, best supportive care; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAS-28, disease activity score in 28 joints; HAQ, health assessment questionnaire; ICER, incremental cost-effectiveness ratio; MTX, methotrexate; PBO, placebo; QALYs, quality-adjusted life years; RA, rheumatoid arthritis; RTX, rituximab; UPA, upadacitinib

The scenario and sensitivity analyses for the comparison of UPA with PBO / BSC at this position are provided in Table 105.

Table 105. ERG scenario analyses: Position 2b vs PBO / BSC: Moderate RA: MTX tolerant, RTX tolerant, failed ≥2 csDMARDs

	∆Cost	∆QALY	ICER
Base case sequences	[redacted]	[redacted]	£35,958
Scenario 01 sequences	[redacted]	[redacted]	£39,308
Scenario 02 sequences	[redacted]	[redacted]	£44,619
Scenario 03 sequences	[redacted]	[redacted]	£47,892
Scenario 04 sequences	[redacted]	[redacted]	£43,507
SA01a: COMPARE EULAR	[redacted]	[redacted]	£44,163
SA01b: COMPARE EULAR mapped	[redacted]	[redacted]	£69,164
SA01c: NEXT EULAR Mapped	[redacted]	[redacted]	£94,563

	∆Cost	∆QALY	ICER
SA01d: MONOTHERAPY EULAR mapped	[redacted]	[redacted]	n.a.
SA02: PBO / BSC 0% EULAR responses	[redacted]	[redacted]	£16,729
SA03: Company HAQ to pain mapping	[redacted]	[redacted]	£30,512
SA04: Company HAQ to DAS-28 intercept	[redacted]	[redacted]	£38,757

Abbreviations: BSC, best supportive care; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAS-28, disease activity score in 28 joints; EULAR, European League Against Rheumatism; HAQ, health assessment questionnaire; ICER, incremental cost-effectiveness ratio; MTX, methotrexate; n.a., not applicable; PBO, placebo; QALYs, quality-adjusted life years; RA, rheumatoid arthritis; RTX, rituximab; UPA, upadacitinib

5.4.8 ERG modelling results: Position 2c: Moderate RA: MTX intolerant, RTX intolerant, failed ≥2 csDMARDs

The ERG base case results for the comparison of UPA with intensified csDMARDs at this position are provided in Table 106.

Table 106. ERG base case: Position 2c vs csDMARDs: Moderate RA: MTX intolerant, RTX intolerant, failed ≥2 csDMARDs

	Costs	QALYs	∆Cost	∆QALY	ICER
Int. csDMARDs	[redacted]	[redacted]			
UPA	[redacted]	[redacted]	[redacted]	[redacted]	£52,359

Abbreviations: csDMARD, conventional synthetic disease-modifying antirheumatic drug; ICER, incremental cost-effectiveness ratio; MTX, methotrexate; PBO, placebo; QALYs, quality-adjusted life years; RA, rheumatoid arthritis; RTX, rituximab; UPA, upadacitinib

The ERG base case results for the comparison of UPA with PBO / BSC at this position are as provided in Table 107.

Table 107. ERG base case: Position 2c vs PBO / BSC: Moderate RA: MTX intolerant, RTX intolerant, failed ≥2 csDMARDs

	Costs	QALYs	∆Cost	∆QALY	ICER
PBO / BSC	[redacted]	[redacted]			
UPA	[redacted]	[redacted]	[redacted]	[redacted]	£37,991

Abbreviations: csDMARD, conventional synthetic disease-modifying antirheumatic drug; ICER, incremental cost-effectiveness ratio; MTX, methotrexate; PBO, placebo; QALYs, quality-adjusted life years; RA, rheumatoid arthritis; RTX, rituximab; UPA, upadacitinib

The scenario and sensitivity analyses for the comparison of UPA with intensified csDMARDs at this position are as below.

Table 108. ERG scenario analyses: Position 2c vs csDMARDs: Moderate RA: MTX intolerant, RTX intolerant, failed ≥2 csDMARDs

	ΔCost	ΔQALY	ICER
Base case sequences	[redacted]	[redacted]	£52,359
Scenario 01 sequences	[redacted]	[redacted]	£59,025
Scenario 02 sequences	[redacted]	[redacted]	£66,968
Scenario 03 sequences	[redacted]	[redacted]	£73,633
Scenario 04 sequences	[redacted]	[redacted]	£70,860
SA03: Company HAQ to pain mapping	[redacted]	[redacted]	£45,755
SA04: Company HAQ to DAS-28 intercept	[redacted]	[redacted]	£56,626

Abbreviations: BSC, best supportive care; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAS-28, disease activity score in 28 joints; HAQ, health assessment questionnaire; ICER, incremental cost-effectiveness ratio; MTX, methotrexate; PBO, placebo; QALYs, quality-adjusted life years; RA, rheumatoid arthritis; RTX, rituximab; UPA, upadacitinib

The scenario and sensitivity analyses for the comparison of UPA with PBO / BSC at this position are provided in Table 109.

Table 109. ERG scenario analyses: Position 2c vs PBO / BSC: Moderate RA: MTX intolerant, RTX intolerant, failed ≥2 csDMARDs

	ΔCost	ΔQALY	ICER
Base case sequences	[redacted]	[redacted]	£37,991
Scenario 01 sequences	[redacted]	[redacted]	£43,378
Scenario 02 sequences	[redacted]	[redacted]	£50,812
Scenario 03 sequences	[redacted]	[redacted]	£56,199
Scenario 04 sequences	[redacted]	[redacted]	£50,050
SA01a: COMPARE EULAR	[redacted]	[redacted]	n.a.
SA01b: COMPARE EULAR mapped	[redacted]	[redacted]	n.a.
SA01c: NEXT EULAR Mapped	[redacted]	[redacted]	n.a.
SA01d: MONOTHERAPY EULAR mapped	[redacted]	[redacted]	£76,405
SA02: PBO / BSC 0% EULAR responses	[redacted]	[redacted]	£17,114
SA03: Company HAQ to pain mapping	[redacted]	[redacted]	£31,887
SA04: Company HAQ to DAS-28 intercept	[redacted]	[redacted]	£41,400

Abbreviations: BSC, best supportive care; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAS-28, disease activity score in 28 joints; EULAR, European League Against Rheumatism; HAQ, health assessment questionnaire; ICER, incremental cost-effectiveness ratio; MTX, methotrexate; n.a., not applicable; PBO, placebo; QALYs, quality-adjusted life years; RA, rheumatoid arthritis; RTX, rituximab; UPA, upadacitinib

5.4.9 ERG modelling results: Position 3a: Severe RA, MTX intolerant, RTX tolerant, failed ≥2 csDMARDs

The ERG estimates of the cost effectiveness of UPA among severe RA patients who are MTX intolerant, RTX tolerant and have failed to respond to at least two csDMARDs are provided in Table 110.

Table 110. ERG modelling: Position 3a: Severe RA, MTX intolerant, RTX tolerant, failed ≥2 csDMARDs

					ICERs		
	Costs	**QALYs**	**Costs**	**QALYs**	**Increm.**	**UPA**	**UPA+MTX**
UPA	[redacted]	[redacted]	[redacted]	[redacted]	Reference	..	..
ADA	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant	..
GOL	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant	..
ETN	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant	..
CTZ	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant	..
TFC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant	..
BRC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant	..
SRL	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant	..
TCZ SC	[redacted]	[redacted]	[redacted]	[redacted]	£651k	£651kSW	..
TCZ IV	[redacted]	[redacted]	[redacted]	[redacted]	Ext.Dom.	£656kSW	..

Abbreviations: ADA, adalimumab; BRC, baricitinib; csDMARDs, conventional synthetic disease modifying antirheumatic drugs; CTZ, certolizumab pegol; ETN, etanercept; ext. dom., extended dominated; ICER, incremental cost-effectiveness ratio; increm., incremental; IV, intravenous; MTX, methotrexate; QALYs, quality adjusted life years; SC, subcutaneous; SRL, sarilumab; TCZ, tocilizumab; TFC, tofacitinib; UPA, upadacitinib

5.4.10 ERG modelling results: Position 3b: Severe RA, MTX tolerant, RTX tolerant, failed ≥2 csDMARDs

The ERG estimates of the cost effectiveness of UPA among severe RA patients who are MTX tolerant, RTX tolerant and have failed to respond to at least two csDMARDs are provided in Table 111.

Table 111. ERG modelling: Position 3b: Severe RA, MTX tolerant, RTX tolerant, failed ≥2 csDMARDs

					ICERs		
	Costs	**QALYs**	**∆Cost**	**∆QALY**	**Increm.**	**UPA**	**UPA+MTX**
UPA+MTX	[redacted]	[redacted]	[redacted]	[redacted]	..	..	..
IFX + MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	..	Dominant
ADA + MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	..	Dominant
ETN + MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	..	Dominant

					ICERs		
	Costs	QALYs	∆Cost	∆QALY	Increm.	UPA	UPA+MTX
GOL + MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	..	Dominant
TFC + MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	..	Dominant
CTZ + MTX	[redacted]	[redacted]	[redacted]	[redacted]	£142mn	..	£142mnSW
BRC + MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	..	Dominant
SRL + MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	..	Dominant
TCZ_{SC}+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	..	Dominant
TCZ_{IV}+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	..	Dominant
ABT_{IV}+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	..	Dominant
ABT_{SC}+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	..	Dominant

Abbreviations: ABT, abatacept; ADA, adalimumab; BRC, baricitinib; csDMARDs, conventional synthetic disease modifying antirheumatic drugs; CTZ, certolizumab pegol; ETN, etanercept; GOL, golimumab; ICER, incremental cost-effectiveness ratio; IFX, infliximab; increm., incremental; IV, intravenous; MTX, methotrexate; QALYs, quality adjusted life years; SC, subcutaneous; SRL, sarilumab; TCZ, tocilizumab; TFC, tofacitinib; UPA, upadacitinib

5.4.11 ERG modelling results: Position 4b: Severe RA, MTX tolerant, RTX intolerant, failed one bDMARD

The ERG estimates of the cost effectiveness of UPA among severe RA patients who are MTX tolerant, RTX intolerant and have failed to respond to one bDMARD are provided in Table 112.

Table 112. ERG modelling: Position 4b: Severe RA, MTX tolerant, RTX intolerant, failed one bDMARD

					ICERs		
	Costs	QALYs	∆Cost	∆QALY	Increm.	UPA	UPA+MTX
UPA+MTX	[redacted]	[redacted]	[redacted]	[redacted]	..	..	
ADA+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	..	Dominant
IFX+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	..	Dominant
GOL+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	..	Dominant
CTZ+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	..	Dominant
TFC+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	..	Dominant
ETN+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	..	Dominant
BRC+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	..	Dominant
TCZ_{SC}+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Ext.Dom.	..	£940kSW
SRL+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Ext.Dom.	..	£680kSW
ABT_{IV}+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	..	Dominant

					ICERs		
	Costs	QALYs	ΔCost	ΔQALY	Increm.	UPA	UPA+MTX
TCZ_{IV}+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£483k	..	£483kSW
ABT_{SC}+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	..	Dominant

Abbreviations: ABT, abatacept; ADA, adalimumab; BRC, baricitinib; csDMARDs, conventional synthetic disease modifying antirheumatic drugs; CTZ, certolizumab pegol; ETN, etanercept; GOL, golimumab; ICER, incremental cost-effectiveness ratio; IFX, infliximab; increm., incremental; IV, intravenous; MTX, methotrexate; QALYs, quality adjusted life years; SC, subcutaneous; SRL, sarilumab; TCZ, tocilizumab; TFC, tofacitinib; UPA, upadacitinib

5.4.12 ERG modelling results: Position 5: Severe RA, MTX tolerant, RTX tolerant, failed one bDMARD

The ERG estimates of the cost effectiveness of UPA among severe RA patients who are MTX tolerant, RTX tolerant and have failed to respond to one bDMARD are provided in Table 113.

Table 113. ERG modelling: Position 5: Severe RA, MTX tolerant, RTX tolerant, failed one bDMARD

					ICERs		
	Costs	QALYs	ΔCost	ΔQALY	Increm.	UPA	UPA+MTX
RTX+MTX	[redacted]	[redacted]	[redacted]	[redacted]	..	..	Dominated
UPA+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	..	..

Abbreviations: ICERs, incremental cost-effectiveness ratio; increm., incremental; MTX, methotrexate; QALYs, quality-adjusted life years; RTX, rituximab; UPA, upadacitinib

5.4.13 ERG modelling results: Position 6: Severe RA, MTX tolerant, RTX tolerant, failed RTX

The ERG estimates of the cost effectiveness of UPA among severe RA patients who are MTX tolerant, RTX tolerant and have failed to respond to RTX are provided in Table 114.

Table 114. ERG modelling: Position 6: Severe RA, MTX tolerant, RTX tolerant, failed RTX

					ICERs		
	Cost	QALY	ΔCost	ΔQALY	Increm.	UPA	UPA+MTX
UPA+MTX	[redacted]	[redacted]			..	..	
SRL+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	..	Dominant
TCZ_{SC}+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Ext.Dom.	..	£1mnSW
TCZ_{IV}+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£505k	..	£505kSW

Abbreviations: ICERs, incremental cost-effectiveness ratio; increm., incremental; IV, intravenous; MTX, methotrexate; QALYs, quality-adjusted life years; SRL, sarilumab; TCZ, tocilizumab; UPA, upadacitinib

5.5 Conclusions of the cost-effectiveness section

The intention of the company model is to largely mirror that of TA375. The key conceptual difference is that the company model includes a relationship between the HAQ and the DAS-28 which permits it to model moderate RA patients worsening to severe RA. Some input values also differ from those of TA375, mainly in terms of the company cDMARD-IR NMA results, the company bDMARD-IR NMA results and the company HAQ to pain score mapping.

The company presents validation data that suggests that if the modelling of the transition from moderate RA to severe RA is turned off and the TA375 mapping from HAQ to pain scores is applied, the company model closely replicates the results of the model of TA375.

The key difference from the TA375 modelling is that moderate RA patients can progress to be severe RA patients. This requires that the relationship between the HAQ and the DAS-28 be specified. The company estimates this from the three-month and six-month data of the SELECT trials. This is then used to extrapolate over the 45-year time horizon of the model. It may be questionable to use the six-month data when the HAQ and the DAS-28 are generally improving to extrapolate over 45 years when the HAQ is generally modelled as worsening. There is also a question about the disappearing company intercept term and whether it should be applied in the modelling. The application of the intercept term generally worsens the cost effectiveness estimates.

The ERG corrects some drug costs. The ERG prefers the HAQ to inpatient costs mapping and the HAQ to pain mapping of TA375. The former has little impact upon results. The latter is more important, but in itself is unlikely to change the overall conclusions.

The ERG thinks that the csDMARD-IR NMA results should be applied to patients who are bDMARD naïve and that the bDMARD-IR NMA results should be applied to patients who are bDMARD experienced. In the modelling of moderate RA patients this implies that for those progressing to severe RA the clinical effectiveness of first-line ADA for treatment of severe RA in the UPA arm should be drawn from the bDMARD-IR NMA while in the comparator arm it should be drawn from the csDMARD-IR NMA. The response rates of the bDMARD-IR NMA are typically worse than those of the csDMARD-IR NMA. But due to a lack of evidence, company assumptions mean that the response rates for ADA monotherapy in the csDMARD-IR NMA are a little worse than in the bDMARD-IR NMA. In the light of this the ERG thinks that the cost effectiveness

estimates for MTX tolerant moderate RA patients are likely to be more reliable than the cost-effectiveness estimates for MTX intolerant moderate RA patients.

For moderate RA patients the company models treatment sequences where after UPA it is possible to intensify csDMARDs. ERG modelling suggests that among moderate RA patients it is more cost effective to intensify csDMARDs prior to using UPA and to use UPA among those failing to response to intensified csDMARDs.

The main difference between the ERG modelling and the company modelling is in the modelling of moderate RA patients. The company thinks that when UPA is compared with BSC, BSC should be assumed to have 0% EULAR response rates. The ERG notes that in all SELECT trials there were considerable EULAR response rates in the control arms. Whether the response rates in the control arms were due to natural recovery or a pure trial or PBO effect is not known. The ERG thinks that BSC should be assumed to have the EULAR response rates of PBO in the company NMA or of the control arms in the SELECT trials. If the company approach is accepted UPA is estimated to be cost effective for moderate RA patients at conventional willingness to pay thresholds. If the ERG approach is accepted UPA is estimated to be not cost effective for moderate RA patients at conventional willingness to pay thresholds.

It should be noted that the company NMA results for placebo and intensified csDMARDs may be subject to more uncertainty than those for advanced DMARDs. But applying the head to head results of the SELECT trials generally results in qualitatively similar cost effectiveness estimates for the modelling of moderate RA patients.

A key question if UPA is approved among moderate RA patients is whether, as a last in line therapy, if a patient fails to achieve a moderate EULAR response but shows some DAS-28 improvement they would have UPA withdrawn. The ERG thinks that if those trialling UPA who receive some benefit but do not achieve a EULAR response will remain on UPA the cost effectiveness of UPA for moderate RA patients would be considerably worse that the estimates presented in this chapter. A related question is the possible ease of manipulating DAS-28 scores, given the significance of the patient reported general health visual analogue score to its calculation.

A difference between the ERG modelling and both the company modelling and the modelling of TA375 is that the ERG does not include a final line of MTX monotherapy. The ERG thinks that it is not appropriate to model patients who have failed on other lines of therapy such as intensified csDMARDs, and by implication have already previously failed on MTX monotherapy, as having a response to a last line of MTX monotherapy.

But the modelling that includes this somewhat worsens the cost effectiveness estimates. The ERG thinks that it is likely that those who do not respond to their final line of treatment will receive some ongoing treatment and that this will have some effect, if not a EULAR response. If this was included in the modelling the ERG thinks that this would worsen the cost effectiveness estimates.

The ERG revisions to the company modelling of severe RA patients do not particularly affect the cost-effectiveness estimates and the results that should be drawn from them.

UPA is estimated to be cost effective among those who have failed to respond to RTX. It should be noted that these patients will have had at least two previous advanced DMARDs. The bDMARD-IR NMA estimates may not be reliable among these patients. It can also be noted that less than 20% of SELECT-BEYOND patients were RTX experienced.

It should be stressed that all results in this document include the UPA patient access scheme but do not include the other advanced DMARDs' PASs or the confidential prices of the biosimilars. The prices for biosimilars of ADA and ETN have a particularly large effect upon results, as presented in the cPAS appendix.

6 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

The ERG modelling of moderate RA patients differs from the company in four main ways.

- Having modelled a comparison of (1) intensification of csDMARDs after trialling UPA with (2) intensification of csDMARDs before trialling UPA and found (1) to be not cost effective, the main ERG modelling does not consider intensification of csDMARDs after trialling UPA.
- Where UPA is compared with BSC, the ERG applies the PBO response rates of the company csDMARD-IR NMA or the SELECT trials' head-to-head results for UPA compared to the control arm.
- The ERG applies the TA375 HAQ to pain mapping.
- The ERG corrects some comparator drug and administration costs.

The ERG typically estimates that among moderate RA patients UPA is not cost effective, with cost effectiveness estimates exceeding £30k per QALY and often exceeding £50k per QALY. The ERG ICERs are tabulated in section 5.4 above.

If the treatment sequences for those transitioning from moderate RA to severe RA are differentiated by arm as seems reasonable this tends to worsen the cost effectiveness estimates. This particularly applies if UPA is used for severe RA in the comparator arm.

Applying the company HAQ to pain mapping function typically improves the cost effectiveness estimates but does not qualitatively change the main thrust of the results.

The exception to this is if it is assumed that (1) there was no natural recovery in the SELECT trials' comparator arms and (2) any PBO effect in the SELECT trials should not be applied. This causes the ERG to estimate UPA to be cost effective compared to BSC among moderate RA patients.

The ERG costs effectiveness estimates among severe RA patients are qualitatively similar to the company estimates.

Unquantifiable issues include:

- What should be assumed for those who are without a response and are at end of line? These patients are assumed to receive palliative care with no benefit.

Moderate RA patients may tend to be treated with whatever combination of csDMARDs worked best for them, even if a EULAR response was not achieved. The ERG thinks that including this would worsen the cost effectiveness estimates.

- If UPA is trialled as last in line among moderate RA patients would those who got some benefit from it but did not achieve a EULAR response tend to remain on it? The ERG thinks that if they would this would considerably worsen the cost-effectiveness estimates.

- Is it reasonable to extrapolate the company HAQ to DAS relationship based upon six month improvements in the SELECT trials to 45 years when the HAQ is generally modelled as worsening? The ERG thinks that if this relationship breaks down over time this could worsen the cost effectiveness estimates, though whether this is more of a modelling issue than a real world concern is debatable.

- Are EULAR response rates the same at different lines of treatment? The response rates in the bDMARD-IR NMA are typically worse than those of the csDMARD-IR NMA. The ERG thinks that this does not particularly affect the modelling of moderate RA patients, but it might mean that progressing to severe RA is more serious and so more to be avoided. What effect this would have upon the cost effectiveness estimates is difficult to speculate upon, in part due to the bDMARD-IR NMA applying from first-line therapy for severe RA in the UPA arm but only applying from second-line therapy for severe RA in the comparator arm.

- Are the clinical effectiveness estimates applicable to those who have failed RTX? The ERG notes that these patients would have failed at least two lines of advanced DMARDs and that only a small proportion of SELECT-BEYOND patients were RTX experienced.

It should be stressed that all results in this document include the UPA patient access scheme but do not include the other advanced DMARDs' patient access schemes or the confidential prices of the biosimilars. The prices for biosimilars of ADA and ETN have a particularly large effect upon results, as presented in the cPAS appendix.

7 End of life

No evidence was presented as to a survival benefit arising from UPA. The CS does not address end of life criteria; therefore, end of life criteria are unlikely to be met.

8 Overall conclusions

The ERG reviewed the clinical and cost-effectiveness for UPA in adults with moderate and severe RA. The clinical effectiveness evidence supported a benefit for UPA versus relevant comparators. The safety profile of UPA was generally consistent with that of PBO as well as the active comparators ADA and MTX. Some concerns over the robustness of the SLR process and procedures raise questions about the robustness of the clinical effectiveness evidence.

The ERG noted that NMA results covered a range of positions in the treatment pathway, and encompassed substantial clinical heterogeneity in treatment experience and disease severity of trial populations. This remains a major source of uncertainty in interpretations of NMA results.

Moreover, the use of csDMARD-experienced or bDMARD-experienced estimates of effectiveness was a point of difference in the company's application of NMA results and the ERG's application of NMA results in cost-effectiveness modelling.

The main differences between the ERG economic modelling and the company economic modelling are:

- The treatment sequences. Is it sensible to model EULAR responses to a last line of treatment with MTX monotherapy when by definition these patients will have previously failed on MTX monotherapy?
- The treatment sequences. Is it sensible or likely to be cost effective to try UPA before trying intensified csDMARDs?
- Should natural recovery and the PBO effect be included in the comparator arm given that they will be present in the UPA arm?
- Is the HAQ to pain mapping of TA375 more reliable than the company estimates from the SELECT trials?
- Are the ERG revised drug costs more accurate?

8.1 Implications for research

The ERG considered there to already be considerable RCT evidence for the potential benefit of UPA for this indication. However, the ERG considered that the clinical evidence base would be further strengthened by an RCT incorporating pre-stratification by baseline disease severity in order to offer greater clarity about the impact of disease

severity on the clinical effectiveness of UPA, and therefore its optimal positioning in the treatment pathway for moderate and severe RA.

Future analyses should seek to consider through within-trial, pre-planned subgroups, the differential effectiveness of DMARDs based on treatment history and experience. In addition, future NMAs may include a more explicit approach to accounting for effect modification according to treatment history and disease severity, and the implications of this for cost-effectiveness. Baseline risk adjustment as an analysis strategy is unlikely to yield clinically meaningful results given a) the use of existing treatment pathways and, thus, treatment history to shape forward treatment decisions and b) the difficulty in translating these findings to clinical practice.

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Contribution of authors

Dr Max Barnish (Research Fellow) provided overall project management, managed the clinical effectiveness team, critiqued the clinical effectiveness evidence, contributed to writing the clinical effectiveness chapter, wrote the background, decision problem and conclusions sections, and contributed to writing the executive summary.

Dr Ewen Cummins (Health Economist) reviewed the economics of the CS.

Dr Helen Coelho (Research Fellow) critiqued the clinical effectiveness evidence; wrote the assessment of bias in included trials and in the trials included in the NMA, critiqued the inclusion criteria, study selection, and data extraction, and critiqued the safety data.

Dr Rhona Johnston (Computer Programmer) reviewed and ran the electronic models.

Mr David Packman (Research Assistant) examined the methodology for the NMA with reference to the NICE Technical Support recommendations and contributed to the writing and editing the ERG report. He checked the company's data extraction for the NMA and the reasons for inclusion or exclusion of the studies identified in the relevant previous appraisals.

Ms Naomi Shaw (Information Specialist) wrote the sections of the report relating to the critique of the literature searches and managed the ERG EndNote library.

Dr Richard C Haigh (Consultant Rheumatologist) served as clinical advisor to the ERG.

Ms Louise Crathorne (Senior Research Fellow) critiqued the review of cost-effectiveness studies, contributed to the writing of the report, and reviewed and edited the ERG report.

Prof G.J. Melendez-Torres (Professor of Social and Clinical Epidemiology) critiqued the NMA, supported review of the clinical effectiveness evidence and is the guarantor of the work.

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Appendix 1. Additional searches undertaken by the ERG

Database: Ovid MEDLINE(R) ALL <1946 to August 05, 2019> Search Strategy:

1 exp arthritis, rheumatoid/ (109237)

2 rheumatoid arthritis.mp. (101391)

3 or/1-2 (142519)

4 janus kinase inhibitors/ (184)

5 (JAK* adj inhibitor*).tw. (2400)

6 janus kinase inhibitor*.tw. (469)

7 tumor necrosis factor-alpha/ (120216)

8 exp monoclonal antibodies/ (224445)

9 tumo?r necrosis* factor*.tw. (135649)

10 TNF-alpha.tw. (121814)

11 exp upadacitinib/ or (upadacitinib or ABT-494).af. (46)

12 exp adalimumab/ or (adalimumab or Humira or trudexa or Amjevita or Amgevita or Cyltezo or Halimatoz or Hefiya or Hyrimoz or Hulio or abp501 or Imraldi or Solymbic or Exemptia or Adfrar).af. (7742)

13 exp etanercept/ or (etanercept or Enbrel or Benepali or SB4 or 185243-69-0 or 200013-86-1 or Erelzi or Lifmior or TuNEX or ENIA11 or Brenzys or Intacept or Etacept or Davictrol).af. (8312)

14 exp infliximab/ or (infliximab or Remicade or Remsima or CT-P10 or CT-P13 or 170277-31-3 or Inflectra or Renflexis or Zessly or Revellex or Ixifi or Flixabi or Flammegis or Infimab).af. (14030)

15 exp golimumab/ or (golimumab or Simponi or CNTO 148 or cnto-148 or 476181-74-5).af. (1103)

16 exp certolizumab pegol/ or (certolizumab or Cimzia or CDP870 or 428863-50-7).af. (1186)

17 exp tocilizumab/ or (tocilizumab or Actemra or RoActemra or 375823-41-9 or LusiNEX or atlizumab or R1569).af. (2734)

18 exp abatacept/ or (abatacept or Orencia or CTLA-4Ig or 332348-12-6).af. (3601)

19 exp tofacitinib/ or (tofacitinib or tasaocitinib or CP-690550 or Xeljanz or 540737-29-9 or tasocitinib).af. (1130)

20 exp rituximab/ or (rituximab or Rituxan or Mabthera or 174722-31-7 or Tuxella or Rituzena or Ritemvia or Blitzima or Truxima or Riximyo or Rixathon or Reditux or Zytix or AcellBia or Maball or MabTas or Rituxirel).af. (21589)

21 anakinra/ or (anakinra or Kineret or 143090-92-0).af. (5700)

22 baricitinib/ or (baricitinib or Olumiant or LY3009104 or LY 3009104 or 1187594-09-7).af. (202)

23 exp sarilumab/ or (sarilumab or Kevzara or SAR 153191 or SAR153191 or REGN 88 or REGN88 or 1189541-98-7).af. (87)

24 exp sirukumab/ or (sirukumab or CNTO-136 or CNTO136 or 1194585-53-9 or Plivensia).af. (49)

25 exp filgotinib/ or (Filgotinib or GLPG0634 or GLPG-0634).af. (65)

26 exp peficitinib/ or (Peficitinib or ASP015K).af. (39)

27 or/4-26 (452201)

28 randomized controlled trial.pt. (486665)

29 controlled clinical trial.pt. (93195)

30 randomized.ab. (451498)

31 placebo.ab. (199946)

32 Clinical Trials as Topic/ (187867)

33 randomly.ab. (316207)

34 trial.ti. (203103)

35 28 or 29 or 30 or 31 or 32 or 33 or 34 (1232128)

36 exp animals/ not humans.sh. (4605671)

37 35 not 36 (1133313)

38 3 and 27 and 37 (2772)

39 exp arthritis, rheumatoid/ (109237)

40 rheumatoid arthritis.mp. (101391)

41 39 or 40 (142519)

42 exp upadacitinib/ or (upadacitinib or ABT-494).af. (46)

43 exp adalimumab/ or (adalimumab or Humira or trudexa).af. (7737)

44 exp etanercept/ or (etanercept or Enbrel or Benepali or SB4 or 185243-69-0 or 200013-86-1).af. (8311)

45 exp infliximab/ or (infliximab or Remicade or Remsima or CT-P10 or CT-P13 or 170277-31-3).af. (14027)

46 exp golimumab/ or (golimumab or Simponi or CNTO 148 or cnto-148 or 476181-74-5).af. (1103)

47 exp certolizumab pegol/ or (certolizumab or Cimzia or CDP870 or 428863-50-7).af. (1186)

48 exp tocilizumab/ or (tocilizumab or Actemra or RoActemra or 375823-41-9).af. (2712)

49 exp abatacept/ or (abatacept or Orencia or CTLA-4Ig or 332348-12-6).af. (3601)

50 exp tofacitinib/ or (tofacitinib or tasaocitinib or CP-690550 or Xeljanz or 540737-29-9).af. (1126)

51 exp rituximab/ or (rituximab or Rituxan or Mabthera or 174722-31-7).af. (21589)

52 anakinra/ or (anakinra or Kineret or 143090-92-0).af. (5700)

53 baricitinib/ or (baricitinib or Olumiant or LY3009104 or LY 3009104 or 1187594-09-7).af. (202)

54 exp sarilumab/ or (sarilumab or Kevzara or SAR 153191 or SAR153191 or REGN 88 or REGN88 or 1189541-98-7).af. (87)

55 exp sirukumab/ or (sirukumab or CNTO-136 or CNTO136 or 1194585-53-9).af. (49)

56 exp filgotinib/ or (Filgotinib or GLPG0634 or GLPG-0634).af. (65)

57 exp peficitinib/ or (Peficitinib or ASP015K).af. (39)

58 or/42-57 (54246)

59 Randomized controlled trials as Topic/ (125554)

60 Randomized controlled trial/ (486665)

61 Random allocation/ (99887)

62 Double blind method/ (152508)

63 Single blind method/ (27122)

64 Clinical trial/ (517294)

65 exp Clinical Trials as Topic/ (328712)

66 (clinic$ adj trial$1).tw. (338742)

67 ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw. (165465)

68 placebo$.tw. or Placebo/ (206463)

69 Randomly allocated.tw. (26714)

70 (allocated adj2 random).tw. (788)

71 or/59-70 (1379868)

72 Case report.tw. (292443)

73 Letter/ (1038052)

74 Historical article/ (353122)

75 Case study.tw. (67309)

76 or/72-75 (1732546)

77 71 not 76 (1345369)

78 41 and 58 and 77 (2930)

79 41 and 42 (31)

80 78 or 79 (2946)

81 animal/ not (human/ and animal/) (4572711)

82 80 not 81 (2936)

83 38 not 82 (882)

Appendix 2. Health utilities and costs searches

Health utilities search

The company completed searches to identify health-related quality of life studies (HRQoL) or health utilities literature in December 2017. Searches were updated in April 2019. The health-related quality of life searches are reported in Appendix H of the CS.

The following bibliographic databases were searched: Ovid MEDLINE, Embase, EBM Reviews incorporating the Cochrane Library databases (CDSR, CENTRAL, DARE, HTA and NHS EED). The search uses a combination of indexing terms (e.g. MeSH in MEDLINE) and free-text (i.e. title and abstract) for the population (rheumatoid arthritis) and health utilities. Additional searches were conducted on reference lists of included studies, conference proceedings, HTA websites and other relevant websites (e.g. EuroQOL, ScHARRHud).

Update searches completed in April 2019 did not use all relevant date fields to limit searches (see Section 4.1.1 for further details). The company did not cite a validated filter for identifying health-related quality of life literature, however, appropriate terminology was included in search strategies.

Costs search

The company completed searches to identify cost and resource use literature in December 2017. Searches were updated in April 2019. The cost and resource use searches are reported in Appendix I of the CS.

The following bibliographic databases were searched: Ovid MEDLINE, Embase, EBM Reviews incorporating the Cochrane Library databases (CDSR, CENTRAL, DARE, HTA, NHS EED) and EconLit. Additional searches were conducted on reference lists of included studies, HTA websites, conference proceedings and other relevant websites (CEA Registry and EconPapers within RePEc). Searches were limited to literature published from 2008.

Update searches completed in April 2019 did not use all relevant date fields to limit searches (see Section 4.1.1 for further details).

Upadacitinib for treating moderate to severe rheumatoid arthritis [ID1400]

Addendum #2 Biosimilar Prices

10/10/2019

1 Biosimilar prices

Adalimumab, etanercept, infliximab and rituximab all have biosimilars. The Commercial Medicines Unit (CMU) has negotiated commercial in confidence (CIC) price discounts for these.

For etanercept, infliximab and rituximab, in line with TA375, the ERG has applied the lowest biosimilar price in its comparator patient access scheme (cPAS) analyses.

For adalimumab the picture is more complicated. In order to preserve the biosimilar market for adalimumab, NHS England has split the country into 11 regional groups, with each regional group being given a list containing either two or three treatments:

- Humira and a first-line biosimilar which is citrate free; or,
- Humira, a first-line biosimilar which contains citrate and a second-line biosimilar which is citrate free but is more expensive than the first-line biosimilar which contains citrate.

Access to the market was awarded on the basis of the competitiveness of the prices tendered. Trusts pay the supplier at the set invoice price, but are refunded a set reference price with the difference between the two being retained by the trust. The reference price has been set to also cover hospital costs of switching patients to the best value biosimilars. The reference price "*covers the cost of both first and second line biosimilar products ensuring patients are able to access a citrate-free product and providers are fully reimbursed for this where clinically required*". If more than one treatment is suitable for the patient, the best value biological medicine should be chosen.

In order for companies to be awarded market share, a two-stage process was used, involving a guaranteed share element for offers below a specified threshold price, and the use of a second stage in which the remaining share was allocated based on price ranking. The regional allocations are as below (Table 1)[1]:

[1] Regional Medicines Optimisation Committee Briefing Best Value Biologicals: Adalimumab Update 6: July 2019

Table 1. Adalimumab market allocations

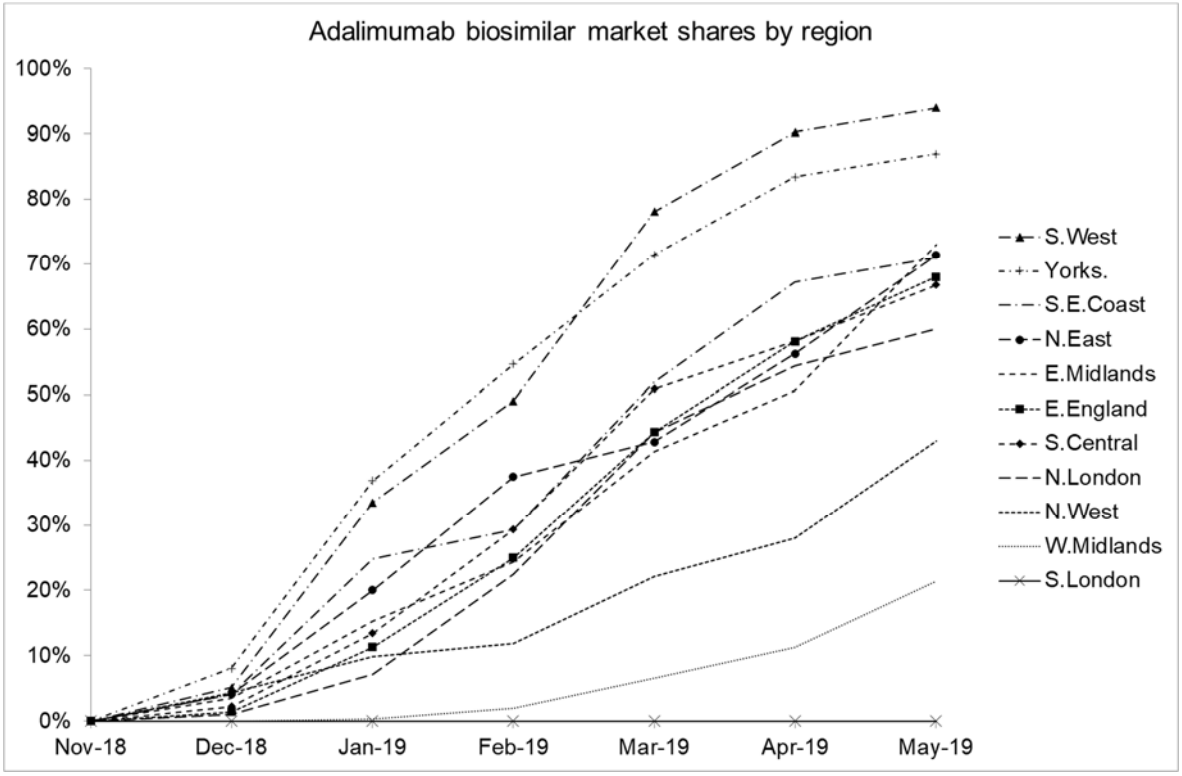
Region	First-line	Second-line	20 mg	Originator
E.Midlands E.England S.East S.Central S.West	Imraldi	Amgevita	Amgevita	Humira
N.East N.West Yorks.	Amgevita	n.a.		
N.London W.Midlands	Hyrimoz	Amgevita		
S.London	Hulio	n.a.		

Manufacturers were invited to tender two prices, one excluding homecare costs and the other including it. The reference price including homecare costs for the 40 mg dose is £3,550 in all regions except South London, where it is slightly higher at £3,662: £270 per pack of two prefilled pens and £282 per pack of two pre-filled pens respectively.

The reference price is not the cost to the NHS but appears to be the ceiling price paid by trusts to the suppliers. The price paid by trusts to the suppliers is the relevant cost for the economics. Market share data[2] for the biosimilars to May 2019 is as below (Figure 1), south London remaining at 0%.

[2] Data taken from graph

Figure 1. Biosimilar market share by region



Weighting the regions equally results in an average 60% biosimilar use at May 2019, compared to the true figure of 64%. The ERG is ignorant of the patient numbers in each region so cannot apply a weighted average, and views the 60% to be sufficiently close to the actual 64% for it to be used for current purposes.

For adalimumab the ERG calculates a weighted average price based upon the May 2019 market shares. Where two biosimilars are available to a region the ERG applies the price of the cheaper biosimilar.

It can be noted that at May 2019 there remained a strong upward trend in the market share taken by the biosimilars. As a consequence, the ERG weighted average price for adalimumab is likely to overestimate the current weighted average price.

The above also gives rise to the possibly awkward situation of some biosimilars being cheaper than upadacitinib, but not being approved for use among moderate RA patients. It seems possible that:

- Approving biosimilars among moderate RA patients and reserving upadacitinib for severe patients might be more cost effective than approving upadacitinib among moderate RA patients.
- If both biosimilars and upadacitinib were considered head-to-head among moderate RA patients, the biosimilars might be the more cost effective.

- Linked to the above, sequencing the biosimilars before upadacitinib might be more cost effective than sequencing upadacitinib before the biosimilars.

The advent of biosimilars may argue for an MTA of bDMARDs for both moderate RA and for severe RA.

Upadacitinib for treating moderate to severe rheumatoid arthritis [ID1400]

Addendum #3 Model Validation

22/10/2019

1 Company error check Issue 7 and TA375 modelling approach

Issue 7 in the company's Factual Accuracy Check (FAC) on the Evidence Review Group (ERG) report stated that TA375 assumed 0% European League Against Rheumatism (EULAR) response rates for best supportive care (BSC) and that the company modelling approach was therefore in line with the TA375 modelling approach. The company FAC therefore claimed that the ERG modelling approach that applied the EULAR response rates from the randomised controlled trial (RCT) control arms was not aligned with the TA375 modelling approach. Since the company did not identify a factual error under Issue 7 in the FAC, the ERG did not revise the ERG report to address this Issue.

The ERG has now reviewed the Assessment Group (AG) report[1] for TA375 (dated 12 August 2013) and the corresponding monograph publication.[2] There are some minor differences between the AG report and the monograph in terms of the reported treatment sequences that are modelled, which may be typos, but for current purposes these differences do not matter. The treatment sequences reported in the AG report are shown below in Table 1 through Table 4.

Table 1. TA375: MTX eligible: Severe RA: csDMARD naive

Line of Tx	Sequence 1	Sequence 2	Sequence 3	Sequence 4
1st line	MTX	MTX	MTX	bDMARD+MTX
2nd line	Int cDMARDs	Int cDMARDs	Int cDMARDs	RTX+MTX
3rd line	NBT	bDMARD+MTX	TCZ+MTX	TCZ+MTX
4th line	..	RTX+MTX	RTX+MTX	MTX
5th line	..	TCZ+MTX	MTX	Int cDMARDs
6th line	..	MTX	NBT	NBT
7th line	..	NBT	..	..

Key: bDMARD, biologic disease modifying anti-rheumatic drug; csDMARD, conventional synthetic disease modifying anti-rheumatic drug; MTX, methotrexate; NBT, non-biologic therapy; RA, rheumatoid arthritis; RTX, rituximab; TCZ, tocilizumab

Table 2. TA375: MTX eligible: Severe RA: csDMARD experienced

Line of Tx	Sequence 1	Sequence 2	Sequence 3
1st line	MTX	bDMARD+MTX	TCZ[+MTX[1]]
2nd line	NBT	RTX+MTX	RTX+MTX
3rd line	..	TCZ[+MTX[1]]	MTX
4th line	..	MTX	NBT
5th line	..	NBT	..

Key: ; csDMARD, conventional synthetic disease modifying anti-rheumatic drug; MTX, methotrexate; NBT, non-biologic therapy; RA, rheumatoid arthritis; RTX, rituximab; TA, technology appraisal; TCZ, tocilizumab; Tx, treatment

A third population of methotrexate (MTX) eligible moderate/severe rheumatoid arthritis (RA) conventional synthetic disease modifying anti-rheumatic therapy (csDMARD) experienced was also modelled. This applied the treatment sequences of Key: bDMARD, biologic disease modifying anti-rheumatic drug; csDMARD, conventional synthetic disease modifying anti-rheumatic drug; MTX, methotrexate; NBT, non-biologic therapy; RA, rheumatoid arthritis; RTX, rituximab; TCZ, tocilizumab

Table 2 above.

Table 3. TA375: MTX ineligible: Severe RA: csDMARD naive

Line of Tx	Sequence 1	Sequence 2	Sequence 3
1st line	Int cDMARDs	Int cDMARDs	bDMARD
2nd line	csDMARD	bDMARD	bDMARD
3rd line	NBT	bDMARD	Int csDMARDs
4th line	..	csDMARD	csDMARD
5th line	..	NBT	NBT

Key: bDMARD, biologic disease modifying anti-rheumatic drug; csDMARD, conventional synthetic disease modifying anti-rheumatic drug; int., intensified; NBT, non-biologic therapy; TA, technology appraisal

Table 4. TA375: MTX ineligible: Severe RA: csDMARD experienced

	Sequence 1	Sequence 2
1st line	csDMARDs	bDMARD
2nd line	csDMARD	bDMARD
3rd line	NBT	csDMARD
4th line	..	NBT

[1] MTX is not mentioned here in Table 179 but it seems likely this is a typo.

Key: bDMARD, biologic disease modifying anti-rheumatic drug; csDMARD, conventional synthetic disease modifying anti-rheumatic drug; NBT, non-biologic therapy; RA, rheumatoid arthritis; TA, technology appraisal

A third population of MTX ineligible moderate/severe RA csDMARD experienced was also modelled. This applied the treatment sequences of Key: bDMARD, biologic disease modifying anti-rheumatic drug; csDMARD, conventional synthetic disease modifying anti-rheumatic drug; int., intensified; NBT, non-biologic therapy; TA, technology appraisal

Table 4.

Both the AG report and the HTA monograph state that "*it was assumed that non-biologic therapy would be associated with no initial EULAR response, unlike MTX where the results from the NMA indicated that MTX had a significant EULAR response*." As a consequence, all the treatment sequences modelled in TA375 have a first-line treatment with non-zero EULAR response rates. The 0% EULAR response rates only apply to the NBT as the last in line treatment. This is as per the ERG modelling.

In the light of the above, the ERG considers that the ERG modelling approach is aligned with that of TA375 and that the modelling approach of the company is not. At a minimum, it cannot be concluded that the ERG modelling approach is not aligned with the modelling approach of TA375.

The above may also raise some questions about the modelling approach adopted by the company in its model validation work and its estimates of tables A.19 and A.20 of the company addendum (dated 27 August 2019) and how these relate to the Issue 7 the company raised at FAC.

2 ERG modelling comparing company model with TA375 model

The TA375 AG supplied the ERG with a copy of the TA375 electronic model. The ERG has attempted to replicate modelling results from the company model using the TA375 electronic model. The ERG chose the following eight arbitrary treatment sequences, the treatments within them being chosen due to the ready availability of clinical effectiveness estimates in the company NMA.

Table 5. Treatment sequences modelled by the ERG

Sequence	Treatment 1	Treatment 2	Treatment 3	Treatment 4
Sequence 1	Int csDMARDs	IFX+MTX	BSC	..
Sequence 2	Int csDMARDs	ADA+MTX	IFX+MTX	BSC
Sequence 3	Int csDMARDs	GOL+MTX	IFX+MTX	BSC
Sequence 4	ADA+MTX	IFX+MTX	Int csDMARDs	BSC
Sequence 5	ADA+MTX	IFX+MTX	BSC	..
Sequence 6	GOL+MTX	IFX+MTX	BSC	..
Sequence 7	ADA+MTX	GOL+MTX	IFX+MTX	BSC
Sequence 8	GOL+MTX	ADA+MTX	IFX+MTX	BSC

Key: ADA, adalimumab; BSC, best supportive care; csDMARD, conventional synthetic disease modifying anti-rheumatic drug; GOL, golimumab; IFX, infliximab; MTX, methotrexate; NBT, non-biologic therapy

The ERG modified the company model to apply the TA375 health assessment questionnaire (HAQ) to pain mapping function and the TA375 HAQ costs. The ERG modified the TA375 model to apply the company initial six month and ongoing drug and administration costs, the company NMA results and the company severe RA baseline patient characteristics. This work was undertaken by the ERG and the TA375 AG bears no responsibility for it. The company model was run over 10,000 patients while the TA375 model was run over 3,000 patients due to the validation work reported in TA375. This resulted in the following estimates.

Table 6. ERG results using company model and TA375 model

	Total discounted costs			Total discounted QALYs		
Sequence	**Company**	**TA375**	**Ratio**	**Company**	**TA375**	**Ratio**
Sequence 1	£69,924	£42,985	163%	7.550	7.160	105%
Sequence 2	£87,415	£54,367	161%	8.034	7.691	104%
Sequence 3	£92,788	£57,991	160%	8.086	7.926	102%
Sequence 4	£103,377	£67,452	153%	8.175	7.812	105%
Sequence 5	£104,661	£73,882	142%	7.903	7.410	107%
Sequence 6	£111,266	£83,501	133%	7.939	7.461	106%
Sequence 7	£124,454	£93,475	133%	8.378	8.004	105%
Sequence 8	£126,292	£95,259	133%	8.372	7.968	105%

Key: QALYs, quality adjusted life years; TA, technology appraisal

There is a reasonable correspondence between the QALY estimates.

The cost estimates of the company model are considerably higher than those arrived at by the ERG using the TA375 model.

It is notable that within the sequences 1-4 that contain intensified csDMARDs the cost estimates that the ERG derives using the company model are somewhat higher than those the ERG derives using the TA375 model. This is a concern and suggests either that the ERG has implemented costings within the model validation exercise incorrectly or that the company model may be biased in favour of the more effective advanced DMARDs.

It is also notable that while the cost estimates for the Sequences 5-8 that only contain the advanced DMARDs are higher when using the company model than the TA375 model, they are increased by similar proportionate amounts. As a consequence, the incremental cost-effectiveness ratios (ICERs) across Sequences 5-8 are less affected by model choice than the ICERs across Sequences 1-8.

In the light of this, while the TA375 model estimates may be reasonably aligned with those of the company model when comparing advanced DMARDs against one another, it may result in worse ICERs when comparing advanced DMARDs with csDMARDs and BSC. If the company model estimates upadacitinib (UPA) to be cost effective relative to csDMARDs and BSC, it is not clear that the TA375 model will necessarily do likewise. Given the positions sought, this seems most likely to affect the assessment of UPA for moderate RA patients, though it should be borne in mind that the above modelling is of severe RA patients and that the TA375 model does not contain the facility to model moderate RA patients worsening to severe RA.

If this may affect decision making, it may be reasonable for the company to send the ERG the company model(s) used during the company model validation work, itemising the changes made from the company base case to arrive at its estimates of tables A.19 and A.20 of the company addendum (dated 27 August 2019). The ERG would then be able to cross check this implementation and its correspondence with the reported model outputs of TA375.

3 References

1. ScHARR University of Sheffield. Technology Assessment Report Commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Clinical Excellence: Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for the treatment of rheumatoid arthritis not previously treated with disease-modifying anti-rheumatic drugs and after the failure of conventional disease-modifying anti-rhuematic drugs only: systematic review and economic evaluation. 2013.

2. Stevenson M, Archer R, Tosh J, Simpson E, Everson-Hock E, Stevens J, et al. Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for the treatment of rheumatoid arthritis not previously treated with disease-modifying antirheumatic drugs and after the failure of conventional disease-modifying antirheumatic drugs only: systematic review and economic evaluation. Health Technology Assessment. 2016;20(35):1-610.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check

Upadacitinib for previously treated moderate to severe active rheumatoid arthritis [ID1400]

You are asked to check the ERG report to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on Friday 20 September 2019** 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.

The factual accuracy check form should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 The technology

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Incomplete description of the technology is provided. On page 17, the technology is described as: *"The intervention in the decision problem is UPA, an oral Janus kinase (JAK)-1 inhibitor"* Also, on page 35, the technology is described similarly as: *"an oral JAK-1 inhibitor"*	AbbVie kindly request that the sentence is amended to the following: *"The intervention in the decision problem is UPA, a selective oral Janus kinase (JAK)-1 inhibitor"*	Upadacitinib has increased selectivity for JAK1 over JAK2, JAK3 and TYK2, with the ability to inhibit signalling of key cytokines involved in the pathogenesis of RA.	The ERG does not believe its original statement to be factually incorrect. However, the word 'selective' has been added as requested for additional clarity. **Action: p.17 replaced 'an oral' with 'a selective oral'.**

Issue 2 The comparators

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Incomplete description of the comparators included is provided. On page 17, the ERG report describes the comparators as: *"Comparators in this appraisal varied depending on disease severity as well as tolerance or intolerance to MTX"*	AbbVie kindly request that the sentence is amended: *"Comparators in this appraisal varied depending on disease severity, the number of csDMARD failures, as well as tolerance or intolerance to MTX"*	Comparators in the analysis varied depending on whether the RA patients experienced one or two csDMARD failures.	The ERG does not believe its original statement to be factually incorrect. However, the phrase 'the number of csDMARD failures' has been added for additional clarity. **Action: p.17 added 'the number of csDMARD failures'.**

Also, on page 35, the comparators are categorised only in terms of disease activity, tolerance or intolerance to MTX			

Issue 3 Summary of clinical effectiveness evidence submitted by the company

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 18 of the report states the following: *"The SELECT-COMPARE trial (through Week 26), a head-to-head comparison with ADA, demonstrated that the ACR20 response rate at Week 12 was **numerically** higher among UPA 15 mg QD treated patients compared with the 327 ADA-treated patients, at 71% versus 63% (p<0.05)"* Page 87: *"The SELECT-COMPARE trial (through Week 26), a head-to-head comparison with ADA, demonstrated that the ACR20 response rate at Week 12 was **numerically** higher among UPA 15 mg QD treated patients compared with the 327 ADA-treated patients, at 71% versus 63% (p<0.05)."*	AbbVie kindly request that the sentence is amended to the following: Page 18: *"The SELECT-COMPARE trial (through Week 26), a head-to-head comparison with ADA, demonstrated that the ACR20 response rate at Week 12 was **significantly** higher among UPA 15 mg QD treated patients compared with the 327 ADA-treated patients, at 71% versus 63% (p<0.05)"* Page 87: *"The SELECT-COMPARE trial (through Week 26), a head-to-head comparison with ADA, demonstrated that the ACR20 response rate at Week 12 was **significantly** higher among UPA 15 mg QD treated patients compared with the 327 ADA-treated patients, at 71% versus 63% (p<0.05)."*	The difference in ACR20 response at week 12 was statistically significantly higher among UPA 15 mg treated patients compared to ADA.	The ERG has made the requested amendment: **Action: p.18 and p.87 replaced 'numerically' with 'significantly'.**

Issue 4 Summary of clinical effectiveness: statistical significance for SF-36 PCS and EQ-5D-5L for the SELECT-COMPARE trial

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Incorrect p-value results for mean change from baseline for the SF-36 PCS at 12 weeks and EQ-5D-5L at 14 weeks for the SELECT-COMPARE trial. On Page 19, the ERG report states *"Similar results were found for the SF-36 PCS at 12 weeks: there was greater improvement with UPA 15 mg QD than with PBO (mean change from baseline 7.9 versus 3.6 respectively, p<0.001 for SELECT COMPARE, 7.6 versus 3.0 respectively, p≤0.001 for SELECT NEXT; 5.8 versus 2.4, p<0.001 for SELECT BEYOND)."* *"At 14 weeks, there was greater improvement on both the EQ-5D-5L index and the SF-36-PCS with UPA 15 mg QD monotherapy compared with MTX monotherapy (EQ-5D-5L 0.2 vs 0.1 respectively, p=0.001; SF-36 PCS 8·3 versus 4·3 respectively, p<0·001)."* The same p-values are reported on page 82, which states: *"At week 12, there was an improvement from baseline in mean current health status as measured by the EQ-5D-5L*	AbbVie kindly request that the sentences are amended with the correct equation for the p-values. *"Similar results were found for the SF-36 PCS at 12 weeks: there was greater improvement with UPA 15 mg QD than with PBO (mean change from baseline 7.9 versus 3.6 respectively, p<0.001 for SELECT COMPARE, 7.6 versus 3.0 respectively, p<0.001 for SELECT NEXT; 5.8 versus 2.4, p<0.001 for SELECT BEYOND)."* *"At 14 weeks, there was greater improvement on both the EQ-5D-5L index and the SF-36-PCS with UPA 15 mg QD monotherapy compared with MTX monotherapy (EQ-5D-5L 0.2 vs 0.1 respectively, p<0.001; SF-36 PCS 8·3 versus 4·3 respectively, p<0·001)."*	An incorrect p-value was reported for mean change from baseline for the SF-36 PCS at 12 weeks for the SELECT-COMPARE trial on page 19 of the ERG report.	The ERG has made the requested amendments. **Action: p.19 and p.82 p-value equations amended.**

index with UPA 15 mg QD compared with PBO (0.2 versus 0.1, p=0.001; 0.2 for UPA 30 mg). Similarly, on the SF-36 PCS, there were significant improvements for the UPA 15mg group compared with PBO (mean change from baseline 7.6 versus 3.0 respectively, p≤0.001; 8.0 for UPA 30 mg).”			

Issue 5 Summary of clinical effectiveness: NMA results for ACR20 for bDMARD-experienced population

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 20, the ERG document states: *“In the bDMARD-experienced population, UPA 15 mg in combination with csDMARDs yielded a probability of ACR20 of [redacted]; of ACR50 of [redacted] and of ACR70 of [redacted]* Also, on page 138 the ERG document states: *“UPA 15 mg in combination with csDMARDs yielded a probability of ACR20 of [redacted] of ACR50 of [redacted] and of ACR70 of [redacted]*	AbbVie kindly requests that this is amended to clarify that this is based on the SUCRA analysis. Page 20: *“In the bDMARD-experienced population, UPA 15 mg in combination with csDMARDs yielded a probability of ACR20 of [redacted] of ACR50 of [redacted] and of ACR70 of [redacted] **based on the SUCRA analysis**.”* Page 138: *“UPA 15 mg in combination with csDMARDs yielded a probability of ACR20 of [redacted]; of ACR50 of [redacted]) and of ACR70 of [redacted] **based on the SUCRA analysis**.”*	It is unclear whether the values presented relate to the initial base-case NMA or the SUCRA analysis.	This is not a factual error, as the statements relate to the analyses presented in the ERG report. **Action: No revision required**

Issue 6 Model description

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Throughout the report, it is stated that the main difference of the AbbVie model from the model produced by the assessment group for TA375 is that it models the progression from moderate RA to severe RA: Page 23: "*The structure and inputs to it mirror much of that of TA375. The main differences are that the company: models the progression from moderate RA to severe RA, relying upon a HAQ to DAS-28 mapping derived from the SELECT trials*" Page 25: *"The key difference from the TA375 modelling is that moderate RA patients can progress to be severe RA patients"* Page 198: *"It appears that a key model difference from the TA375 model is that moderate RA patients can see their DAS-28 worsen to >5.1 and so become severe RA patients"* Page 233:	AbbVie kindly request that this reference is amended throughout to the following: *"the main difference of the model from TA375 is* ***that in line with the modification requested by the appraisal committee in the most recent RA drug appraisal, sarilumab (TA485),*** *it models the progression from moderate RA to receiving advanced therapies for severe RA"*	The modification to the TA375 model was a specific modification requested by the appraisal committee in the most recent RA appraisal of sarilumab (TA485). The amendment clarifies that this is not an AbbVie innovation and an approach requested and endorsed by the appraisal committee in the most recent RA drug appraisal.	The ERG does not believe its original statement to be factually incorrect. **Action: no revision required.**

"The intention of the company model is to largely mirror that of TA375. The key conceptual difference is that the company model includes a relationship between the HAQ and the DAS-28 which permits it to model moderate RA patients worsening to severe RA" Page 233: *"The key difference from the TA375 modelling is that moderate RA patients can progress to be severe RA patients"*			

Issue 7 BSC EULAR response rate

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Missing information as to the reason why BSC is assumed to have a 0% EULAR response rate: Page 23: *"EULAR response rates are taken from the company csDMARD-IR NMA and bDMARD-IR NMA. BSC is assumed to have a 0% EULAR response rate"* Page 26: *"A key difference between the company and the ERG is that the company thinks that when UPA is compared with BSC, BSC should be assumed to have 0% EULAR response rates"* Page 205: *"But among moderate RA patients the company modelling approach assumes 0% ACR20, 0% ACR50 and 0% ACR70 response rates in the **comparator** arm"* Page 234: *"The company thinks that when UPA is compared with BSC, BSC should be assumed to have 0% EULAR response rates"*	AbbVie kindly request that this is amended throughout to the following: *"BSC is assumed to have a 0% EULAR response rate, **in line with the assumption made in TA375**"* Specifically, the wording on page 205 of the ERG report: *"But among moderate RA patients the company modelling approach assumes 0% ACR20, 0% ACR50 and 0% ACR70 response rates ~~in the comparator arm~~ **for BSC when it is the first-line intervention in the comparator arm, in line with TA375.**"*	This is an important omission as it is significant to note that this assumption is in line with the assumption made in TA375. And specifically, it should be made clear that the company model differs from the ERG model in the response rate values assigned to BSC in the first-line position in the comparator arm in moderate RA. The company model (in line with TA375) assumes 0% response rate, while the ERG model assumes PBO response rate from the NMA. At present the wording is ambiguous and could be interpreted incorrectly.	The ERG does not believe its original statement to be factually incorrect. **Action: no revision required.**

Issue 8 EULAR response rates in control arms

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The report refers throughout to significant EULAR response rates in the control arms of the trials. Page 26: *"The ERG notes that in all SELECT trials there were significant EULAR response rates in the control arms. Whether the response rates in the control arms were due to natural recovery or to a pure trial or PBO effect is not known"* Page 234: *"The ERG notes that in all SELECT trials there were considerable EULAR response rates in the control arms. Whether the response rates in the control arms were due to natural recovery or a pure trial or PBO effect is not known"*	AbbVie kindly request that this is amended throughout to reflect the background therapy in the control arms: "*…in all SELECT trials there were significant EULAR response rates in the control arms,* ***which included background csDMARDS****. Whether the response rates in the control arms were due to natural recovery or to a pure trial or PBO effect,* ***or due to the efficacy of csDMARDs*** *is not known*	It is important to correct that the control arms in the trials included both placebo and csDMARDs. Response rates in the trials could also be attributed to the effects of csDMARDs.	The ERG does not believe its original statement to be factually incorrect. **Action: no revision required.**

Issue 9 Diversions from TA375

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Missing information where the ERG modelling diverges from TA375. Pages 30-31 • *Having modelled a comparison of (1) intensification of csDMARDs after trialling UPA with (2) intensification of csDMARDs before trialling UPA and found (1) to be not cost effective, the main ERG modelling does not consider intensification of csDMARDs after UPA .* •*Where UPA is compared with BSC, the ERG applies the PBO response rates of the company csDMARD-IR NMA or the SELECT trials' head-to-head results for UPA compared to the control arm .*	AbbVie kindly requests that this is amended to the following: • *Having modelled a comparison of (1) intensification of csDMARDs after trialling UPA with (2) intensification of csDMARDs before trialling UPA and found (1) to be not cost effective, the main ERG modelling does not consider intensification of csDMARDs after UPA.* ***This is not in line with the approach followed in TA375.*** •*Where UPA is compared with BSC, the ERG applies the PBO response rates of the company csDMARD-IR NMA or the SELECT trials' head-to-head results for UPA compared to the* ~~*control*~~ ***comparator*** *arm.* ***This is not in line with the approach followed in TA375.***	It is important to understand and clearly state where there are divergences from the approach followed in TA375.	The ERG does not believe its original statement to be factually incorrect. **Action: no revision required.**

Issue 10 Proportion of patients achieving low disease activity in SELECT-NEXT trial

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Incorrect proportion of patients who achieved low disease activity **(DAS-28 - CRP ≤3.2)** at 12 weeks from the SELECT-NEXT trial is reported. On Page 46-47, it is written: *"Similarly, there was a significant between-group difference in the proportion of patients who achieved low disease activity **(DAS-28 - CRP ≤3.2)** at 12 weeks: 47.9% of those receiving UPA 15mg compared with 17.2% of those receiving PBO, p<0.001"*	AbbVie kindly requests that the values is amended to 48.4%	In the SELECT-NEXT trial, 48.4% of patients receiving UPA achieved low disease activity.	The ERG does not believe its original statement to be factually incorrect. **Action: no revision required.**

Issue 11 Cost effectiveness: incorrect reporting of population in Position 4b in Table 47

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The heading of Table 47 on page 168 reads: "*Sequence: 4b: Severe RA: MTX tolerant, RTX tolerant, failed one bDMARD while it refers to RTX intolerant population"*	AbbVie kindly request to reword the title of Table 47 to Sequence: "*4b: Severe RA: MTX tolerant, RTX intolerant, failed one bDMARD"*	The treatment sequences reported in Table 47 refer to the RTX intolerant population as per the heading of section 5.2.8.	The ERG has corrected this typographical error. **Action: Table 47 caption 'tolerant' replaced by 'intolerant'.**

Issue 12 Cost effectiveness: treatment sequences following first-line RTX+MTX for population 4A

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The title of Table 47 on page 168 reads: "*Sequence: 4b: Severe RA: MTX tolerant, RTX tolerant, failed one bDMARD while it refers to RTX intolerant population"*	AbbVie kindly request to reword the title of Table 47 to: "*Sequence: 4b: Severe RA: MTX tolerant, RTX **intolerant**, failed one bDMARD"*	The treatment sequences reported in Table 47 refer to the RTX intolerant population as per the heading of section 5.2.8.	The ERG has corrected this typographical error. The ERG noted that Issues 11 and 12 are the same. **Action: Table 47 caption 'tolerant' replaced by 'intolerant'.**

Issue 13 Quality assessment of studies included in the network meta analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Two NMAs incorrectly referred to on page 126: *"The company appraised the quality of the 61 trials included in the two NMAs (55 that were included in the NMA for the bDMARD-experienced population and 12 that were included in the NMA for the csDMARD-experienced population, noting that six trials were included in both NMAs)"*	AbbVie kindly request that this is amended to the following: *"The company appraised the quality of the 61 trials included in the two NMAs (55 that were included in the NMA for the **csDMARD-experienced** population and 12 that were included in the NMA for the **bDMARD-experienced** population, noting that six trials were included in both NMAs)"*	The csDMARD NMA has been incorrectly referred to as the bDMARD NMA and vice versa.	The ERG has made the requested amendment. **Action: p.126 text amended as suggested.**

Issue 14 Table 1. Estimates of EULAR treatment effect in csDMARD-experienced population at six months, excluding SELECT-SUNRISE

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>ERG response</th></tr>
<tr>
<td>Table 29 includes incorrect values and incorrectly labelled columns. The posterior median column is repeated twice with different values for the moderate EULAR response category in each column. The posterior median values in the good EULAR response columns are incorrect.</td>
<td>AbbVie request the table is amended with the correct table headings and values below:
<table>
<tr><th></th><th colspan="2">No response</th><th colspan="2">Moderate Response</th><th colspan="2">Good Response</th></tr>
<tr><th>Treatment</th><th>Posterior Median</th><th>(95% CrI)</th><th>Posterior Median</th><th>(95% CrI)</th><th>Posterior Median</th><th>(95% CrI)</th></tr>
<tr><td>csDMARD</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Abatacept 10 mg/kg + csDMARD</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Abatacept 125 mg + csDMARD</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Adalimumab 40 mg</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Adalimumab 40 mg + csDMARD</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Baricitinib 2 mg + csDMARD</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Baricitinib 4 mg + csDMARD</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Certolizumab 200 mg + csDMARD</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Etanercept 50 mg</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Etanercept 50 mg + csDMARD</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Golimumab 50 mg + csDMARD</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
</td>
<td>The values and headings are incorrectly reported.</td>
<td>The ERG has corrected the table.
Action: Table 29 replaced.</td>
</tr>
</table>

	Infliximab 3 mg/kg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
	Intensive csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
	Rituximab 2000 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
	Sarilumab 150 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
	Sarilumab 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
	Sarilumab 200 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
	Tocilizumab 8 mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
	Tocilizumab 8 mg/kg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
	Tocilizumab 162 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
	Tofacitinib 10 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
	Tofacitinib 5 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
	Tofacitinib 5 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
	Upadacitinib 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
	Upadacitinib 15 mg + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
	Abbreviations: EULAR, European League Against Rheumatism; csDMARD, conventional synthetic disease modifying antirheumatic drug; CrI, credible interval; RA, rheumatoid arthritis.								

Issue 15 NICE reference case checklist

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Missing information. The synthesis evidence row of table 34 on page 159 reads: *"The company applies the clinical effectiveness estimates of its two NMAs: the csDMARD-IR NMA and the bDMARD-IR NMA.* *Given the NICE methods guide, it can be argued that the head to head results of the SELECT trials should be applied in the modelling where UPA is being compared to BSC, control or PBO"* In addition, page 191 reads: *"It should be noted that the main innovation of the company model is in the modelling of moderate RA patients, and how they transition to severe RA. It appears that this aspect of the company model was turned off for the above validation exercise. It would have been helpful if the company had provided an additional comparison with this aspect of the model turned on"*	AbbVie kindly request rewording the sentence to the following: Table 34: *"The company applies the clinical effectiveness estimates of its two NMAs: the csDMARD-IR NMA and the bDMARD-IR NMA.* *Given the NICE methods guide, it can be argued that the head to head results of the SELECT trials should be applied in the modelling where UPA is being compared to BSC, control or PBO.* ***This was explored in a scenario analysis in the CS****."* Page 191: *"It should be noted that the main innovation of the company model is in the modelling of moderate RA patients, and how they transition to severe RA. It appears that this aspect of the company model was turned off for the above validation exercise. It would have been helpful if the company had provided an additional comparison with this aspect of the model turned on.* ***This was explored in a scenario analysis in the CS"***	Both of these were presented in the scenario analyses shown in Table 86 in the original submission and Table A.18. in the addendum to the submission. It is incorrect to state that this was not explored.	The ERG does not believe its original statement to be factually incorrect. The company model validation exercise does not show the effects upon the validation results against those of TA375 with the progression to severe RA turned on. The ERG recognises that a scenario analysis that turns off this aspect of the model is presented in table A18, but this is not the same thing. Given the descriptions of scenarios 1-4 of section B.3.8.3 it does not appear that the company has presented analyses comparing upadacitinib with the control/placebo arm effect estimates. **Action: no revision required.**

Issue 16 Cost effectiveness: efficacy assumptions for position 4a

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 167, the ERG report states the following for population 4a: *"The effectiveness of all treatments other than TCZ_{IV} and TCZ_{SC} is assumed to be the same as BRC+MTX, taken from the bDMARD-IR NMA".*	AbbVie kindly request rewording the sentence to exclude *TCZ_{IV} and TCZ_{SC}* *"The effectiveness of all treatments is assumed to be the same as BRC+MTX, taken from the bDMARD-IR NMA".*	For population 4a (monotherapy), the effectiveness of all treatments without exception were assumed to be the same in the most recently updated version of the CEM.	The ERG has made the requested amendment. **Action: p.167 text deleted as requested.**

Issue 17 Cost effectiveness: assumptions for MTX tolerant, RTX intolerant, failed one bDMARD population

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 168, the ERG report states the following for population 4b: *"ADA+MTX is assumed to have the same efficacy as BRC+MTX, taken from the bDMARD-IR NMA".*	AbbVie kindly request adding the additional comparators including IFX+MTX and ETN+MTX which are assumed to have the same efficacy as BRC+MTX *ADA+MTX, ETN+MTX and IFX+MTX are assumed to have the same efficacy as BRC+MTX, taken from the bDMARD-IR NMA".*	The current sentence can be interpreted as only ADA+MTX is assumed to have the same efficacy as BRC+MTX.	The ERG does not believe its original statement to be factually incorrect. However, for additional clarity, the ERG has added reference to these additional comparators. **Action: p.168 reference to *ETN+MTX and IFX+MTX added***

Issue 18 SELECT trials: Control arm ACR response rates

Description of problem

Inaccurate labelling of table 74 on page 205 of the ERG report in relation to the control arms:

		PBO/control arm			UPA arm		
SELECT	**Cont.**	**ACR 20**	**ACR 50**	**ACR 70**	**ACR 20**	**ACR 50**	**ACR 70**
COMPARE (Wk 12)	**PBO**	36 %	15 %	5 %	71 %	45 %	25 %
COMPARE (Wk 26)	**PBO**	36 %	21 %	10 %	67 %	54 %	35 %
NEXT	**PBO**	36 %	15 %	6 %	64 %	38 %	21 %
MONOTHERAPY	**MTX**	41 %	15 %	3 %	68 %	42 %	23 %
BEYOND	**PBO**	28 %	12 %	7 %	65 %	34 %	12 %

Table 75 on page 206 is labelled as the following:

			EULAR re		
			Cont.		
SELECT-COMPARE	**Wk**	**Cont**	**Mod.**	**Good**	**Mod.**
NRI	26	**PBO**	24%	17%	19%

Description of proposed amendment

AbbVie kindly requests adding the control group interventions for each trial as described in the tables below:

		PBO/control arm			
SELECT	**Cont.**	**ACR 20**	**ACR 50**	**ACR 70**	
COMPARE (Wk 12)	**PBO +MTX**	36%	15%	5%	
COMPARE (Wk 26)	**PBO + MTX**	36%	21%	10%	
NEXT	**PBO +csDMARD**	36%	15%	6%	
MONOTHERAPY	**MTX**	41%	15%	3%	
BEYOND	**PBO + csDMARD**	28%	12%	7%	

Table 75:

			EULAR resp			
			Cont.		UP	
SELECT-COMPARE	**Wk**	**Cont**	**Mod.**	**Good**	**Mod.**	
NRI	26	**PBO+MTX**	24%	17%	19%	
LOCF	26	**PBO+MTX**	36%	18%	31%	
Modelling UPA+csDMARD	..	BSC	0%	0%	31%	

Table 77:

Justification for amendment

The PBO/control arms of the trials included background therapy with MTX or csDMARDs. This should be reported accurately to avoid confusion and the misunderstanding leading to an incorrect interpretation on the efficacy of PBO.

ERG response

The ERG does not believe its original statement to be factually incorrect.

Both arms of the SELECT trials highlighted by the company received ongoing background MTX / csDMARDs.

Action: no revision required.

LOCF	26	**PBO**	36%	18%	31%
Modelling UPA+csDMARD	..	BSC	0%	0%	31%

Table 77 on page 207 is labelled as the following:

			EULAR re		
			Control		
SELECT	**Wk**	**Cont**	**Mod.**	**Good**	**Mod.**
For comparison with UPA+csDMARDs modelling					
COMPARE	12	**PBO**	24%	22%	31%
COMPARE	26	**PBO**	23%	23%	30%
NEXT	12	**PBO**	24%	22%	31%
Modelling UPA+csDMARD	..	BSC	0%	0%	31%
For comparison with UPA monotherapy modelling					
MONOTHERAPY	14	MTX	25%	25%	31%
Modelling UPA	..	BSC	0%	0%	30%

The title of table 78 on page 209 is labelled as the following:

"Table 2. SELECT trials: Control arm ACR responses over time"

59%	-5%	41%							
42%	31%	42%							
SELECT		**Wk**	**Cont**	**EULAR response rates**					
				Control		**UPA**		**Net**	
				Mod.	**Good**	**Mod.**	**Good**	**Mod.**	**Good**
For comparison with UPA+csDMARDs modelling									
COMPARE		12	**PBO+MTX**	24%	22%	31%	40%	7%	18%
COMPARE		26	**PBO+MTX**	23%	23%	30%	40%	7%	17%
NEXT		12	**PBO+csDMARD**	24%	22%	31%	36%	6%	14%
Modelling UPA+csDMARD		..	BSC	0%	0%	31%	42%	31%	42%
For comparison with UPA monotherapy modelling									
MONOTHERAPY		14	MTX	25%	25%	31%	38%	6%	14%
Modelling UPA		..	BSC	0%	0%	30%	38%	30%	38%

Table 78:

*"Table 3. SELECT trials: Control arm **(PBO+csDMARD)** ACR responses over time"*

Issue 19 Modelling assumption

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Missing information on page 208: *"When considering the trials' data for comparisons with UPA+MTX, the ERG will apply SELECT-COMPARE week data"*	AbbVie do not have the information to propose an amendment.	It is not clear whether the 12 week data were used here, and if so was the NRI or LOCF approach used. It would aid understanding to include this missing information.	The ERG does not believe its original statement to be factually incorrect. The ERG has added further information for additional clarity. The efficacy data applied is within the ERG revised model that was sent to NICE: ERG worksheet columns AG:AN. **Action: p.208 additional clarifying text added. The relevant section now reads:** **"**When considering the trials' data for comparisons with UPA+MTX, the ERG will apply SELECT-COMPARE data supplied by the company at clarification. The company has only supplied the week 26 SELECT-COMPARE EULAR response rates, as reported in table 76 above so the ERG does not have the values before rescue therapy. The ERG selects the LOCF values on the basis of LOCF being the

			default method for analysing secondary variables in the SELECT-COMPARE CSR. The less optimistic SELECT-NEXT response rates are provided as a scenario analysis. When considering the trials' data for comparisons with UPA, the ERG will apply the Week 12 response rates of SELECT-MONOTHERAPY."

Issue 20 SELECT trials: Control arm ACR responses over time

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Incorrect information on page 209: *"Within SELECT-COMPARE the proportion of patients with an ACR20 response remained largely unchanged between Week 12 and Week 26. But among those with an **ACR20** response there is evidence of further improvements"*	AbbVie request this should be changed to the following: *"Within SELECT-COMPARE the proportion of patients with an ACR20 response remained largely unchanged between Week 12 and Week 26. But among those with an **ACR50** response there is evidence of further improvements"*	ACR50 is incorrectly referred to as ACR20.	The ERG does not believe its original statement to be factually incorrect. ACR20 patients encompass ACR 50 patients **Action: no revision required.**

Issue 21 Tociluzumab IV vs. tociluzumab SC vs. sarilumab SC

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Incorrect information on page 215: "ERG expert opinion notes that there is a strong patient preference for IV over SC"	AbbVie request this should be changed to the following: *"ERG expert opinion notes that there is a strong patient preference for SC over IV"*	This should be corrected to state SC over IV.	The ERG has corrected this typographical error. **Action: p215 - typographical error corrected.**

Issue 22 ERG scenario analyses: Position 2b vs csDMARDs: Moderate RA: MTX tolerant, RTX tolerant, failed ≥2 csDMARDs

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 104 and 105 on pages 227 and 228: - Incremental QALY for scenario 01 - Incremental QALY for scenario 03 - Incremental QALY for SA01a: COMPARE EULAR	AbbVie do not have the information to propose an amendment.	These QALYs could not be replicated as per the suggestion by the ERG to review the outputs of the analysis.	The ERG does not believe its original statement to be factually incorrect. The requested data are within the ERG revised company model submitted to NICE. The scenarios only change the treatment sequences. There was an error in the report submitted to NICE for position 2b scenarios 01 and 03 which was corrected in a revised version sent to NICE on 12 September 2019. It seems likely that the

			company received the uncorrected version. The ERG has rerun the analyses and arrives at the same net QALYs for SA1a in table 105. There was an error in an implementation of the ERG revised model ERG worksheet AG3:AN3, but the ERG thought it had corrected this in the revised model it sent to NICE. But it is possible that the company copy incorrectly looks up these values. When running SA1a the company is asked to cross check that the values in ERG worksheet AG3:AN3 correspond to the COMPARE values in the cells below. The model also has to be run twice: once for UPA [ERG B3] with BSC as the comparator [ERG B14] and once for BSC [ERG B3]. These runs result in the net QALYs reported for SA1a in table 105. **Action: no revision required.**

Issue 23 Overall report: Inconsistent labelling of bDMARDs

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Throughout the report, JAK inhibitors are incorrectly referred to as bDMARDs	AbbVie kindly request changing these instances to the term “advanced therapy” instead as this covers all MoAs without the need to specify.	JAK inhibitors are not biologics and therefore should not be referred to as such.	The ERG did not refer to JAK inhibitors as being bDMARDS. The ERG does not believe its original statements to be factually incorrect. There were two company tables that included JAK inhibitors as bDMARDS – the ERG has adjusted this company table in reproduction. The ERG has made edits to text for additional clarity where the meaning may be misunderstood by the reader. **Action: relevant company tables amended. Textual edits in ERG report made for clarity (p. 25, 41, 154, 166)**

NICE National Institute for Health and Care Excellence

Technical engagement response form

Upadacitinib for previously treated moderate to severe active rheumatoid arthritis [ID1400]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical 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 questions below. You do not have to answer every question. 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 summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **Thursday 21 November 2019**

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 technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- 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.

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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 Ltd**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**

Questions for engagement

Issue 1: Response rates for best supportive care	
1. What does best supportive care (BSC) consist of in NHS clinical practice? How often is it used in both moderate and severe RA in clinical practice as a last line treatment?	**BSC in NHS clinical practice would usually consist of re-challenge with a previously failed csDMARD plus corticosteroids.** **BSC is used:** • **in patients with moderate disease who have failed on recommended treatment options but whose disease is not severe enough to qualify for advanced therapy** • **in patients with severe disease who have failed on all available and recommended treatment options** • **in the model this is captured by patients who have exhausted all treatment options initially receiving csDMARDs and upon failure receiving BSC in order to capture the diminishing efficacy of csDMARDs over time** Based on clinical advice from ten rheumatologists at an advisory board, the ERG clinical expert, and NICE clinical expert, AbbVie's understanding is that BSC does exist in clinical practice and is used in both moderate and severe rheumatoid arthritis (RA) patients when clinicians have exhausted all possible treatment options for their patients. In practice, when clinicians have exhausted all possible treatment options for their patients, they are likely to re-challenge patients with a combination of csDMARDs that may have worked best previously alongside steroid treatment while acknowledging that efficacy will be greatly reduced and no expectation of a disease modifying effect. In the technical engagement papers associated with this appraisal, the clinical expert explained: ***"If someone fails all options a number of approaches can occur. In reality, if someone has already failed csDMARDs it is usually futile to try the same csDMARDs again. This is reflected in the EULAR recommendations that state that once patients fail the first csDMARDs then this selects them as poor prognosis individuals who should receive tsDMARDs or bDMARDs. However, even though it might be futile different combinations of csDMARDs and corticosteroids may be used as there is currently no other choice… Re-trying csDMARDs that are very unlikely to work may as well be palliative care as they will not work" (Pg. 719 technical engagement papers)*** The clinical expert refers to this as palliative care, acknowledging there would be no disease modifying effect associated with this. In addition, it is expected that what constitutes BSC would be no different for patients who have tried and failed on upadacitinib after the introduction of upadacitinib in clinical practice to what is taking place in existing clinical practice for patients who have tried and failed existing treatment options. As detailed by the ERG clinical expert in the ERG report: ***"…UPA might be withdrawn and patients placed back on whichever combination of csDMARDs proved best" (Pg. 211 ERG report)***

	Therefore, it is expected that the same approach would be taken in clinical practice after the failure of upadacitinib as it is currently.
2. Which of the following assumptions is the most appropriate to use in the model for BSC? a) Use the placebo EULAR response rates from the upadacitinib phase III trials or the NMA, for BSC b) Assume that the response rate for BSC is 0%	**The most appropriate assumption to use in the model for BSC is zero response: untreated RA is a progressive disease.** **The preliminary NICE preferred approach is not appropriate as:** • **The intention is to model assumptions relating to clinical practice. It is important to understand what placebo would constitute in clinical practice** • **The assumption of placebo equating to natural recovery in untreated patients is not supported by the evidence base which demonstrates progressive decline in functionality (explained in detail under 1 below).** • **The inclusion of placebo in the comparator arm to address the issue that the efficacy of upadacitinib seen in in the clinical trials may be inflated because of the trial setting is not methodologically sound. The appropriate methodological approach would be to net off the inflated efficacy of upadacitinib directly from the upadacitinib arm (explained in detail under 2 below).** • **The approach of assuming 0% efficacy for BSC is aligned to the approach in TA375. The understanding of the ERG that this approach is not aligned to the approach in TA375 based on the ERG validation exercise of the AbbVie model against the TA375 model (as stated in the ERG model validation report addendum) is undermined by operational issues outlined in section 3 of this response.** Broadly two rationales are described for using a response rate greater than zero for BSC within the "background / description of the issue" section related to this issue in the technical report (p.16 and p.17): 1) The need to model natural recovery through setting a response rate of greater than zero for BSC in the comparator arm only 2) To adjust for the fact that placebo effect contributes to some proportion of the benefit observed in the upadacitinib arms in the SELECT trials through setting a response rate of greater than zero for BSC in the comparator arm only Each rationale is explored in detail below. **<u>1) The need to model natural recovery through setting a response rate of greater than zero for BSC</u>** The most appropriate assumption to use in the model regarding a response rate for BSC is 0%. Applying a response rate greater than 0% in the HE model for BSC results in patients upon being initiated on BSC returning to a Health Assessment Questionnaire Disability Index (HAQ) score which is lower than their baseline HAQ score. This equates to an improvement in functionality relative to baseline and implies natural recovery. Previous RA appraisals, including TA375 have relied on UK observational datasets to map HAQ trajectories over time for patients on BSC.

	These databases have consistently demonstrated that there is no improvement in functionality over time for patients on BSC, rather, functionality is observed to decrease as HAQ is seen to increase with time (1-4). A response rate greater than zero is therefore not appropriate for BSC as it implies some form of natural recovery. However, if a response rate greater than 0% for BSC is used in the model the following should be noted: • The csDMARD-IR NMA is a more appropriate source for placebo response as this included three studies which contributed data from arms which included pure placebo. The upadacitinib phase III trials are not an appropriate source for placebo response since all patients in the control arm (placebo arm) were placed on placebo plus background csDMARD. • AbbVie notes that the ERG has made assumptions not only about the experience of natural recovery for patients at the point of initiating BSC but also over time. AbbVie do not believe that those experiencing natural recovery (placebo effect) have a HAQ trajectory more preferential than those on csDMARDs or BSC over time. The ERG exploratory analysis does assume such a preferential HAQ trajectory. AbbVie believe that if it is to be modelled, then the HAQ trajectory associated with those experiencing natural recovery (placebo effect) should have a HAQ trajectory the same as those on csDMARDs or BSC. The ICERs presented by the ERG are substantially reduced if the AbbVie HAQ trajectory assumption is used as shown in Table 1– Scenario 1 • If the assumption is that natural recovery is present, this assumption should apply equally to BSC after upadacitinib failure as well as after csDMARD failure in the comparator arm (in moderate RA). There is no clinical rationale for assuming natural recovery in the comparator arm after csDMARD failure but not in the upadacitinib arm after upadacitinib failure. Presently the exploratory analysis carried out by the ERG (for moderate RA) assumes a response rate higher than 0% for patients initiated on BSC in the comparator arm but a 0% response rate for those initiated on BSC in the UPA arm (following upadacitinib failure and withdrawal). The associated ICERs presented by the ERG are substantially reduced if the AbbVie assumption of the same response rate being used for patients initiated on BSC in the comparator arm and the upadacitinib arm of the HE model are applied. This is shown in Table 1 - Scenario 2.

*Table 1: Impact of assumptions of HAQ trajectory and PBO/natural recovery on ICERs (after two or more csDMARD failures, moderate RA)**

Scenario	Comparison	Source of efficacy for PBO / natural recovery	HAQ trajectory assumption for PBO / natural recovery	With transition to severe RA advanced therapies	Without transition to severe RA advanced therapies
NICE preferred base case**	UPA combo then BSC VERSUS natural recovery (PBO effect) then BSC	PBO + background csDMARD arm of SELECT-NEXT UPA Phase III study	natural recovery has preferential HAQ trajectory compared to being on csDMARDs / BSC*	£94,563*	£84,566
Scenario 1	UPA combo then BSC VERSUS natural recovery (PBO effect) then BSC	PBO + background csDMARD arm of SELECT-NEXT UPA Phase III study	natural recovery has the same HAQ trajectory to being on csDMARDs / BSC	£49,555	£51,156
Scenario 2	UPA combo then natural recovery (PBO effect) then BSC VERSUS natural recovery (PBO effect) then BSC	PBO + background csDMARD arm of SELECT-NEXT UPA Phase III study	natural recovery has the same HAQ trajectory to being on csDMARDs / BSC	£21,295	£27,724

***All analyses use ERG preferred severe RA treatment sequences / TA375 HAQ to pain utility map / ERG revised drug (list price) and administration and HAQ costs / ERG preferred csDMARD-IR NMA efficacy for bDMARD-IR naïve patients and bDMARD-IR NMA efficacy for bDMARD experienced patients**
****NICE technical engagement report (highest ICER in most plausible ICER range on page 14) - assumes transition to severe RA advanced therapies**

2) To adjust for the fact that placebo effect contributes to some proportion of the benefit observed in the upadacitinib arms in the SELECT trials through setting a response rate of greater than zero for BSC in the comparator arm only

This is captured within the "Background / description of the issue" section related to this issue in the technical report (pg.16) in the following statement: "Even if there were no natural recovery or a delayed treatment effect, the ERG advised that it would expect a PBO effect to be present in both arms of a trial (contributing some proportion of the benefit observed in the upadacitinib arm). Therefore, the cost-effectiveness results should not include the PBO effect in only the intervention arm. The ERG noted that by doing so the company's modelling implies a much larger relative treatment effect for UPA over the control arm than is present in the results from the SELECT trials"

It is important to note the following in the framing of the issue in the statement above:

- The NICE methods guide (section 6.2.2) states that the selection of the appropriate comparators should take into account factors such as "*established NHS practice in England*", which is not necessarily the same as the control arm of the clinical trials. The modelled comparator arm is therefore not synonymous with the control arm of the upadacitinib clinical trials but with existing clinical practice in the absence of upadacitinib. Consequently, any inclusion of a placebo effect within the comparator arm must be addressing an issue that relates to either existing clinical practice or indirectly addressing an issue relating to the efficacy assigned to upadacitinib in the upadacitinib arm.
- It is not stated in the technical engagement report how the use of a response rate for BSC which equates to placebo would address an issue relating to clinical practice in concrete terms other than an observation by the technical team that it is "concerned that applying a 0% response rate to BSC may bias the cost effectiveness results in favour of UPA" (pg. 17, technical engagement report).
- The only interpretation that AbbVie have been able to infer from this concern from the technical team is that the upadacitinib efficacy demonstrated in its clinical trials consists of some efficacy which is specific to a trial setting and will not manifest in real life clinical practice. AbbVie infers that this is being equated to the placebo response estimated from the NMA. If this interpretation is correct the inclusion of this placebo effect in the comparator arm of the HE model is not a methodologically sound approach to estimating the cost effectiveness of upadacitinib with this placebo effect "netted off" because it involves netting off benefit (indirectly) from the upadacitinib arm whilst requiring upadacitinib to incur the drug cost (and continuation rate) associated with a higher upadacitinib efficacy (i.e. without the placebo effect netted off). A methodologically more robust approach is to net the placebo effect off in the NMA and apply a reduced efficacy to the upadacitinib arm (with a consequently reduced efficacy aligned to a reduced continuation rate). The ICERs are sensitive to the method used as shown in Table 2 below:

Table 2: Implication of netting off placebo effect in the NMA (after two or more csDMARD failures, moderate RA)

Scenario	Comparison	Source of efficacy for PBO and UPA combo	HAQ trajectory assumption for PBO / natural recovery	With transition to severe RA advanced therapies	Without transition to severe RA advanced therapies
ERG approach* **	UPA combo then BSC VERSUS PBO then BSC*	1) UPA combo: base case csDMARD-IR NMA 2) PBO: base case csDMARD-IR NMA*	Natural recovery has preferential HAQ trajectory compared to being on csDMARDs / BSC*	£35,958*	£38,676
Scenario 1** **	UPA combo then BSC VERSUS BSC	UPA combo: csDMARD-IR NMA which nets off PBO** PBO: N/A	N/A	£18,537	£23,432

***from page 33 of technical engagement report**
**** NMA presented for the first time as part of the technical engagement consultation by AbbVie (see Table 3 below).**
*****Analysis uses ERG preferred severe RA treatment sequences / TA375 HAQ to pain utility map / ERG revised drug and administration and HAQ costs / ERG preferred csDMARD-IR NMA efficacy for bDMARD-IR naïve patients and bDMARD-IR NMA efficacy for bDMARD experienced patients**
******Analysis uses ERG preferred severe RA treatment sequences / TA375 HAQ to pain utility map / ERG revised drug and administration and HAQ costs / csDMARD-IR NMA efficacy for bDMARD-IR naïve and bDMARD experienced patients (PBO netted off NMA only available for csDMARD-IR NMA because no placebo trials in bDMARD-IR NMA so downstream advanced therapy efficacy modelled using csDMARD-IR NMA efficacy)**

Table 3: Treatment comparison and net response vs control of 24-week estimated EULAR response mapped from AbbVie base case csDMARD-IR NMA(This is new analysis and as such has also been submitted in a separate document alongside this response)

	Base case NMA		*Used for scenario 1 - Table 2	
Treatment	**Moderate Response (95% CrI)**	**Good Response (95% CrI)**	**Treatment vs PBO Moderate Response (95% CrI)**	**Treatment vs PBO Good Response (95% CrI)**
csDMARD	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab combo	[redacted]	[redacted]	[redacted]	[redacted]
Rituximab combo	[redacted]	[redacted]	[redacted]	[redacted]
Sarilumab combo	[redacted]	[redacted]	[redacted]	[redacted]
Upadacitinib combo	[redacted]	[redacted]	[redacted]	[redacted]

***These were calculated by first translating the ACR NMA results at the MCMC iteration-level to EULAR probabilities and then taking the differences in EULAR probabilities at the MCMC iteration-level between treatment vs. either csDMARD and PBO.**

3) Model validation in relation to issue 1 overall

A general point that relates to both 1) and 2) above is AbbVie's response to the following statement in the technical team preliminary judgement and rationale section for issue 1 (page 18) "*The technical team notes that the ERG model validation addendum suggests that the ERG approach is more consistent with the methods accepted by the committee in TA375, compared to the company's approach (see ERG model validation addendum)*". It is important to consider the following:

- AbbVie's preferred approach of applying a 0% response rate for BSC reflects that preferred by the assessment group in TA375. From the strategies modelled section of the TA375 assessment group report (pg. 347) the following is stated "***It was assumed that non-biologic therapy would be associated with no initial EULAR response, unlike MTX where the results from the NMA indicated that MTX***

had a significant EULAR response. [Next sentence. New Paragraph] This description is in line with the data on HAQ progression that was presented by Norton et al". Non biologic therapy in the TA375 report refers to BSC.

- The work associated with the ERG model validation is associated with the errors detailed in a document (titled "*An evaluation of the ERG's approach documented in the ERG Report Addendum 3: Model Validation and recommended updates*") submitted to NICE in conjunction with this consultation response. These errors have a substantial impact on cost and QALY estimates using the TA375 model and invalidate the conclusions made in the ERG model validation addendum. These include:
    - Monitoring costs not included for any drugs (only for BSC) by the ERG in their revision of the TA375 model which means the total costs reported in the addendum substantially underestimate the correct TA375 output
    - Drug costs for those drugs labelled as "discrete" in the TA375 model (specifically ABT IV, IFX, RTX, TCZ IV) are implemented incorrectly by the ERG in their revision of the TA375 model which means the total costs reported in the addendum constitute a substantial underestimate of the correct TA375 output
    - After correcting these for these two issues in the ERG-revised TA375 model, AbbVie note a reasonable correspondence in total costs between the AbbVie and the TA375 revised models. The ERG report addendum states that the AbbVie total cost outputs are 33%-63% higher than the output from the TA375 model. Once costings are appropriately implemented in the TA375 model, the AbbVie and TA375 model are well aligned in terms of total costs (AbbVie total costs are 7%-13% higher than the TA375 model). AbbVie concur with the conclusion in the ERG report addendum that there is a reasonable correspondence in the QALY estimates between the two models (2%-7% higher in the AbbVie model).

The impact of AbbVie corrections on the response period and subsequent yearly drug costs for the 4 treatments (ADA, int csDMARDs, GOL, IFX) plus BSC included in the eight sequences run by the ERG in the addendum are summarised in Table 4 and Table 5 below:

Table 4: Response Period costs (first 6 months): ERG revised TA 375 model vs AbbVie revised TA375 model

	ERG revised TA375 model			AbbVie revised TA375 model			Drug plus admin and monitoring (difference between ERG revised and AbbVie revised TA375)	% impact of AbbVie changes upon drug costs used in ERG-revised TA375 model
	Drug and Admin	Monitoring	Drug plus admin and monitoring	Drug and Admin	Monitoring	Drug plus admin and monitoring		
ADA	£4,060	£0	£4,060	£4,060	£1,927	£5,987	-£1,927	-47%
Int csDMARDs	£107	£0	£107	£107	£1,927	£2,034	-£1,927	-1802%
GOL	£4,997	£0	£4,997	£4,997	£1,927	£6,924	-£1,927	-39%
IFX	£7,108	£0	£7,108	£7,108	£1,927	£9,034	-£1,927	-27%
BSC	£396	£804	£1,200	£360	£828	£1,188	£12	1%

Table 5: Subsequent yearly costs (after first 6 months): ERG revised TA 375 model vs AbbVie revised TA375 model

	ERG revised TA375 model			AbbVie revised TA375 model			Drug plus admin and monitoring (difference between ERG revised and AbbVie revised TA375)	% impact of AbbVie changes upon drug costs used in ERG-revised TA375 model
	Drug and Admin	Monitoring	Drug plus admin and monitoring	Drug and Admin	Monitoring	Drug plus admin and monitoring		
ADA	£8,121	£0	£8,121	£8,121	£1,657	£9,778	-£1,657	-20%
Int csDMARDs	£215	£0	£215	£215	£1,657	£1,872	-£1,657	-770%
GOL	£9,994	£0	£9,994	£9,994	£1,657	£11,651	-£1,657	-17%
IFX	£4,572	£0	£4,572	£8,412	£1,657	£10,068	-£5,497	-120%
BSC	£792	£1,608	£2,400	£720	£1,657	£2,377	£23	1%

	Furthermore in relation to model validation, it is important to note that the ICERs produced using the AbbVie preferred modelling approach is validated by the fact that they are matched to the expectations expressed in the recently produced NICE Technology Appraisal Review Proposal paper: Review of TA375 (https://www.nice.org.uk/guidance/ta375/evidence/consultation-paper-may-2019-pdf-6779359118) (5) which makes the following statement: • "A recent review of the cost-effectiveness of biological DMARDs in England using the model from TA375 (Stevenson et al 2017) reported exploratory analyses showing that the cost of biological DMARDs would need to be lowered by around 50% to reduce the most plausible ICER for moderate disease (£51,100) to a range that is considered a cost-effective use of NHS resources (that is, £20,000 to £30,000 per QALY gained)". • Using the approach preferred preliminarily by NICE for the appraisal of upadacitinib in moderate RA (as stated in the UPA technical report) would yield the ICERs shown in Table 6 for the TA375 biological DMARDs if their cost (at the time of the appraisal) is lowered by 50% (transition to advanced therapies once reach DAS 28 > 5.1 switched off as a function to align to TA375). These ICERs do not match the expectations of the TA375 review proposal paper whilst those using AbbVie's preferred approach do (as shown in Table 6).

Table 6: Difference in plausible ICER range between approach preferred by NICE in current appraisal versus TA375 appraisal (after two or more csDMARD failures, moderate RA)

	Assumed annual price (half that used in TA375)	Using NICE preliminary preferred approach (plausible ICERs reflecting those on p14 of the technical engagement report)*	Using AbbVie preferred approach (two differences to NICE preferred approach) – see Table 8
ADA+	£4,578	£61,088 to £82,442	£29,333 to £34,688
INF+	£3,965	£62,005 to £86,270	£28,588 to £33785
ETN +	£4,648	£67,374 to £91,727	£30,500 to £36,450

***All analyses use ERG preferred severe RA treatment sequences / TA 375 HAQ to pain utility map / ERG revised drug and administration and HAQ costs / ERG preferred csDMARD-IR NMA efficacy for bDMARD-IR naïve patients and bDMARD-IR NMA efficacy for bDMARD experienced patients**

Table 7: Difference in lower end of ICER range between approach preferred by NICE in current appraisal versus TA375 appraisal (after two or more csDMARD failures, moderate RA)

	Using NICE preliminary preferred approach (plausible ICERs on p14 of the technical engagement report)*	Using AbbVie preferred approach (two differences to NICE preferred approach)* - see Table 8	Table within consultation response which outlines AbbVie preferred approach
NICE approach (lower end)	£47,466	£24,039	Table 9 – Scenario 3
NICE approach (upper end)	£94,563	£21,295	Table 1 – Scenario 2

***All analyses use ERG preferred severe RA treatment sequences / TA 375 HAQ to pain utility map / ERG revised drug and administration and HAQ costs / ERG preferred csDMARD-IR NMA efficacy for bDMARD-IR naïve patients and bDMARD-IR NMA efficacy for bDMARD experienced patients**

Table 8: Key differences between the NICE preliminary preferred approach and AbbVie relating to ICER sensitivity

	Using NICE preferred approach	Difference 1 – treatment sequencing	Difference 2 – HAQ trajectory associated with Placebo / natural recovery
NICE approach (lower end plausible ICER)	UPA then BSC VERSUS csDMARD then BSC	UPA then csDMARD then BSC VERSUS csDMARD then BSC	Not relevant
NICE approach (upper end plausible ICER)	UPA then BSC VERSUS PBO/Natural recovery then BSC	UPA then PBO/Natural recovery* then BSC VERSUS PBO/Natural recovery then BSC	NICE assume for PBO / natural recovery HAQ trajectory preferential to that on csDMARDs / BSC AbbVie assume for PBO / natural recovery HAQ trajectory the same as that on csDMARDs / BSC

***AbbVie argue earlier in their response to issue 2 earlier that natural recovery should not be modelled. However, if it is to be modelled it should be modelled as occurring after UPA failure as well as in the comparator arm.**

3. Do people with RA experience a natural recovery of their symptoms? If so what proportion of people experience this and for how long?

- **RA is a progressive disease. Short term improvement on placebo has been observed after a few a months' treatments in clinical trials but to equate this improvement to a spontaneous improvement in clinical practice runs is undermined by the evidence from observational datasets which demonstrates functional decline in untreated patients over time.**

RA is understood and well accepted to be a progressive autoimmune disease associated with increasing functional decline. As referred to in response to question 2, there exist well established trajectories of disease progression based on observational databases which demonstrate a decline in functionality for patients with RA over time. It is expected that these trajectories of disease progression would capture any level of natural recovery within this population were it occurring. Natural recovery in patients with RA is expected to be rare and short-lived as evidenced by clinical expert opinion:

"Natural recovery is very rare, particularly in people with established disease that has been treated for some time. I would estimate that it happens in less than 5% of patients. When natural recovery does occur, it is usually for a short period of time, after which disease returns." (Pg. 717, technical engagement papers)

If patients with RA were to experience natural recovery, you would expect the level of natural recovery to be the same as it is in current clinical practice for untreated patients who have exhausted all possible treatment options as it would be for untreated patients after the introduction and failure of upadacitinib.

Issue 2: Clinical pathway and positioning of upadacitinib	
4. Would UPA be used before intensified csDMARDs for treating moderate RA in clinical practice (position 1a and 1b)?	• **The company believes that, if made available, upadacitinib could be used before intensified csDMARDs for treating moderate RA in clinical practice.** Whilst the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) guidelines do recommend other advanced therapies after the failure of two csDMARDs, they recognise that there is a group of moderate patients with poor prognostic factors who would benefit from earlier treatment. An indicator of poor prognostic factors in patients which would indicate the need to treat earlier include: • Patients who remain in moderate to high disease activity according to composite measures after therapy with one csDMARD • high acute phase reactant levels • high swollen joint counts • presence of RF and/or anti-citrullinated protein antibody (ACPA), especially at high levels • presence of early erosions (6) The importance of poor prognostic factors in these patients is also reflected in NICE Clinical Guidelines for RA which stipulate that the target of remission rather than low disease activity should be considered for people with an increased risk of radiological progression (presence of anti-CCP antibodies or erosions on X-ray at baselines assessment). Therefore, in countries where ACR and EULAR guidelines are followed, patients with RA can be treated with advanced therapies after the failure of one csDMARD: ***"It should be noted that bDMARDs are used earlier in the pathway in other developed countries, such as after 1 csDMARD failure." (Pg. 716, technical engagement papers)*** AbbVie believe that upadacitinib is cost-effective compared to existing treatments after one csDMARD and is therefore a cost-effective use of resources. Clinicians should have the flexibility to exercise their judgement around whether it is more suitable to use after one or two csDMARD failure for their patients. It should be noted that if patients fail on upadacitinib, it is expected that patients would be put on the combination of csDMARDs that is deemed most appropriate as discussed in response to question 1.
5. Would you expect UPA be continued in the moderate RA population if some clinical	• **The company believes that upadacitinib would be discontinued if response criteria are not met, as is routinely done with other therapies.** Based on clinical advice from ten rheumatologists at an advisory board and the NICE clinical expert, it is understood that there are clear rules on treatment discontinuation from both NICE clinical guidelines and existing published technology appraisal guidance. NICE guidelines for the management of rheumatoid arthritis in adults (NG100) are clear on the treat-to-target strategy for patients in moderate and severe RA. The treat-to-target strategy specifies that active RA in adults should be treated with the aim of achieving a target of remission or low disease activity

benefit was achieved, even though the EULAR response criteria had not been met? What clinical benefits would need to be shown?	if remission cannot be achieved. This is well established in clinical practice with patients reviewed every 3 to 6 months depending on whether the target has been achieved. We would anticipate the same would be followed in clinical practice after the introduction of upadacitinib: ***"For all treatments, including UPA, treatment would be stopped if the patient did not meet the definition of a EULAR response, typically after 3 or 6 months. The exception to this is MTX, which may be continued as part of combination treatment due to its effectiveness as an add-on therapy." (Pg. 716, technical engagement papers)*** In addition, technology appraisal guidance recommendations for other advanced therapies specify that treatment should only be continued if there is a moderate response measured against EULAR criteria at 6 months after starting therapy. If there is an initial response within 6 months, treatment should be withdrawn if at least a moderate EULAR response is not maintained. We would anticipate that this approach since it is applied for all advanced treatments would also apply to upadacitinib.
6. Following the failure of 2 or more csDMARDs (position 2, **Error! Reference source not found.**, section 1.2), is BSC or csDMARDs used in practice (and therefore, the most relevant comparator)?	• **The company believes that in moderate RA, after the failure of 2 or more csDMARDs (synonymous with exhausting all existing treatment options), further use of csDMARDs plus steroids would be used in NHS practice. This would constitute re-challenge with csDMARDs that have previously failed and will therefore be associated with diminished efficacy.** As discussed in response to question 1, based on clinical advice from ten rheumatologists at an advisory board, the ERG clinical expert, and NICE clinical expert, our understanding is that in practice, when clinicians have exhausted all possible treatment options for their patients, they are likely to put patients on a combination of csDMARDs (whichever combination may have worked best previously) with steroid treatment. They would do so while acknowledging that efficacy will be further reduced with a minimal expectation of a disease modifying effect. Similarly, clinicians advise that the csDMARDs which would be used in present practice once they have exhausted treatment options would likewise be used in the future following the introduction and failure of upadacitinib. This approach most accurately reflects existing and anticipated future clinical practice and is in line with the treatment sequence used in moderate RA in the baricitinib (TA466), tofacitinib (TA480) and sarilumab (TA485) appraisals: • BARI/TOFA/SARI → MTX → BSC versus MTX → BSC The NICE preliminary preferred base case assumes csDMARDs will be used in the comparator arm when patients have run out of options but not in the upadacitinib arm when they have withdrawn treatment and similarly run out of options. The ICERs are substantially reduced if the AbbVie/TA466/TA480/TA485 preferred approach is used in place of the NICE preliminary preferred base case assumption as shown in **Table 9** - Scenario 1. Whilst the ICERs are less sensitive to the efficacy of the csDMARD, scenarios 2 or 3 in the table below are more appropriate

efficacy sources to use than that for intensive csDMARDs (used in in the NICE preferred case) given that patients have already been tried on and failed csDMARD treatment in this situation.

*Table 9: Impact of different treatment sequences on ICERs (after two or more csDMARD failures, moderate RA)***

Scenario	Comparison	Source of efficacy estimate for csDMARD	With transition to severe RA advanced therapies	Without transition to severe RA advanced therapies
NICE preferred base case*	UPA combo then BSC VERSUS csDMARD then BSC*	intensive csDMARD: base case csDMARD-IR NMA*	£47,466*	£50,999
Scenario 1	UPA combo then csDMARD then BSC VERSUS csDMARD then BSC	intensive csDMARD (both arms): base case csDMARD-IR NMA	£22,741	£27,838
Scenario 2	Same as Scenario 1	csDMARD (both arms): base case csDMARD-IR NMA	£21,128	£26,571
Scenario 3	Same as Scenario 1	1) csDMARD (comparator arm): base case csDMARD-IR NMA 2) csDMARD (UPA arm): base case bDMARD-IR NMA	£24,039	£28,754

***NICE technical engagement report (lowest ICER in most plausible ICER range on page 14) - assumes transition to severe RA advanced therapies**
****All analyses use ERG preferred severe RA treatment sequences / TA375 HAQ to pain utility map / ERG revised drug and administration and HAQ costs / ERG preferred csDMARD-IR NMA efficacy for bDMARD-IR naïve patients and bDMARD-IR NMA efficacy for bDMARD experienced patients**

The decision not to include a csDMARD after upadacitinib failure in the UPA arm may be influenced by the following statement on page 18 of the report "***The ERG feels that a BSC response should only be modelled where BSC is used at the same line of treatment as an active treatment on the comparator model arm. This is because assumptions about response to BSC may be particularly important in***

	comparisons between model arms with different numbers of active treatments in their pathways. In these circumstances, applying a last-line BSC response to patients on a model arm with more would potentially model results implicitly, because patients on that arm will have more chances to experience a response". Whilst this statement refers to the comparison to BSC, it is also being applied to the comparison against a csDMARD and suggests an a priori constraint to the modelling which aims to equalise treatment sequences rather than reflect clinical practice. AbbVie considers that this is inappropriate if it prevents (as in this case) clinical practice with and without upadacitinib being captured accurately. As noted previously, this would also be a divergence from base-case assumptions in previous appraisals including TA375, TA466, TA480, TA485: • BARI/TOFA/SARI → MTX → BSC versus MTX → BSC (TA466, TA480, TA485) • bDMARD+MTX → RTX+MTX → TCZ IV+MTX → MTX → BSC versus MTX → BSC (TA375) AbbVie note that the EULAR data from our clinical trials provides a useful estimate of both upadacitinib and csDMARD efficacy. With this in mind, we provide below EULAR outcomes for both the full trial dataset and the moderate subgroup in an additional document alongside this response (titled EULAR outcomes from SELECT trials).
7. Would UPA be considered as a first-line bDMARD for treating severe RA?	Our understanding is that upadacitinib would be considered as a first-line treatment option for treating severe RA.
8. Is there sufficient evidence to consider the clinical and cost effectiveness of UPA at position 4a	It is important to understand that no advanced therapy to date has clinical data relevant to the population in question, however a number of those have been recommended for use in this population based on the recognition of unmet need and the extrapolation of data in the csDMARD-IR population to the bDMARD-IR population. In the SELECT phase III program, upadacitinib achieved all primary endpoints across all assessed patient populations, including when used as monotherapy in patients with an inadequate response to MTX. Importantly, levels of efficacy observed with upadacitinib monotherapy were comparable with those observed with upadacitinib plus MTX in both csDMARD and bDMARD inadequate responder populations as noted in Table 10 below.

(severe RA, failed 1 bDMARD, MTX intolerant, RTX tolerant)?

Table 10: Efficacy of upadacitinib as monotherapy and combination therapy

	SELECT-COMPARE			SELECT-NEXT		SELECT-MONOTHERAPY		SELECT-BEYOND	
Endpoints	**Week 12**			**Week 12**		**Week 14**		**Week 12**	
	PBO (+MTX)	**ADA (+MTX)**	**UPA 15 mg (+MTX)**	**PBO (+ csDMARDs)**	**UPA 15 mg (+ csDMARDs)**	**MTX**	**UPA 15 mg QD**	**PBO (+ csDMARDs)**	**UPA 15 mg (+ csDMARDs)**
	N=651	**N=327**	**N=651**	**N=221**	**N=221**	**N=216**	**N=217**	**N = 169**	**N = 164**
ACR20 response (%)	36.4	63***	70.5***#	35.7	63.8***	41.2	67.7***	28.4	64.6***
Clinical remission based on DAS28 (CRP) (%)	6.1	18.0***	28.7***##	10	30.8***	8.3	28.1***	9.5	28.7***
LDA DAS28(CRP) (%)	13.8	28.7***	45.0***##	17.2	48.4***	19.4	44.7***	14.2	43.3***

Abbreviations: ACR20 = American College of Rheumatology 20%, ADA = adalimumab; csDMARDs = conventional synthetic DMARDs; PBO = placebo; MTX = methotrexate; QD = once daily; UPA = upadacitinib

*** Statistically significant at 0.001 level for UPA vs placebo

#, ## Statistically significant at 0.05, and 0.001 level respectively for UPA vs ADA

9. Would UPA be used as a monotherapy in MTX-tolerant populations, or would it be used only with MTX, in

AbbVie understands from feedback from ten rheumatologists at an advisory board that if the option of using updadacitinib as monotherapy is available then clinicians would welcome this option and it would be used as monotherapy. As discussed in response to question 8 and seen in Table 10, levels of efficacy observed with upadacitinib monotherapy were comparable with those observed with upadacitinib plus MTX in both csDMARD and bDMARD inadequate responder populations in the SELECT phase III program.

clinical practice?	
10. Is MTX monotherapy used as a last-line treatment in MTX-tolerant populations?	Based on clinical expert advice gained by the ERG from their clinical expert, NICE clinical expert, and the clinical expert adviser for the academic group in TA375, AbbVie's understanding is that when you have exhausted all treatment options, a combination of csDMARDs that worked best previously may be used (including methotrexate (MTX)). MTX, as one example of a csDMARD, has been used as a proxy in this situation as in reality patients are likely to derive minimal benefit from csDMARDs used as a last-line treatment. This was also the approach taken by the assessment group in TA375. It is important to note the assumption of what would be used in clinical practice after exhausting all treatment options and the assumed efficacy of this last line of treatment would be no different for patients who have tried and failed on upadacitinib after the introduction of upadacitinib in clinical practice to existing clinical practice.
11. Are the company's or ERG's treatment sequences the most appropriate (see table 6 section 4 and appendix)?	• **The company do not agree with the preliminary NICE preferred treatment sequencing proposed in moderate RA while broadly agree with the approach proposed in severe RA** • **A key difference to the proposed approach and company preferred approach in moderate RA is in relation to assumptions on what would happen in clinical practice after the failure of upadacitinib; this has a significant impact on ICERs** AbbVie do not agree with the preliminary NICE preferred treatment sequencing proposed in moderate RA whilst we broadly agree with that used in severe RA. Firstly, we will describe why the decision regarding treatment sequencing in moderate RA is one (of two) critically important decisions to which ICER estimates are sensitive. Secondly, we will provide the rationale for why the AbbVie proposed treatment sequences better reflect clinical practice. The difference in the treatment sequences used by AbbVie and the ERG in moderate RA are one of the two differences which explain the substantial differences in our respective ICER estimates as outlined in Table 9 in response to question 6. The key difference to which ICER estimates are sensitive are outlined below in relation to positions 2a, 2b and 2c (after two or more csDMARD failures)) in Table 13 (pages 39-44) in the technical report: • The key feature to which ICERs are sensitive is not whether UPA is compared to csDMARDs or PBO / natural recovery • The key feature to which ICERs are sensitive is the assumption around what would happen in clinical practice after the failure of upadacitinib, i.e. if UPA is compared to a csDMARD (after two or more csDMARD failures), the assumption as to whether patients would likewise receive a csDMARD after UPA failure as indicated in Table 9. • The key feature to which ICERs are sensitive is the assumption around what would happen in clinical practice after two or more csDMARD failure, i.e. if UPA is compared to natural recovery/placebo, the assumption as to whether patients would likewise experience

natural recovery after UPA failure as indicated in Table 1 (PBO in positions 2a, 2b and 2c is used by the ERG as an estimate of natural recovery as outlined in part A of AbbVie's response to question 2).

Specifically, in relation to position 2 in moderate RA in Table 13 of the technical engagement report (after two or more csDMARD failures), AbbVie note the following in relation to AbbVie's proposed and preferred treatment sequences:

- This position of after two or more csDMARD failures is synonymous with the situation in clinical practice where patients have tried and failed all existing treatment options in moderate RA
- Based on clinical advice from ten rheumatologists at an advisory board, the ERG clinical expert, and NICE clinical expert, our understanding is that in practice, when clinicians have exhausted all possible treatment options for their patients, they are likely to put patients on a combination of csDMARDs that may have worked best previously.
- In practice whether this is represented in the HE model by patients going onto MTX or a different csDMARD is of limited relevance (refer to **Table 9**] although since (as advised by the clinical experts) the efficacy of these drugs is diminished in this circumstance the decision by the ERG to model intensive csDMARDs in this position with their relatively high efficacy seems counterintuitive.
- Similarly, clinicians advise that the csDMARDs that would be used in present practice once they have exhausted treatment options would likewise be used in the future following the introduction and failure of upadacitinib. This is line with the AbbVie approach which is in line with the treatment sequence used in moderate RA in the baricitinib, tofacitinib and sarilumab appraisals (advanced therapy followed by MTX followed by BSC versus MTX then BSC). The ERG's base case assumes csDMARDs will be used in the comparator arm when patients have run out of options but not in the upadacitinib arm when they have withdrawn treatment and similarly run out of options.
- AbbVie describe the reasons why in our opinion placebo as an estimate of natural recovery is not an appropriate comparator in moderate RA to upadacitinib in our part 1 response to question 2. However, if natural recovery is considered to be occurring in patients who have run out of treatment options after two or more csDMARD failures in existing clinical practice it should likewise similarly be considered to occur in the upadacitinib arm after the failure of upadacitinib when patients will likewise have run out of treatment options.

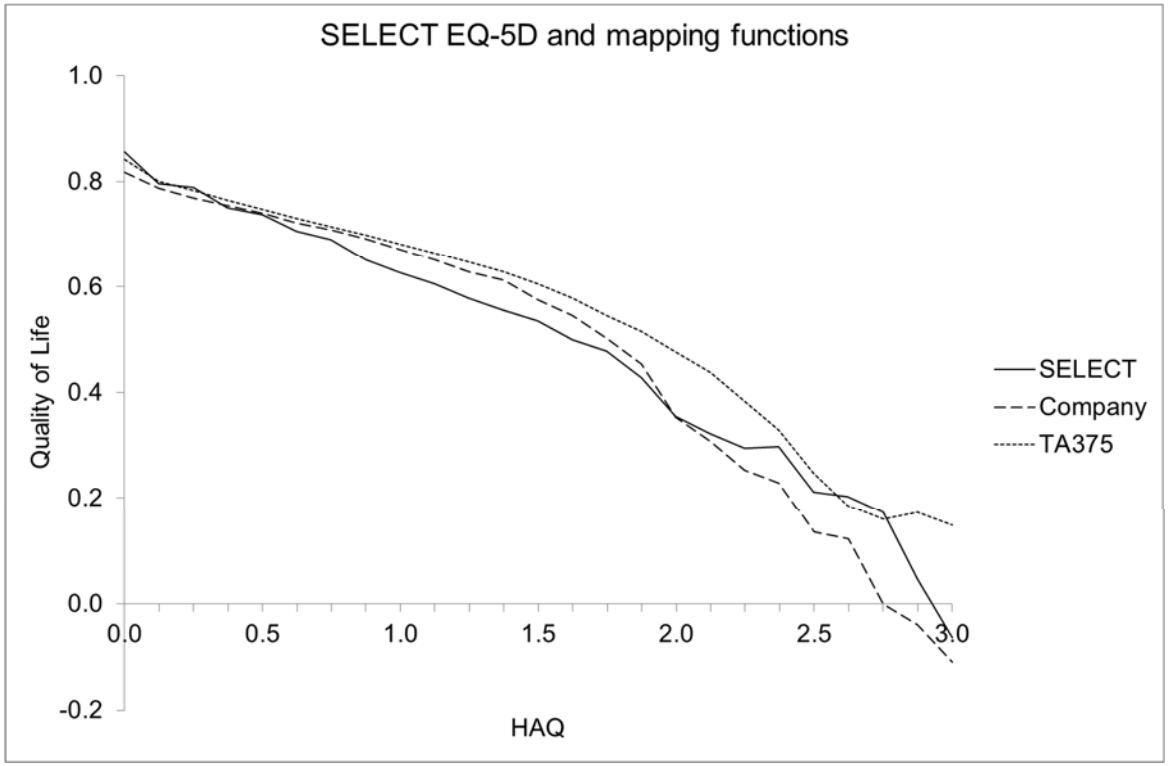
Other issues in relation to the moderate RA treatment sequences presented in Table 13 are as follows:

- AbbVie believe that it is important to consider the use of upadacitinib in positions 1a and 1b as outlined in our answer to question 4
- AbbVie believe it is important to consider the use of upadacitinib monotherapy in position 2b and 1b (methotrexate eligible patients) as outlined in our response to question 9
- AbbVie do not believe it is appropriate to consider upadacitinib in the comparator arm as is done in sequences 2/3/4 for positions 2a, 2b and 2c. The comparator arm should reflect existing practice and (even in scenario analyses should not consist of the treatment under appraisal).

	AbbVie broadly agree with the ERG's preferred base case treatment sequences in severe RA (both where upadacitinib is being initiated in severe RA and where it is initiated in moderate RA and patients transition to receive severe RA advanced therapies). However, from clinical advice received, AbbVie understand that patients who fail all treatments in severe RA (as in moderate RA) will receive the combination of csDMARDs which have previously worked best for them. This is reflected in the AbbVie sequencing within our submission by MTX as a last line treatment which is different to the sequencing presented by the ERG. AbbVie recognise that in severe RA this difference has minimal impact on ICER estimates and consequently we agree with the decision in severe RA to exclude MTX as a last line of treatment in severe RA on pragmatic grounds. Specifically, in relation to Table 13 (pages 39-44) of the technical report and the severe RA treatment sequences presented, AbbVie note therefore the following: • The sequences presented by the company and ERG concur for positions 3a, 5 and 6 (apart from the company's inclusion of MTX as a last line therapy as addressed above) • For positions 3b and 4b, the company agrees with the decision to substitute SRL for TCZ (and also for those sequences where moderate RA patients transition onto severe RA advanced therapies where this is relevant) • For position 4a which has not been considered by the ERG the company believe that this should be considered for the reasons outlined in our response to question 8 • AbbVie believe it is important to consider the use of upadacitinib monotherapy in position 3b, 4b, 5 and 6 (methotrexate eligible patients) as outlined in our response to question 9.
Issue 3: Model inputs and assumptions	
12. Would you expect the relationship between HAQ and DAS-28 to change over time?	AbbVie has modelled this relationship in line with request from the ERG and accepted by the appraisal committee in the most recent RA appraisal of sarilumab (TA485). AbbVie have assumed this approach or the alternative approach of a 1:1 relationship suggested by the sarilumab ERG as most appropriate. The relationship being mapped is to identify the change in HAQ from baseline in moderate RA patients associated with a DAS 28 score of 5.1. These are patients in the early and inflammatory stages of disease for whom the following is relevant. The evidence suggests that HAQ DI is significantly correlated with DAS scores in early disease prior to the development of permanent joint damage as has been shown in both a 6 year (7) and 12 year study (8).
13. Should the intercept term from the company's	The intercept of the change in HAQ to change in DAS map represents non-HAQ related changes in DAS, and consequently it is not appropriate to apply this in the linear mixed effect model. In addition, the application of the intercept may not be appropriate as evidenced by the rate of transition of patients from moderate to severe RA observed in UK clinical practice. For untreated moderate patients, without using the intercept in the model, 7% of patient transition to a DAS 28 of 5.1 at two years. Data from the UK ERAN dataset (9) suggests 19% of moderate RA

repeated measures linear mixed effects model be used in the modelling?	patients transition to severe RA at two years (9, 10). This suggests that the map from HAQ to DAS 28 using the linear mixed model without the intercept may underestimate the number of patients transitioning to a DAS 28 of 5.1 relative to that observed in reality. The use of the intercept would reduce the 7% figure and consequently increase the level of underestimation of the true rate of transition further. The use of the intercept would therefore make already conservative ICER estimates even more conservative.
14. Is the HAQ to pain mapping from TA375 more reliable than the company estimates from the SELECT trials?	AbbVie believe estimates from the SELECT trial would be a better fit than the TA375 map. The trial data were also found to provide a better fitting map in the tofacitinib (TA480) RA appraisal: • Both approaches demonstrated similar performance/fit in a quantitative comparison with SELECT trials' observed EQ-5D values • The utility estimates based on the trial-based map showed a slightly more favourable fit than the utility estimates based on the TA375 map • The root mean squared error (RMSE) was smaller for the trial-based map approach, indicating a better fit, for both the full dataset comparison (trial-based map RMSE: 0.172, TA375 map RMSE: 0.180) • For a subset of data excluding extreme HAQ values (HAQ > 2.5) (trial-based map RMSE: 0.170, TA375 map RMSE: 0.179). Visually, the estimated utility from the trial-based map was also a better fit than the TA375 map: • The utility values estimated with TA375 map were consistently higher than the utility observed in the SELECT trials and did not follow the rapid decrease in utility at the tail end of the HAQ spectrum • In contrast, the utility estimated with the trial-based map was generally closer to the observed SELECT trial values, and showed a similar trend throughout the HAQ score spectrum

Figure 1: EQ-5D by HAQ observed in SELECT trials and estimated based on trial-based and TA375 HAQ-to-pain map



Using the HAQ to pain mapping in TA375, a counterintuitive trend materialises. Higher HAQ values are associated with reduced pain for HAQ values higher than 2.625. This reverse trend is not demonstrated using the map based upon the SELECT trials as seen in the figures below.

Figure 2: HAQ-to-pain map based on (a) NDB and (b) ERAS data reported in TA375, Figure 114

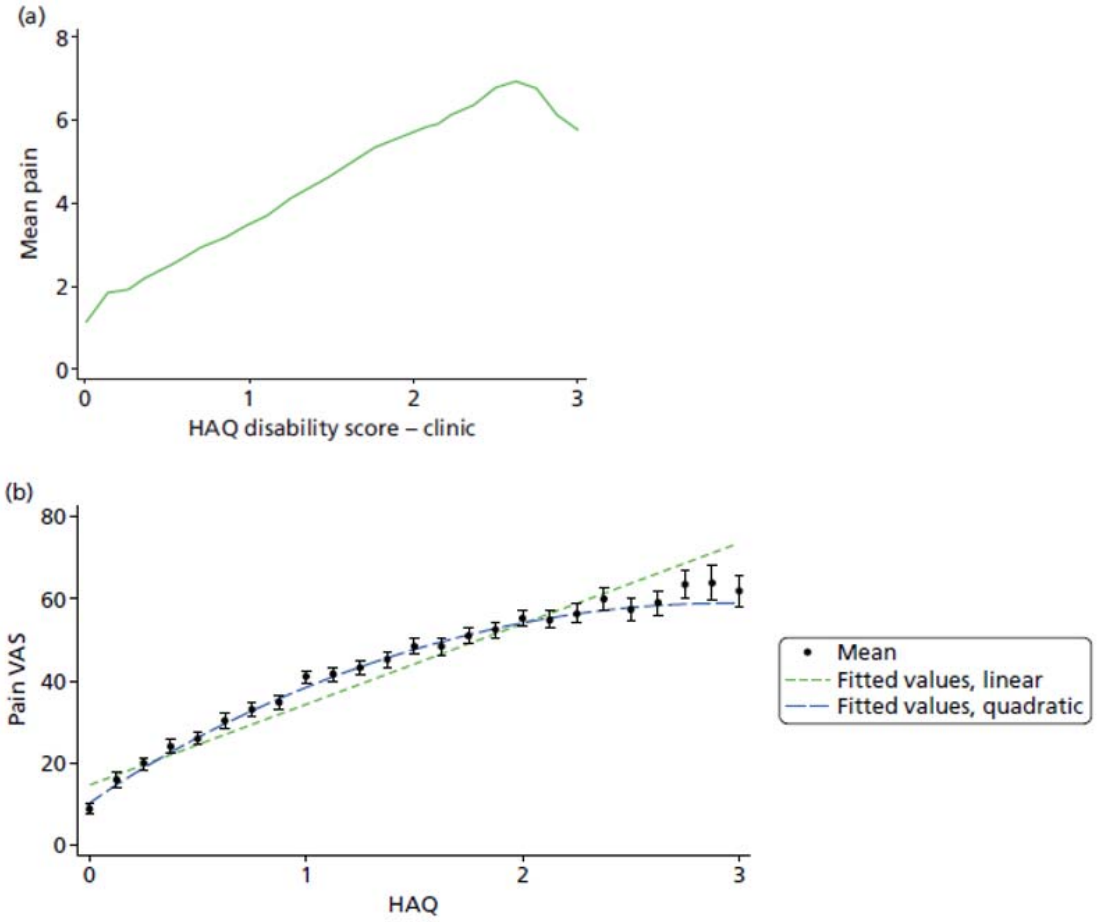
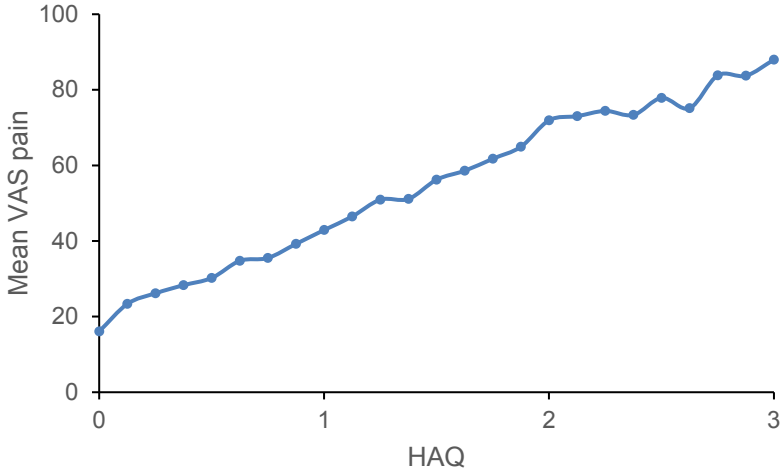


Figure 3: HAQ-to-pain map based on SELECT trials.



The model is sensitive to the choice of HAQ to pain map as shown in **Table 11.**

*Table 11: Impact of choice of HAQ to pain map on ICERs (after two or more csDMARD failures, moderate RA)**

	Comparison	Source of efficacy estimate for csDMARD and upa combo	TA375 HAQ to pain utility map	SELECT trial based HAQ to pain utility map	Source within response document
AbbVie preferred base case (lower range of plausible ICER)	UPA combo then csDMARD** then BSC **VERSUS** csDMARD** then BSC	SELECT-NEXT trial data for the upa + csDMARD and the PBO + csDMARD arms*	£21,295	£17,951	See Table 1 – Scenario 2

***All analyses use ERG preferred severe RA treatment sequences / ERG revised drug and administration and HAQ costs / ERG preferred csDMARD-IR NMA efficacy for bDMARD-IR naïve patients and bDMARD-IR NMA efficacy for bDMARD experienced patients:**
****Used by ERG to model PBO effect / natural recovery**

*Table 12: Impact of choice of HAQ to pain map on ICERs (after two or more csDMARD failures, moderate RA)**

	Comparison	Source of efficacy estimate for csDMARD and upa combo	TA 375 HAQ to pain utility map	SELECT trial based HAQ to pain utility map	Source within response document
AbbVie preferred base case (lower range of plausible ICER)	UPAUPA combo then csDMARD then BSC **VERSUS** csDMARD then BSC	1) csDMARD (comparator arm): base case csDMARD-IR NMA 2) csDMARD (UPA arm): base case bDMARD-IR NMA	£24,039	£20,630	See Table 9 – Scenario 3

All analyses use ERG preferred severe RA treatment sequences / ERG revised drug and administration and HAQ costs / ERG preferred csDMARD-IR NMA efficacy for bDMARD-IR naïve patients and bDMARD-IR NMA efficacy for bDMARD experienced patients

15. Would a treatment be	AbbVie accept EULAR response will vary depending on line of treatment and therefore it would be better to model efficacy based on line of therapy.

expected to provide the same level of EULAR response rate regardless of the line of treatment?	
Issue 4: Network meta-analysis	
16. Is the company or ERG's approach the most appropriate regarding the application of the results of the two NMAs at different points in the treatment pathway?	AbbVie accept the ERG approach is more appropriate, namely the results of the csDMARD-IR NMA should be applied to the biologic naïve patients and the results of the bDMARD-IR NMA should be applied for the biologic experienced patients.
17. Are the clinical effectiveness estimates	AbbVie believe it is appropriate to apply the efficacy results of upadacitinib from AbbVie's base case bDMARD-IR NMA (reproduced below) to the corresponding results for tocilizumab and sarilumab as an estimate of its relative effectiveness compared to the only drugs presently recommended for use in this population. In considering whether upadacitinib is cost effective against these two drugs it will be important for

applicable to the population who have failed RTX?

NICE to consider the relative drug acquisition costs for these two treatments (including their confidential PAS discounts). AbbVie believe that the following needs to be considered:

1. If upadacitinib is less costly than sarilumab whether the estimate of upadacitinib being at least as effective as sarilumab based on the bDMARD-IR NMA results can be used to assume that upadacitinib is likely to be cost effective in this position versus sarilumab
2. If upadacitinib is less costly than tocilizumab whether the potentially higher benefits associated with tocilizumab based on the bDMARD-IR NMA results associated with higher costs result in tocilizumab having acceptable ICERs at a threshold of £20,000 to £30,000. This will determine whether upadacitinib is cost effective in this position
3. The results of the analyses outlined in bullet points 1 and 2 above could be subject to sensitivity analyses to determine the extent to which estimates of waning of efficacy of all three drugs under consideration relative to efficacy reported in the bDMARD-IR NMA will impact upon cost effectiveness estimates
4. Clearly, if upadacitinib is more costly than either sarilumab or tocilizumab a different perspective to its likely cost effectiveness will be taken to the one outlined in the two bullet points above

Table 13: Base case: bDMARD-experienced RA NMA (page 106 of AbbVie original NICE submission)

Treatment	No Response (95% CrI)[1]	Moderate Response (95% CrI)[1]	Good Response (95% CrI)[1]
Sarilumab 200 mg + csDMARD	[redacted]	[redacted]	[redacted]
Upadacitinib 15 mg + csDMARD	[redacted]	[redacted]	[redacted]
Tocilizumab 162 mg + csDMARD	[redacted]	[redacted]	[redacted]
Tocilizumab 8 mg/kg + csDMARD	[redacted]	[redacted]	[redacted]

Abbreviations: ACR, American College of Rheumatology; csDMARD, conventional synthetic disease modifying antirheumatic drug; EULAR, European League Against Rheumatism; RA, rheumatoid arthritis.

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ID1400: Upadacitinib for treating moderate to severe rheumatoid arthritis. Comparison of AbbVie model output to TA375 model

Assumptions

Assumptions for moderate and severe RA:

- Patient baseline characteristics: AbbVie assumptions retained (model submitted 150819)
- Clinical effectiveness inputs: AbbVie assumptions retained (model submitted 150819)
- Adverse event rates: AbbVie assumptions retained (model submitted 150819)
- Drug and administration costs: AbbVie assumptions retained (model submitted 150819) except adalimumab price. The price of adalimumab is aligned to the price used in TA375 of £9187. On page 361 of the TA375 ERG report it is stated that the manufacturers all used similar costs for the biologics. The £9187 cost is taken from page 229 of this report (https://www.nice.org.uk/guidance/ta375/documents/rheumatoid-arthritis-adalimumab-etanercept-infliximab-certolizumab-pegol-golimumab-abatacept-and-tocilizumab-review-appendix-1-updated-assessment-report2) which relates to the costs provided by BMS. This cost is also referred to in the following paper produced as part of the review of TA375 in May 2019 on page 7: https://www.nice.org.uk/guidance/ta375/evidence/consultation-paper-may-2019-pdf-6779359118.
- Time to treatment discontinuation curves: AbbVie assumptions retained (model submitted 150819) which are the same as TA375
- HAQ to pain: TA375 base case assumption
- HAQ and pain to QoL function: TA375 base case assumption
- HAQ to cost function: Abbvie assumptions retained (model submitted 150819)
- Change in HAQ (occurs at 6 months): Abbvie assumptions retained (model submitted 150819) which is the same as TA375

- Treatment discontinuation (Gamma): Abbvie assumptions retained (model submitted 150819) which is the same as TA375
- Monitoring costs for BSC (Yes): Abbvie assumptions retained (model submitted 150819) which is the same as TA375

- HAQ progression for BSC and csDMARDs: TA375 base case assumption

Relevant only for severe RA:

- The treatment sequences used are outlined in Table 1 (aligned to TA375) and can be found in the ERG report on page 355: https://www.nice.org.uk/guidance/ta375/documents/rheumatoid-arthritis-adalimumab-etanercept-infliximab-certolizumab-pegol-golimumab-abatacept-and-tocilizumab-review-appendix-1-updated-assessment-report2.

Table 1: Treatment sequences in severe RA

First-line treatment	Second-line treatment	Third-line treatment	Fourth-line treatment	Fifth-line treatment
MTX	BSC			
ADA + MTX	RTX + MTX	TCZ IV + MTX	MTX	BSC
CTZ + MTX	RTX + MTX	TCZ IV + MTX	MTX	BSC
ETN + MTX	RTX + MTX	TCZ IV + MTX	MTX	BSC
GOL + MTX	RTX + MTX	TCZ IV + MTX	MTX	BSC
IFX + MTX	RTX + MTX	TCZ IV + MTX	MTX	BSC

Relevant only for or moderate RA:

- Transition to severe RA recommended advanced therapies: Function in AbbVie model switched off to align with TA375

- The treatment sequences used are outlined in Table 2 (aligned to TA375) and can be found in the ERG report on page 355: https://www.nice.org.uk/guidance/ta375/documents/rheumatoid-arthritis-adalimumab-etanercept-infliximab-certolizumab-pegol-golimumab-abatacept-and-tocilizumab-review-appendix-1-updated-assessment-report2.

Table 2: Treatment sequences in moderate RA

First-line treatment	Second-line treatment	Third-line treatment	Fourth-line treatment	Fifth-line treatment
MTX	BSC			
ADA + MTX	RTX + MTX	TCZ IV + MTX	MTX	BSC

Validation of ICERs between the TA375 and AbbVie model

Severe RA

Table 3: Validation of severe RA ICERs between TA375 and the AbbVie model

	AbbVie Model (using TA375 base case pain VAS scores)	TA375 base case model*
MTX	Reference	Reference
ADA + MTX	£41,853	£42,194
ETN + MTX	£40,504	£42,014
IFX + MTX	£38,978	£39,884
CTZ + MTX	£41,287	£41,015
GOL + MTX	£42,060	£42,087

Abbreviations: ADA = adalimumab, CTZ = certolizumab pegol, ETN = etanercept, GOL = golimumab, IFX = infliximab, MTX = methotrexate, TCZ = tocilizumab.

* Found at: https://www.nice.org.uk/guidance/TA375/documents/rheumatoid-arthritis-adalimumab-etanercept-infliximab-certolizumab-pegol-golimumab-abatacept-and-tocilizumab-review-id537-committee-papers-appendices-1319217. Revised ICERs following corrected errors prepared SCHARR Table 4

- Re-run on 27th Oct 2019 by AbbVie with more disaggregated costs as shown in Table 4.

Table 4: Validation of severe RA ICERs with disaggregated costs

	MTX	ADA + MTX	IFX + MTX	GOL + MTX	ETN + MTX	CTZ + MTX
Cost (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug and admin cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monitor cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HAQ cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Indirect cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Effectiveness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total LYs	14.196	14.196	14.196	14.196	14.196	14.196
Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER		£41,853	£38,978	£42,060	£40,504	£41,287

Moderate RA

The model was run twice with the ADA + MTX arm against UPA and then the MTX arm against UPA to provide the required output.

Note the treatment sequence used in the submission made by AbbVie on 23rd August 2019 incorrectly used the treatment sequence of ADA + MTX followed by MTX then BSC (the MTX treatment sequence used was correct). In Table A.20, the value £63,293 was therefore incorrectly attributed to the ICER obtained using the AbbVie model to match the analysis carried out for TA375 when this value should have been £55,866 as shown in Table 5 (an ICER 12% lower than the one estimated in TA375 for the same analysis using the parameters assumed to be the same)

Table 5: Validation of moderate RA ICERs between TA375 and the AbbVie model (ADA+MTX versus MTX after two csDMARD-IR)

Population	AbbVie model (ICER per QALY gained)	NICE TA375 report, ICER per QALY gained* (2015 £)
csDMARD-IR, moderately active RA	**£55,866**	**£51,472** (changed from previous ICER shown. The rationale for why this is the most appropriate is provided at the end of the document.
Abbreviations: csDMARD= conventional disease-modifying anti-rheumatic drug; ICER= Incremental cost-effectiveness ratio; QALY= quality-adjusted life year; RA= Rheumatoid Arthritis; UPA= upadacitinib		

* Found in section 17. Revised ICERs following the correction of identified errors prepared ScHARR at: https://www.nice.org.uk/guidance/TA375/documents/rheumatoid-arthritis-adalimumab-etanercept-infliximab-certolizumab-pegol-golimumab-abatacept-and-tocilizumab-review-id537-committee-papers-appendices-13192

- Re-run on 27th Oct 2019 by AbbVie with more disaggregated costs as shown in Table 6.

Table 6: Validation of moderate RA ICERs with disaggregated costs

	MTX	ADA + MTX
Cost (£)	[redacted]	[redacted]
Drug and admin cost	[redacted]	[redacted]
Monitor cost	[redacted]	[redacted]
HAQ cost	[redacted]	[redacted]
AE cost	[redacted]	[redacted]
Indirect cost	[redacted]	[redacted]
Other cost	[redacted]	[redacted]
Incremental costs	[redacted]	[redacted]
Effectiveness	[redacted]	[redacted]
Total LYs	15.254	15.254
Total QALYs	[redacted]	[redacted]
Incremental QALYs	[redacted]	[redacted]
ICER		£55,866

Rationale for ICERs shown from TA375 for validation

The ICERs quoted for TA375 are in line with the technology appraisal guidance which states on page 67 that *"The Committee considered that the most plausible ICER for biological DMARDs used in severe active rheumatoid arthritis previously treated with methotrexate, was likely to lie between the Assessment Group's base-case ICER (that is, £41,600 per QALY gained) and the Assessment Groups ICER for the severe group with the fastest HAQ progression (that is, £25,300*

per QALY gained) ….. The Assessment Group's base-case ICER for biological DMARDs was £51,100 per QALY gained for the moderate active population".

Note also potentially valuable for validation purposes in moderate RA is this statement from the TA375 review proposal paper produced by NICE in March 2019 which is available at https://www.nice.org.uk/guidance/ta375/evidence/consultation-paper-may-2019-pdf-6779359118. It lists the prices of the biologics at the time of the TA375 review and the implications of a 50% reduction in these prices:

"A recent review of the cost-effectiveness of biological DMARDs in England using the model from TA375 (Stevenson et al 2017) reported exploratory analyses showing that the cost of biological DMARDs would need to be lowered by around 50% to reduce the most plausible ICER for moderate disease (£51,100) to a range that is considered a cost-effective use of NHS resources (that is, £20,000 to £30,000 per QALY gained)"

This paper and the mentioned Stevenson[1] paper is also attached for information.

[1] Stevenson, M. D., Wailoo, A. J., Tosh, J. C., et al. (2017). The cost-effectiveness of sequences of biological disease-modifying antirheumatic drug treatment in England for patients with rheumatoid arthritis who can tolerate methotrexate. The Journal of rheumatology, 160941.

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- 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.

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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)	**Biogen**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Response rates for best supportive care	
1. What does best supportive care (BSC) consist of in NHS clinical practice? How often is it used in both moderate and severe RA in clinical practice as a last line treatment?	
2. Which of the following assumptions is the most appropriate to use in the model for BSC? a) Use the placebo EULAR response rates from the upadacitinib phase III trials or the NMA, for BSC b) Assume that the response rate for BSC is 0%	
3. Do people with RA experience a natural recovery of their symptoms? If so what proportion of people experience this and for how long?	
Issue 2: Clinical pathway and positioning of upadacitinib	
4. Would UPA be used before intensified csDMARDs for treating moderate RA in clinical practice (position 1a and 1b)?	
5. Would you expect UPA be continued in the moderate RA population if some clinical benefit was achieved, even though the	

EULAR response criteria had not been met? What clinical benefits would need to be shown?	
6. Following the failure of 2 or more csDMARDs (position 2, **Error! Reference source not found.**, section 1.2), is BSC or csDMARDs used in practice (and therefore, the most relevant comparator)?	
7. Would UPA be considered as a first-line bDMARD for treating severe RA?	
8. Is there sufficient evidence to consider the clinical and cost effectiveness of UPA at position 4a (severe RA, failed 1 bDMARD, MTX intolerant, RTX tolerant)?	
9. Would UPA be used as a monotherapy in MTX-tolerant populations, or would it be used only with MTX, in clinical practice?	
10. Is MTX monotherapy used as a last-line treatment in MTX-tolerant populations?	
11. Are the company's or ERG's treatment sequences the most appropriate (see table 6 section 4 and appendix)?	
Issue 3: Model inputs and assumptions	
12. Would you expect the relationship between HAQ and DAS-28 to change over time?	

13. Should the intercept term from the company's repeated measures linear mixed effects model be used in the modelling?	
14. Is the HAQ to pain mapping from TA375 more reliable than the company estimates from the SELECT trials?	
15. Would a treatment be expected to provide the same level of EULAR response rate regardless of the line of treatment?	
Issue 4: Network meta-analysis	
16. Is the company or ERG's approach the most appropriate regarding the application of the results of the two NMAs at different points in the treatment pathway?	
17. Are the clinical effectiveness estimates applicable to the population who have failed RTX?	
Issue 5: Other	
18. Additional comments from Biogen	NICE TA375 (published on 26 January 2016) recommends the use of adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis patients with severe disease activity (DAS28 greater than 5.1) not previously treated with DMARDs or after conventional DMARDs only have failed. The above biologic DMARDs were not deemed cost-effective in moderate rheumatoid arthritis (DAS28 score between 3.2 and 5.1). However, since then, biosimilars for adalimumab, etanercept and infliximab have become available at a lower acquisition price, and thus NICE Guidance Executive has decided to proceed with a partial review of TA375 to review the cost-effectiveness for patients with moderate disease activity.

	Biogen would support the use of biologic DMARDs in patients with moderate disease activity. It would allow access to treatment earlier in the disease activity. However, Biogen would like clarification as to how this appraisal will link with the partial review of TA375, considering the partial review does not include Janus-kinase inhibitors? Would upadacitinib be considered as a comparator within the partial review of TA375, if it were to receive a positive recommendation for patients with moderate rheumatoid arthritis disease activity in this appraisal?

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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)	**Pfizer**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None.**

Questions for engagement

Issue 1: Response rates for best supportive care	
1. What does best supportive care (BSC) consist of in NHS clinical practice? How often is it used in both moderate and severe RA in clinical practice as a last line treatment?	Best supportive care (BSC) is a term used for end stage disease and would not be used in the moderate setting. Patients who would be eligible for BSC are normally people with severe RA, that have had an inadequate response to conventional DMARDs (csDMARDs) and have failed to respond to three additional advanced DMARDs. The number of previous treatments differs amongst CCGs (these include a sequence of biological DMARDs and targeted synthetic DMARDs). Therefore our understanding is that BSC is used at the end of the treatment pathway in UK clinical practice. The number of these patients is very small, they only make up a handful of patients per centre. Patients with moderate disease would receive csDMARDs in clinical practice, and therefore it is our understanding that BSC would not be used in this setting and therefore is not a relevant comparator in moderate RA.
2. Which of the following assumptions is the most appropriate to use in the model for BSC? a) Use the placebo EULAR response rates from the upadacitinib phase III trials or the NMA, for BSC b) Assume that the response rate for BSC is 0%	It is our understanding that in moderate RA, BSC would not be offered for patients, but they would be treated with csDMARDs and glucocorticoids.
3. Do people with RA experience a natural recovery of their symptoms? If so what	No comment.

proportion of people experience this and for how long?	
Issue 2: Clinical pathway and positioning of upadacitinib	
4. Would UPA be used before intensified csDMARDs for treating moderate RA in clinical practice (position 1a and 1b)?	No comment.
5. Would you expect UPA be continued in the moderate RA population if some clinical benefit was achieved, even though the EULAR response criteria had not been met? What clinical benefits would need to be shown?	No comment.
6. Following the failure of 2 or more csDMARDs (position 2, **Error! Reference source not found.**, section 1.2), is BSC or csDMARDs used in practice (and therefore, the most relevant comparator)?	Our understanding is that in current UK clinical practice, csDMARDs and glucocorticoids are offered at this position of the pathway.
7. Would UPA be considered as a first-line bDMARD for treating severe RA?	No comment.
8. Is there sufficient evidence to consider the clinical and cost effectiveness of UPA at position 4a (severe RA, failed 1 bDMARD, MTX intolerant, RTX tolerant)?	No comment.
9. Would UPA be used as a monotherapy in MTX-tolerant populations, or would it be used only with MTX, in clinical practice?	No comment.

10. Is MTX monotherapy used as a last-line treatment in MTX-tolerant populations?	No comment.
11. Are the company's or ERG's treatment sequences the most appropriate (see table 6 section 4 and appendix)?	No comment.
Issue 3: Model inputs and assumptions	
12. Would you expect the relationship between HAQ and DAS-28 to change over time?	No comment.
13. Should the intercept term from the company's repeated measures linear mixed effects model be used in the modelling?	No comment.
14. Is the HAQ to pain mapping from TA375 more reliable than the company estimates from the SELECT trials?	No comment.
15. Would a treatment be expected to provide the same level of EULAR response rate regardless of the line of treatment?	No comment.
Issue 4: Network meta-analysis	
16. Is the company or ERG's approach the most appropriate regarding the application of the results of the two NMAs at different points in the treatment pathway?	No comment.

17. Are the clinical effectiveness estimates applicable to the population who have failed RTX?	No comment.

NICE National Institute for Health and Care Excellence

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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)	UCB Pharma Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A

Questions for engagement

Issue 1: Response rates for best supportive care	
1. What does best supportive care (BSC) consist of in NHS clinical practice? How often is it used in both moderate and severe RA in clinical practice as a last line treatment?	UCB is in line with NICE and NHSE guidelines where cDMARDs are used as first line of treatment. If the patient is not responding to above treatment clinicians are advised to prescribe bDMARDs as monotherapy or in combination with cDMARDs. UCB believes that this is inconsistent with previous appraisals, and there is no rationale for doing anything different here. Given the number of treatment options available now, UCB does not think many patients get to last line BSC now.
2. Which of the following assumptions is the most appropriate to use in the model for BSC? a) Use the placebo EULAR response rates from the upadacitinib phase III trials or the NMA, for BSC b) Assume that the response rate for BSC is 0%	UCB's opinion is in line with ERG's preference. UCB believes that use the PBO rate from the NMA to model the effectiveness of BSC is more appropriate as it is not clear whether the control arm response rates were caused by natural recovery of symptoms, a pure PBO effect, or some combination of the two. Also, this approach is more consistent with the methods accepted by the committee during previous TAs.
3. Do people with RA experience a natural recovery of their symptoms? If so what proportion of people experience this and for how long?	Based on UCB's research, there is not much evidence around this request. Some of the findings show that some patients experience spontaneous remission but generally due to the patients presenting with undifferentiated arthritis (so yet to be formally classified as RA).

Issue 2: Clinical pathway and positioning of upadacitinib	
4. Would UPA be used before intensified csDMARDs for treating moderate RA in clinical practice (position 1a and 1b)?	UCB's experience has shown that there is evidence that some moderate patients would benefit for earlier treatment with targeted / biologic DMARDs as identified in TA375 and the approach in this appraisal to moderate patients should be aligned.
5. Would you expect UPA be continued in the moderate RA population if some clinical benefit was achieved, even though the EULAR response criteria had not been met? What clinical benefits would need to be shown?	N/A
6. Following the failure of 2 or more csDMARDs (position 2, **Error! Reference source not found.**, section 1.2), is BSC or csDMARDs used in practice (and therefore, the most relevant comparator)?	UCB's opinion is that the final decision should be aligned with previous appraisals.
7. Would UPA be considered as a first-line bDMARD for treating severe RA?	UCB believes that several factors should be considered before deciding if UPA is a first-line treatment such as cost, efficacy, route of administration, the safety of profile of the product, cost-effectiveness against competitors.
8. Is there sufficient evidence to consider the clinical and cost-effectiveness of UPA at position 4a (severe RA, failed 1 bDMARD, MTX intolerant, RTX tolerant)?	UCB's opinion is in line with NICE's technical team regarding the accurate and sufficient inclusion of treatment sequences. UCB believes that not all the sequences presented within the document are reflecting the NHS practice in England.
9. Would UPA be used as a monotherapy in MTX-tolerant populations, or would it be used only with MTX, in clinical practice?	N/A

10. Is MTX monotherapy used as a last-line treatment in MTX-tolerant populations?	Based on NICE guidelines MTX is generally used as first line of treatment so it quite challenging to be prescribed again as last line treatment as this indicates that MTX had failed previously.
11. Are the company's or ERG's treatment sequences the most appropriate (see table 6, section 4 and appendix)?	UCB is aligned with ERG's opinion.
Issue 3: Model inputs and assumptions	
12. Would you expect the relationship between HAQ and DAS-28 to change over time?	UCB believes that company's assumption regarding the stable relationship between HAQ and DAS-28 over 45 years may include some bias. UCB's opinion is aligned with ERG's about the extrapolation of the 3-6 months of clinical trial evidence. UCB's opinion is also aligned with clinical expert's advice that the HAQ score does generally worsen over time.
13. Should the intercept term from the company's repeated measures linear mixed effects model be used in the modelling?	N/A
14. Is the HAQ to pain mapping from TA375 more reliable than the company estimates from the SELECT trials?	UCB believes that HAQ to pain mapping from TA375 is maybe more reliable as this is based on a larger sample of data (National Databank for Rheumatic Diseases dataset).
15. Would a treatment be expected to provide the same level of EULAR response rate regardless of the line of treatment?	N/A
Issue 4: Network meta-analysis	
16. Is the company or ERG's approach the most appropriate regarding the application of the results of the two NMAs at different points in the treatment pathway?	UCB's opinion is aligned with the technical team's and ERG's approach in terms of the most appropriate NMA results to apply at different points in the pathway. UCB believes that the clinical benefit of treatment varies in the long term which has an impact on the healthcare outcomes for the patient.

17. Are the clinical effectiveness estimates applicable to the population who have failed RTX?	N/A

Upadacitinib for treating moderate to severe rheumatoid arthritis [ID1400]

Addendum #4 Response to Technical Engagement

02/12/2019

1 Comments on network meta-analysis methods

In its response to technical engagement, the company presented a network meta-analysis (NMA) that attempted to 'net out' the effect of the placebo. Methods described were cursory and requisite code was not provided, though the ERG notes that code provided for the original NMA as part of the original submission was also not reproducible.

Referencing the technical team's concern relating to inclusion of a placebo effect, the company states in its response to technical engagement that:

> The only interpretation that AbbVie have been able to infer from this concern from the technical team is that the upadacitinib efficacy demonstrated in its clinical trials consists of some efficacy which is specific to a trial setting and will not manifest in real life clinical practice. AbbVie infers that this is being equated to the placebo response estimated from the NMA. If this interpretation is correct the inclusion of this placebo effect in the comparator arm of the HE model is not a methodologically sound approach to estimating the cost effectiveness of upadacitinib with this placebo effect "netted off" because it involves netting off benefit (indirectly) from the upadacitinib arm whilst requiring upadacitinib to incur the drug cost (and continuation rate) associated with a higher upadacitinib efficacy (i.e. without the placebo effect netted off). A methodologically more robust approach is to net the placebo effect off in the NMA and apply a reduced efficacy to the upadacitinib arm (with a consequently reduced efficacy aligned to a reduced continuation rate).

In providing revised results to the NMA, the company provides the following comment on methods used: 'These were calculated by first translating the ACR NMA results at the MCMC iteration-level to EULAR probabilities and then taking the differences in EULAR probabilities at the MCMC iteration-level between treatment vs. either csDMARD and PBO.'

The ERG notes that it is possible to net the placebo effect off in the NMA using linear combinations and transformations of the probit. To understand how this is done, it is worth considering what was undertaken in the original NMA. Estimates from ACR20, ACR50 and ACR70 were integrated using a latent probit variable. The distribution of the probit variable for each relative treatment effect was then linked to the distribution of the probit variable for the combined reference arms (placebo for the csDMARD inadequate response NMA and csDMARD for the bDMARD inadequate response NMA) to generate the absolute predicted probabilities of treatment.

Thus, based on the methods presented as part of the technical engagement response and the methods presented in the original submission, it appears that what AbbVie have

presented is essentially a ‘risk difference’ approach. This is borne out by subtraction of relative treatment effects between each drug and the relevant reference treatment.

However, the methods presented raise another statistical ambiguity that the ERG could not resolve in its original report; specifically, how reference arms were pooled and used to generate treatment effects. The methods as presented for this new NMA suggest that the model was undertaken simultaneously, which as noted in previous appraisal of RA drugs, could bias estimation of relative treatment effects. For this reason, and because this new NMA does not resolve the original concerns raised by the ERG in its original report, the ERG reiterates its original conclusion:

> While the company’s approach to the NMAs followed precedent in terms of using csDMARD-experienced and bDMARD-experienced groupings and used appropriate statistical techniques, the ERG raised a number of concerns that suggest caution is required when interpreting the results of the NMAs. For example, the ERG noticed some inconsistencies between studies included in this appraisal and included in prior appraisals; inconsistencies in the presentation of results; a number of ambiguities relating to the inclusion and exclusion of trials and the formation of nodes (e.g. for intensive csDMARDs as a treatment strategy). From a statistical perspective, the ERG noted a persisting lack of clarity on how trial arms from reference groups were pooled to generate probabilities across all treatments. The ERG also noted strong assumptions required for the interpretation and application of findings across different points in the treatment pathways, eligibility of populations in networks for all relevant treatments, severities of disease and treatment sequencing, and exclusion of data from potentially informative trials that did not include subgroups.

Findings from the NMA are presented below in Section 2.8.

2 Comments on economic modelling evidence presented

2.1 Company HAQ to DAS28 function and its intercept

The company notes that the disappearing intercept term within its HAQ to DAS28 mapping function relates to improvements in the DAS28 that occurred independently of improvements in the HAQ.

The company states that if the intercept term of the mapping function is not applied the company model estimates that 7% of untreated moderate patients will have become severe at 2 years. The company does not state what percentage of untreated moderate patients is modelled as becoming severe if the intercept term is applied.

The company does not state what it means by "untreated moderate patients". Based upon the 28 August 2019 company model and assuming moderate patients are:

(A) no active treatment and 0% EULAR responses

(B) treated and receive intensified csDMARDs

(C) treated and receive MTX, then intensified csDMARDs

and the company baseline treatment sequences of

(D) UPA+MTX, then intensified csDMARDs, then MTX and

(E) intensified csDMARDs, then MTX

results in the following proportions modelled as transitioning to severe RA.

Table 1. Modelled Moderate RA proportion worsening to Severe RA

Year	A	B	C	D	E
0	0%	0%	0%	0%	0%
1	3%	0%	0%	0%	0%
2	7%	3%	1%	0%	1%
3	11%	6%	2%	1%	2%
4	15%	8%	4%	1%	4%
5	19%	11%	6%	2%	6%

The 7% severe RA patients at year 2 is the result of assuming patients remain untreated. It is notable that the company base case model treatment sequence (E) which is meant to reflect current practice results in only 1% of patients transitioning to severe RA after 2 years.

If the company HAQ to DAS28 intercept term is applied this results in no moderate RA patients being modelled as worsening to severe RA.

The company cites two papers, Deighton et al [1] and Kiely et al[2], as suggesting 19% of moderate RA patients become severe at two years.

The ERG has not been able to find any relevant data in Deighton et al [1] but Kiely et al[2] report data on 302 newly diagnosed patients in the ERAN data base who were followed up for 2 years. Unfortunately, Kiely et al[2] do not clearly distinguish between diagnosis, the end of year 1 and the end of year 2. They only report for year 1 and year 2.

Between year 1 and year 2, 65% were treated with monotherapy csDMARD, 26% with combination csDMARDs and 4% with NSAIDs. Among patients with a DAS28 between 3.2 and 5.1 in year 1, 19% had progressed to a DAS28 of more than 5.1 in year 2.

Based upon Kiely et al[2] the company is correct to note that its model under predicts the proportion of patients who will progress to severe disease after 2 years, though the appropriate Table 1 columns for comparison are B and C, not A.

2.2 HAQ to pain mapping function and QoL values

The company notes that its own mapping HAQ to pain mapping function results in slightly better RMSEs than the TA375 HAQ to pain mapping function when it is used to fit SELECT trial HAQ data to SELECT trial EQ-5D QoL values: 0.172 vs 0.180 for all SELECT trials' observations, and 0.170 vs 0.179 for the HAQ < 2.5 subset. The company describes this as "*a slightly superior fit*".

This is perhaps as would be expected and is most easily seen by assuming that the literature mapping function from HAQ and pain to QoL is perfect. It would be surprising if the SELECT trial bespoke mapping function from HAQ to pain did not result in a better fit to the SELECT trials' QoL data than another mapping function from HAQ to pain estimated from a different source. But this does not imply that the SELECT trial bespoke mapping function from HAQ to pain is superior in general.

As per the ERG report, there is a downward tick in the TA375 mapping function from HAQ to pain mapping function the reasons for which are unknown. The HTA monograph of TA375 (page 260) notes that for simulating the expected pain score associate with the HAQ:

> *"Health Assessment Questionnaire and pain are not related in a simple linear fashion as shown in data from the NDB and data from ERAS, which incorporate 100,398 observations for the NDB and 13,357 from ERAS. Data from the NDB are used to populate the mathematical model, with the mean pain score (and its variance) being estimated for each feasible HAQ score."*

It cannot be definitively determined whether the company mapping based upon SELECT trial data or the TA375 Assessment Group mapping based upon NDB data is superior in general. But the very large number of observations contributing to the TA375 mapping is a strong argument in its favour.

2.3 BSC in TA375 and control/placebo effect

The initial ERG response to the company error check issue 7 and comments on the TA375 modelling approach focussed upon the comparison of treatments at 1st line, with NBT standing for no biologic therapy or BSC.

Table 2. TA375 12 Aug 2013: MTX eligible: Severe RA: cDMARD naive

Line of Tx	Sequence 1	Sequence 2	Sequence 3	Sequence 4
1st line	MTX	MTX	MTX	bDMARD+MTX
2nd line	Int cDMARDs	Int cDMARDs	Int cDMARDs	RTX+MTX
3rd line	NBT	bDMARD+MTX	TCZ+MTX	TCZ+MTX
4th line	..	RTX+MTX	RTX+MTX	MTX
5th line	..	TCZ+MTX	MTX	Int cDMARDs
6th line	..	MTX	NBT	NBT
7th line	..	NBT	..	..

Table 3. TA375 12 Aug 2013: MTX eligible: Severe RA: cDMARD experienced

Line of Tx	Sequence 1	Sequence 2	Sequence 3
1st line	MTX	bDMARD+MTX	TCZ[+MTX[1]]
2nd line	NBT	RTX+MTX	RTX+MTX
3rd line	..	TCZ[+MTX[1]]	MTX
4th line	..	MTX	NBT
5th line	..	NBT	..

A third population of MTX eligible moderate/severe RA cDMARD experienced was also modelled. This applied the treatment sequences of Table 3 above.

Table 4. TA375 12 Aug 2013: MTX ineligible: Severe RA: cDMARD naive

Line of Tx	Sequence 1	Sequence 2	Sequence 3
1st line	Int cDMARDs	Int cDMARDs	bDMARD
2nd line	cDMARD	bDMARD	bDMARD
3rd line	NBT	bDMARD	Int cDMARDs
4th line	..	cDMARD	cDMARD
5th line	..	NBT	NBT

[1] MTX is not mentioned here in Table 179 but it seems likely this is a typo.

Table 5. TA375 12 Aug 2013: MTX ineligible: Severe RA: cDMARD experienced

	Sequence 1	Sequence 2
1st line	csDMARDs	bDMARD
2nd line	csDMARD	bDMARD
3rd line	NBT	csDMARD
4th line	..	NBT

A third population of MTX ineligible moderate/severe RA csDMARD experienced was also modelled. This applied the treatment sequences of Table 5 above.

Both the 12 Aug 2013 AG report and the HTA monograph state that "*It was assumed that non-biologic therapy would be associated with no initial EULAR response, unlike MTX where the results from the NMA indicated that MTX had a significant EULAR response*." As a consequence, all the treatment sequences modelled in TA375 have a 1st line treatment with non-zero EULAR response rates. The 0% EULAR response rates only apply to the NBT as the last in line treatment. This is as per the ERG modelling.

Given the ERG concentration on 1st line treatments, the ERG stated that "*that the ERG modelling approach is aligned with that of TA375 and that the modelling approach of the company is not. At a minimum it cannot be concluded that the ERG modelling approach is not aligned with the modelling approach of TA375*".

The ERG still thinks this. But the company is correct to note that NBT or BSC at the end of the treatment sequences in TA375 is associated with 0% EULAR response rates. If the treatment sequences are of different length the ERG thinks that this will bias the analysis, as reviewed in more detail in section 2.5 and 2.6 below.

2.4 How to net out control/placebo effectiveness

Suppose that in all biologic trials the active intervention arm had a response rate of 35% while the sugar pill/control/placebo arm had a response rate of 30%.

The company position is that the biologic warrants an NHS price that wholly attributes the 35% response rate to the biologic. The ERG position is that the biologic warrants an NHS price that only attributes the net additional 5% response rate to the biologic.

The simplest thought experiment is that the 30% response rate could be attained using sugar pill, at effectively no direct drug cost to the NHS. The cost effectiveness of upadacitinib should be measured against this baseline and the ICER and/or warranted price calculated on this basis.

The company presents analyses which assume that if only the net 5% treatment effect should be attributed to the biologic it should be assumed that only 5% of biologic patients

achieve a response. As a consequence only 5% rather than 35% of biologic patients incur ongoing biologic drug costs. This somewhat improves the ICER.

The ERG thinks that the only elements that might be removed from the treatment effectiveness estimates are those purely associated with being in a trial. There are no estimates for these. But the sugar pill/control/placebo effect should be retained in both arms of the modelling.

2.5 Control/placebo effect and treatment sequences of different length

The ERG position 2a treatment sequences for moderate RA prior to any transition to severe RA for the ERG base case are:

Table 6. Position 2a: ERG sequences for moderate RA

Sequence	1st line	2nd line
1.	UPA	BSC
2a.	csDMARDs	BSC
2b.	PBO	BSC

In the above, retaining the previous illustrative assumed response rates of 35% for the biologics and 30% for control/placebo and further assuming an illustrative 32% response rate for csDMARDs, the response rates modelled are:

Table 7. Position 2a: Illustrative response rates retaining the placebo effect

Sequence	1st line	2nd line
1.	35%	0%
2a.	32%	0%
2b.	30%	0%

This maintains the upadacitinib net treatment effect of 3% against cDMARDs and 5% against control/placebo.

The main ERG report, as summarised briefly in section 2.7 below, argues that UPA followed by csDMARDs is unlikely to be cost effective compared to csDMARDs followed by UPA so does not consider position 1 any further. But ignoring the fact that if upadacitinib were used at position 1 this would preclude it being used more cost effectively at position 2 and only considering position 1, something similar to the following treatment sequences might be suggested by the company.

Table 8. Position 1a: Possible sequences for moderate RA

Sequence	1st line	2nd line	3rd line
1.	UPA	cDMARDs	BSC
2a.	cDMARDs	BSC	BSC

2b.	PBO	BSC	BSC

If the company accepted that csDMARDs should have the 32% response rate applied and that control/placebo should have the 30% response rate applied when juxtaposed with upadacitinib it might suggest the following response rates.

Table 9. Position 1a: Illustrative response rates

Sequence	1st line	2nd line	3rd line
1.	35%	32%	0%
2a.	32%	0%	0%
2b.	30%	0%	0%

This is akin to the approach of TA375, though it should be noted that TA375 only considered the parallel of sequence 2a and not that of sequence 2b. This has the appearance of maintaining the upadacitinib net treatment effect of 3% against csDMARDs and 5% against placebo. But in reality it has simply moved the application of the placebo effect in the upadacitinib arm to 2nd line while removing it from the comparator arms at 2nd line.

The response estimates applied in Table 9 above do not model an overall net treatment effect for sequence 1 that is akin to the net treatment effect. They model an overall net treatment effect for sequence 1 which is akin to the absolute treatment effect.

If it is the net treatment effects which should be modelled, the ERG thinks that whenever BSC is juxtaposed with any active treatment BSC should be attributed the control/placebo response rate; i.e.:

Table 10. Position 1a: Illustrative response rates retaining the placebo effect

Sequence	1st line	2nd line	3rd line
1.	35%	32%	0%
2b.	32%	30%	0%
2b.	30%	30%	0%

As noted in the main ERG report, within the ERG modelling this concern only applies to the moderate RA scenario 4. But it may become an issue within this assessment which is why the ERG reiterates this here.

The company is correct that the ERG position on this differs from TA375.

This may also be a major issue during the upcoming review of TA375.

2.6 Constant effectiveness in treatment sequences of different lengths

The issue of Section 2.5 above is an argument for preferring comparisons of sequences of the same length.

In addition to this, there are concerns about the assumption that treatment effectiveness does not decline by line of treatment. There are suggestions that it does but no concrete estimates that can be applied within the modelling. But given these concerns, a long treatment sequence which applies the clinical effectiveness estimates of the NMAs at 1st, 2nd, 3rd, 4th etc line may be overly optimistic. This may itself introduce bias. But the bias is likely to be considerably worse if treatment sequences of different length are modelled.

It is not uncommon for economic modelling of a new treatment to simply insert the new treatment at the start of the current practice treatment sequence and to then compare this with the current practice treatment sequence. The ERG thinks that this is likely to be biased, and possibly quite badly biased.

This may also be a major issue during the upcoming review of TA375.

2.7 Position 1: Moderate RA: UPA prior to intensified csDMARDs

The company maintains that it is reasonable to consider upadacitinib at position 1, among moderate RA patients who have failed to respond or lost response to MTX.

The ERG agrees.

But the company does not consider the range of mutually exclusive comparator treatment sequences at this position. It ignores the fact that if upadacitinib is used for a patient at position 1 it cannot be used again for this patient at position 2.

When comparing upadacitinib with intensified csDMARDs at position 1 it is necessary to consider the other mutually exclusive treatment sequences at position 1 as in section 5.3.4.13 of the ERG report and its table 81. A subset of these mutually exclusive treatment sequences is presented in Table 11 below.

Table 11. Modified sequence 1b: Moderate RA, one csDMARD fail, MTX tolerant

Sequence	First-line	Second-line	Third-line
1	UPA+MTX	Int csDMARDs	BSC
2	Int csDMARDs	UPA+MTX	BSC
3	UPA	Int csDMARDs	BSC
4	Int csDMARDs	UPA	BSC

In this modelling, for moderate RA patients who transition to severe RA the ERG thinks that for the base case it is more reasonable to model the same severe RA treatment sequence for sequences 1 and 2, and for sequences 3 and 4.

As outlined in section 5.3.4.13 of the ERG report, the cost effectiveness of sequence 1 compared to sequence 2 is £77,658 per QALY. Similarly, the cost effectiveness of sequence

3 compared to sequence 4 is £76,793 per QALY. The company model estimates that upadacitinib is not cost effective at position 1.

Intensifying cheap csDMARDs before upadacitinib is more cost effective than using upadacitinib immediately. The only real patient downside in terms of response is the roughly 15-20% of patients not responding to csDMARDs who would have responded to upadacitinib. But this downside is a wait of 6 months while their lack of response to csDMARDs is assessed, at which point they receive upadacitinib. The upside is that over 50% of patients achieve a response with csDMARDs at considerable lower direct drug costs than if csDMARDs had not been used and all patients had been immediately treated with upadacitinib.

If the company gave greater consideration to the mutually exclusive alternative treatment sequences for moderate RA as above, its model would estimate that upadacitinib is not cost effective at position 1.

2.8 Company revised NMA effectiveness estimates

Given the considerations of section 2.4 above, the company provides revised NMA estimates for effect of upadacitinib relative to intensified csDMARDs and relative to sugar pill/control/placebo the central values of which are presented in Table 12 below.

Table 12. Revised company csDMARD-IR NMA EULAR response rates

	Absolute effects		Net effects					
	NMA		vs Int.csDMARDs*		vs csDMARD: MTX		vs Placebo	
Treatment	Mod.	Good	Mod.	Good	Mod.	Good	Mod.	Good
Placebo	[redacted]							
csDMARD: MTX	[redacted]							
Int.csDMARDs*	[redacted]							
ADA+MTX	[redacted]							
RTX+MTX	[redacted]							
UPA*	[redacted]							
SRL+MTX	[redacted]							
UPA+MTX	[redacted]							

* Net effects calculated by the ERG by simple subtraction.

While the method used to derive the net estimates is more complex, it can most simply be thought of as subtracting the response rates of the intensified csDMARDs from those of the other comparators to arrive at the 4th and 5th columns, subtracting those of MTX to arrive at

the 6th and 7th columns and subtracting those of the placebo control to arrive at the 8th and 9th columns[2].

The company response to Technical Engagement does not report values for intensified csDMARDs or for upadacitinib monotherapy. The reason for these omissions is unknown. These are included in the above, with the net values being inferred by the ERG by simple subtraction.

The company argues that net clinical effectiveness estimates should be used for the economic modelling.

- This means that ongoing upadacitinib drug costs are only incurred by a subset of the [redacted] of patients who respond to upadacitinib monotherapy: [redacted] for the comparison with intensified csDMARDs, [redacted] for the comparison with methotrexate and [redacted] for the comparison with placebo.
- There are similar reductions in the upadacitinib drug costs for the comparisons with upadacitinib plus methotrexate. Of the [redacted] of patients who respond to upadacitinib plus methotrexate response rate, only [redacted] incur ongoing upadacitinib drug costs for the comparison with intensified csDMARDs, [redacted] for the comparison with methotrexate and [redacted] for the comparison with placebo.
- The 0% response rates that are assumed for the comparator arm also causes patients in the comparator arm to worsen to severe RA more quickly and so also incur the costs of the higher costs of the biologic treatments used for treating severe RA more quickly.

There are no obvious grounds for subtracting the methotrexate response rates to apply moderate and good response rates of [redacted] and [redacted] for upadacitinib plus methotrexate and [redacted] and [redacted] for methotrexate within this comparison. Similarly, there are no obvious grounds for subtracting the intensified csDMARDs response rates to apply moderate and good response rates of [redacted] and [redacted] for upadacitinib and [redacted] and [redacted] for intensified csDMARDs within this comparison.

The situation is more complicated for the comparison with sugar pill/control/placebo. It is not ethical to treat patients with sugar pill, though a homeopathy remedy might approximate to this. So unless homeopathy is an option it can be argued that the response rates of the SELECT trials' control arms are not relevant. The questions that arise from this are:

[2] Doing so results in central net values which are marginally different from those reported above, though some of these differences may be due to rounding errors.

1. What do NICE assessments in other areas assume for the effectiveness of BSC where the trial is placebo controlled? Does the modelling of the active treatment arm and the BSC arm tend to be modelled:
    a) using the active arm and the control arm of the trial respectively, or
    b) by applying an estimate of the net trial effect, such as a hazard ratio, to an inferred "real world" BSC taken from the literature or from expert opinion, or
    c) by applying an estimate of the absolute trial effect to an inferred "real world" BSC, though something analogous to a hazard ratio does not readily spring to mind for this.
2. What are the reasons for the response rates observed in the placebo control arms of the SELECT trials and to what extent would these be observed in clinical practice? If the SELECT trials had been of a longer duration would these effects have waned over time? If these effects will wane over time would this be better modelled through consideration of discontinuation rates, rather than simply netting out the comparator response rates from those of upadacitinib.

The answers to these questions are beyond the remit of the ERG. They may also be driven by the proportion of the upadacitinib arm overall response rate which also occurred in the placebo control arm. This was notably high in the SELECT placebo controlled trials.

NICE has requested that the ERG produce cost effectiveness estimates that apply the net estimates of the company NMA so that Committee can better consider this issue. For the comparison with intensified csDMARDs the ERG applies the estimates of the 4th and 5th columns of Table 12 while for the comparison with placebo/BSC, the ERG applies the estimates of the 8th and 9th columns.

Note that within these scenarios the modelling of those transferring to severe RA does not apply any net treatment effects and only applies the absolute treatment effects. The ERG assumes that this was also the approach adopted by the company in its modelling.

2.9 HAQ evolution for BSC/PBO vs upadacitinib

The company correctly points out that in TA375 those responding to MTX or intensified csDMARDs have an initial HAQ improvement but from that point onwards even though remaining on treatment their HAQ progressively worsens. This differs from those responding to a biologic, who have an initial HAQ improvement and from that point onwards while remaining on treatment have a constant HAQ.

TA375 models the HAQ progression differently for biologics than for csDMARDs, using different data sources. BSRBR 36 month data on 10,186 severe RA patients with a mean baseline DAS of 6.55 who were treated with a biologic saw their mean HAQ improvement at 6 months broadly maintained for 3 years. For the csDMARDs quite complicated modelling of 1,460 newly diagnosed ERAS patients' data is used. These 15 years data is used to model the HAQ trajectory for those responding to csDMARDs.

The company is also correct to note that in the ERG modelling where upadacitinib is juxtaposed with BSC/PBO, responders to both upadacitinib and BSC/PBO have an initial HAQ response and from that point onwards while remaining on treatment are assumed to have constant HAQ in both arms.

Which is more appropriate may depend in part upon the size of response for BSC/PBO and the net effect of upadacitinib in addition to this. A small BSC/PBO response rate and a large net upadacitinib response rate may or may not argue for treating the arms differently. But if the BSC/PBO response rate is a large proportion of the upadacitinib response rate, so possibly stemming from the same source, this may make it more difficult to argue for differentiating the HAQ trajectory between the arms.

The ERG provides a scenario analysis which assumes a worsening of HAQ among BSC/PBO responders and a constant HAQ for upadacitinib responders.

2.10 Re-challenge with csDMARDs

The company notes that when clinicians have exhausted all possible treatment options they are likely to re-challenge patients with a combination of csDMARDs. The ERG report noted that most of these patients will have already failed to respond to or have lost response to methotrexate.

The company model does not readily permit an in depth exploration of this. To approximate to patients being re-challenged the ERG presents a scenario analysis that appends MTX to the end of the moderate RA treatment sequences. This is in line with the treatment sequences of the original company modelling and of TA375, but is subject to the caveats noted in section 5.3.4.12 of the original ERG report.

2.11 Company correction of ERG TA375 model implementation

The ERG has not had time to fully parse and rerun the company correction of the ERG TA375 model implementation. But the ERG agrees that it is likely that the ERG has not included various administration and monitoring costs in its TA375 model implementation and so has underestimated total costs for all sequences. The sequences that are modelled are:

Table 13. Treatment sequences modelled by the company

Sequence	Treatment 1	Treatment 2	Treatment 3	Treatment 4
Sequence 1	Int cDMARDs	IFX+MTX	BSC	..
Sequence 2	Int cDMARDs	ADA+MTX	IFX+MTX	BSC
Sequence 3	Int cDMARDs	GOL+MTX	IFX+MTX	BSC
Sequence 4	ADA+MTX	IFX+MTX	Int cDMARDs	BSC
Sequence 5	ADA+MTX	IFX+MTX	BSC	..
Sequence 6	GOL+MTX	IFX+MTX	BSC	..
Sequence 7	ADA+MTX	GOL+MTX	IFX+MTX	BSC
Sequence 8	GOL+MTX	ADA+MTX	IFX+MTX	BSC

The company supplies the following cost effectiveness estimates using the TA375 model modified as per the ERG validation modelling section, but correcting the various administration and monitoring costs.

Table 14. Company validation results using the TA375 electronic model

			Net vs Sequence 1		
Sequence	Costs	QALYs	Δ Costs	Δ QALYs	ICER
Sequence 1	£64,926	7.16			
Sequence 2	£78,306	7.70	£13,380	0.54	£24,778
Sequence 3	£84,102	7.71	£19,176	0.55	£34,865
Sequence 4	£92,003	7.77	£27,077	0.61	£44,389
Sequence 5	£94,925	7.28	£29,999	0.12	£249,992
Sequence 6	£103,059	7.34	£38,133	0.18	£211,850
Sequence 7	£115,347	7.87	£50,421	0.71	£71,015
Sequence 8	£117,518	7.91	£52,592	0.75	£70,123

The company supplies the following cost effectiveness estimates using the company model modified as per the ERG validation modelling section so as to align it as closely as possible with the TA375 model validation exercise[3].

Table 15. Company validation results using the company electronic model

			Net vs Sequence 1		
Sequence	Costs	QALYs	Costs	QALYs	ICER
Sequence 1	£71,311	7.26			
Sequence 2	£88,786	7.91	£17,475	0.65	£26,885
Sequence 3	£93,513	7.93	£22,202	0.67	£33,137
Sequence 4	£104,501	8.03	£33,190	0.77	£43,104
Sequence 5	£106,173	7.65	£34,862	0.39	£89,390

[3] The company table labelling referencing within the text of its addendum 3 is unclear, but it appears that the company position is that the most appropriate values are those of addendum 3 Table 8: Comparison of AbbVie model non base case assumptions vs. the updates TA375 model by AbbVie (sensitivity analysis) (to allow a like with like comparison). Similar values and conclusions result from Table 7 of addendum 3.

Sequence 6	£112,602	7.71	£41,291	0.45	£91,758
Sequence 7	£125,581	8.28	£54,270	1.02	£53,206
Sequence 8	£127,589	8.28	£56,278	1.02	£55,175

While the total costs and total QALYs appear reasonably aligned the net quantities show some divergence with this flowing through to the ICERs.

- The net QALY gains from sequences 5 and 6 over sequence 1 are small in both models, but are larger when using the company model than when using the TA375 model. The company model ICERs are very much more favourable to these biologic treatment sequences than the TA375 model.
- The net QALY gains from sequences 7 and 8 over sequence 1 are larger in both models than those of the previous bullet, but again are larger when using the company model than when using the TA375 model. The company model ICERs are somewhat more favourable to these biologic treatment sequences than the TA375 model.
- If it is more appropriate to compare sequences of the same length and sequences 7 and 8 against sequence 2 the company model ICERs are roughly half those of the TA375 model.

The company model validation work of its addendum 3 appears to suggest that the company model is more favourable to the biologic sequences when comparing them with non-biologic containing sequences than the TA375 model.

Or put another way, the company addendum 3 appears to suggest that the company model results in more favourable ICERs than the TA375 model when comparing a treatment sequence with higher response rate against a treatment sequence with a lower response rate.

3 Additional ERG analyses

The ERG provides the following additional analyses of using upadacitinib to treat moderate RA patients:

- SA05: Applying the company revised NMA net treatment effects for upadacitinib and upadacitinib plus methotrexate and zero response rates for the comparator.
- SA06: For the comparison with BSC assuming a constant HAQ for those responding to upadacitinib but a worsening HAQ using the TA375 csDMARD HAQ progression function for BSC/placebo[4].
- SA07: Moderate RA patients receiving 2nd line MTX after 1st line non-response or discontinuation to reflect the uncertainty around the treatment of non-responding and discontinuing patients and their re-challenge with csDMARDs.

The ERG appends these analyses to those presented in the original ERG report for ease of reference.

3.1 Position 2a: Moderate RA: MTX intolerant, RTX tolerant, failed ≥2 csDMARDs

For the comparison with the intensified csDMARDs the company model estimates the following.

Table 16. ERG scenario analyses: Position 2a vs csDMARDs: Moderate RA: MTX intolerant, RTX tolerant, failed ≥2 csDMARDs

	ΔCost	ΔQALY	ICER
Base case sequences	[redacted]	[redacted]	£52,990
Scenario 01 sequences	[redacted]	[redacted]	£57,335
Scenario 02 sequences	[redacted]	[redacted]	£63,220
Scenario 03 sequences	[redacted]	[redacted]	£67,565
Scenario 04 sequences	[redacted]	[redacted]	£66,328
SA03: Company HAQ to pain mapping	[redacted]	[redacted]	£47,006
SA04: Company HAQ to DAS-28 intercept	[redacted]	[redacted]	£56,626
SA05: Net effect for UPA and 0% for comparator	[redacted]	[redacted]	£27,627
SA06: UPA constant HAQ, comparator worsening HAQ	[redacted]	[redacted]	..
SA07: 2nd line MTX	[redacted]	[redacted]	£56,205

For the comparison with the PBO/BSC the company model estimates the following.

[4] The ERG has implemented this by using MTX as the placeholder for BSC rather than TCV_{IV}.

Table 17. ERG scenario analyses: Position 2a vs PBO / BSC: Moderate RA: MTX intolerant, RTX tolerant, failed ≥2 csDMARDs

	ΔCost	ΔQALY	ICER
Base case sequences	[redacted]	[redacted]	£38,432
Scenario 01 sequences	[redacted]	[redacted]	£41,991
Scenario 02 sequences	[redacted]	[redacted]	£47,907
Scenario 03 sequences	[redacted]	[redacted]	£51,466
Scenario 04 sequences	[redacted]	[redacted]	£46,354
SA01a: COMPARE EULAR	[redacted]	[redacted]	n.a.
SA01b: COMPARE EULAR mapped	[redacted]	[redacted]	n.a.
SA01c: NEXT EULAR Mapped	[redacted]	[redacted]	n.a.
SA01d: MONOTHERAPY EULAR mapped	[redacted]	[redacted]	£87,847
SA02: PBO / BSC 0% EULAR responses	[redacted]	[redacted]	£17,506
SA03: Company HAQ to pain mapping	[redacted]	[redacted]	£32,545
SA04: Company HAQ to DAS-28 intercept	[redacted]	[redacted]	£41,400
SA05: Net effect for UPA and 0% for comparator	[redacted]	[redacted]	£23,833
SA06: UPA constant HAQ, comparator worsening HAQ	[redacted]	[redacted]	£31,220
SA07: 2nd line MTX	[redacted]	[redacted]	£46,101

3.2 Position 2b: Moderate RA: MTX tolerant, RTX tolerant, failed ≥2 csDMARDs

For the comparison with the intensified csDMARDs the company model estimates the following.

Table 18. ERG scenario analyses: Position 2b vs csDMARDs: Moderate RA: MTX tolerant, RTX tolerant, failed ≥2 csDMARDs

	ΔCost	ΔQALY	ICER
Base case sequences	[redacted]	[redacted]	£47,466
Scenario 01 sequences	[redacted]	[redacted]	£51,130
Scenario 02 sequences	[redacted]	[redacted]	£56,678
Scenario 03 sequences	[redacted]	[redacted]	£60,272
Scenario 04 sequences	[redacted]	[redacted]	£57,703
SA03: Company HAQ to pain mapping	[redacted]	[redacted]	£42,014
SA04: Company HAQ to DAS-28 intercept	[redacted]	[redacted]	£50,874
SA05: Net effect for UPA and 0% for comparator	[redacted]	[redacted]	£21,393
SA06: UPA constant HAQ, comparator worsening HAQ	[redacted]	[redacted]	..
SA07: 2nd line MTX	[redacted]	[redacted]	£56,133

For the comparison with the PBO/BSC the company model estimates the following.

Table 19. ERG scenario analyses: Position 2b vs PBO / BSC: Moderate RA: MTX tolerant, RTX tolerant, failed ≥2 csDMARDs

	∆Cost	∆QALY	ICER
Base case sequences	[redacted]	[redacted]	£35,958
Scenario 01 sequences	[redacted]	[redacted]	£39,308
Scenario 02 sequences	[redacted]	[redacted]	£44,619
Scenario 03 sequences	[redacted]	[redacted]	£47,892
Scenario 04 sequences	[redacted]	[redacted]	£43,507
SA01a: COMPARE EULAR	[redacted]	[redacted]	£44,163
SA01b: COMPARE EULAR mapped	[redacted]	[redacted]	£69,164
SA01c: NEXT EULAR Mapped	[redacted]	[redacted]	£94,563
SA01d: MONOTHERAPY EULAR mapped	[redacted]	[redacted]	n.a.
SA02: PBO / BSC 0% EULAR responses	[redacted]	[redacted]	£16,729
SA03: Company HAQ to pain mapping	[redacted]	[redacted]	£30,512
SA04: Company HAQ to DAS-28 intercept	[redacted]	[redacted]	£38,757
SA05: Net effect for UPA and 0% for comparator	[redacted]	[redacted]	£17,249
SA06: UPA constant HAQ, comparator worsening HAQ	[redacted]	[redacted]	£29,190
SA07: 2nd line MTX	[redacted]	[redacted]	£47,567

3.3 Position 2c: Moderate RA: MTX intolerant, RTX intolerant, failed ≥2 csDMARDs

For the comparison with the intensified csDMARDs the company model estimates the following.

Table 20. ERG scenario analyses: Position 2c vs csDMARDs: Moderate RA: MTX intolerant, RTX intolerant, failed ≥2 csDMARDs

	∆Cost	∆QALY	ICER
Base case sequences	[redacted]	[redacted]	£52,359
Scenario 01 sequences	[redacted]	[redacted]	£59,025
Scenario 02 sequences	[redacted]	[redacted]	£66,968
Scenario 03 sequences	[redacted]	[redacted]	£73,633
Scenario 04 sequences	[redacted]	[redacted]	£70,860
SA03: Company HAQ to pain mapping	[redacted]	[redacted]	£45,755
SA04: Company HAQ to DAS-28 intercept	[redacted]	[redacted]	£56,626
SA05: Net effect for UPA and 0% for comparator	[redacted]	[redacted]	£18,289
SA06: UPA constant HAQ, comparator worsening HAQ	[redacted]	[redacted]	..
SA07: 2nd line MTX	[redacted]	[redacted]	£60,586

For the comparison with the PBO/BSC the company model estimates the following.

Table 21. ERG scenario analyses: Position 2c vs PBO / BSC: Moderate RA: MTX intolerant, RTX intolerant, failed ≥2 csDMARDs

	∆Cost	∆QALY	ICER
Base case sequences	[redacted]	[redacted]	£37,991
Scenario 01 sequences	[redacted]	[redacted]	£43,378
Scenario 02 sequences	[redacted]	[redacted]	£50,812
Scenario 03 sequences	[redacted]	[redacted]	£56,199
Scenario 04 sequences	[redacted]	[redacted]	£50,050
SA01a: COMPARE EULAR	[redacted]	[redacted]	n.a.
SA01b: COMPARE EULAR mapped	[redacted]	[redacted]	n.a.
SA01c: NEXT EULAR Mapped	[redacted]	[redacted]	n.a.
SA01d: MONOTHERAPY EULAR mapped	[redacted]	[redacted]	£76,405
SA02: PBO / BSC 0% EULAR responses	[redacted]	[redacted]	£17,114
SA03: Company HAQ to pain mapping	[redacted]	[redacted]	£31,887
SA04: Company HAQ to DAS-28 intercept	[redacted]	[redacted]	£41,400
SA05: Net effect for UPA and 0% for comparator	[redacted]	[redacted]	£18,418
SA06: UPA constant HAQ, comparator worsening HAQ	[redacted]	[redacted]	£29,846
SA07: 2nd line MTX	[redacted]	[redacted]	£49,158

The interpretation of these model results should be read in tandem with the company model validation work of section 2.11 above which may suggest that the company model estimates favourable ICERs for upadacitinib than parallel modelling using the TA375 model.

4 References

1. Deighton C, Hyrich K, Ding T, Ledingham J, Lunt M, Luqmani R, et al. BSR and BHPR rheumatoid arthritis guidelines on eligibility criteria for the first biological therapy. Rheumatology. 2010;49(6):1197-9.

2. Kiely PD, Jayakumar K, Norton S, Williams R, Walsh D, Young A. Relation between year 1 DAS28 status and 2 year disease activity, function and employment in DMARD treated RA patients in the Early Rheumatoid Arthritis Network (ERAN). Rheumatology. 2009;48(Suppl 1):i87.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final technical report

Upadacitinib for treating moderate to severe rheumatoid arthritis

This document is the technical report for this appraisal. It has been prepared by the technical team with input from the lead team and chair of the appraisal committee.

The technical report and stakeholder's responses to it 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 appraisal committee meeting.

The technical report includes:

- topic background based on the company's submission
- a commentary on the evidence received and written statements
- technical judgements on the evidence by the technical team
- reflections on NICE's structured decision-making framework.

This report is based on:

- the evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

The technical report should be read with the full supporting documents for this appraisal.

Issue date: January 2020

1. Topic background

List of abbreviations:

Abbreviations used in this report

Abbreviation	
ABT	abatacept
ACR	American College of Rheumatology
ADA	adalimumab
bDMARD	biologic disease-modifying antirheumatic drug
BRC	baricitinib
BSC	best supportive care
csDMARD	conventional synthetic disease-modifying antirheumatic drug
CTZ	certolizumab pegol
DAS-28	disease activity score 28-joint count
ERG	Evidence Review Group
ETN	etanercept
GOL	golimumab
HAQ-DI	health assessment questionnaire disability index
HRQL	health-related quality of life
ICER	incremental cost-effectiveness ratio
IFX	infliximab
IR	Inadequate response
IV	Intravenous
JAK	Janus kinase
LDA	low disease activity
LOCF	last observation carried forward
MTX	methotrexate
PBO	placebo
RTX	rituximab
SC	subcutaneous
SRL	sarilumab
TA	Technology appraisal
TCZ	tocilizumab
TFC	tofacitinib
TNF-alpha	tumour necrosis factor alpha
UPA	upadacitinib

1.1 Disease background

Rheumatoid arthritis (RA) is an inflammatory autoimmune disease that typically affects the synovial tissue of the small joints of the hands and feet but can affect any synovial joint, causing swelling, stiffness, pain and progressive joint destruction. It is a systemic disease and can affect the whole body, including the lungs, heart and eyes. RA is usually a chronic relapsing condition which has a pattern of flare-ups followed by periods of lower disease activity; however, for some people, the disease is constantly progressive.

Severity of disease can be classified into 4 categories, based on the disease activity score (DAS-28) classification system. A DAS-28 greater than 5.1 indicates high disease activity or severe disease, between 3.2 and 5.1 indicates moderate disease activity, less than 3.2 indicates low disease activity, and less than 2.6 indicates disease remission.

1.2 Treatment pathway (see figure 1)

There is no cure for RA and treatment aims to improve quality of life and to prevent or reduce joint damage. The main aim of management in early disease is to suppress disease activity and induce disease remission, prevent loss of function, control joint damage, maintain pain control and enhance self-management.

For people with newly diagnosed rheumatoid arthritis, NICE guideline 100 ('Rheumatoid arthritis in adults: management') recommends using a conventional disease modifying anti-rheumatic drug (DMARD; including methotrexate, leflunomide and sulfasalazine) as a monotherapy for first-line treatment, ideally beginning within 3 months of the onset of persistent symptoms. When disease remission or low disease activity has not been achieved with DMARD monotherapy it is recommended that additional arthritis csDMARDs (oral methotrexate, leflunomide, sulfasalazine or hydroxychloroquine) are used in combination.

Where the disease has not responded to combination therapy with conventional DMARDs, NICE technology appraisal guidance 375, 466, 480 and 485 recommend biological DMARDs (bDMARDs; adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab, abatacept and sarilumab), or other

immunomodulatory therapies (baricitinib and tofacitinib), in combination with methotrexate for severe RA only.

For those people with severe RA who cannot have methotrexate because it is contraindicated or because of intolerance, the guidance recommends that adalimumab, etanercept, certolizumab pegol, tocilizumab, baricitinib, sarilumab or tofacitinib monotherapy can be used.

Where the disease has not responded adequate or in the case of intolerance to other DMARDs, including at least one tumour necrosis factor (TNF) inhibitor (a therapy subset of biological DMARDs), rituximab in combination with methotrexate is recommended for severe RA only (NICE technology appraisal guidance 195).

Where rituximab is contraindicated or withdrawn because of an adverse event, biological DMARDs (adalimumab, etanercept, infliximab, abatacept, golimumab, tocilizumab, certolizumab pegol and sarilumab), or other immunomodulatory therapies (tofacitinib and baricitinib), in combination with methotrexate, are recommended as options (NICE technology appraisal guidance 195, 225, 247 ,415, 466, 480 and 485).

Where rituximab in combination with methoxtrexate therapy cannot be given because methotrexate is contraindicated or has been withdrawn due to an adverse event, biological DMARDs (adalimumab, etanercept, certolizumab pegol and sarilumab), or other immunomodulatory therapies (tofacitinib and baricitinib), each as a monotherapy, can be used (NICE technology appraisal guidance 195, 415, 466, 480 and 485).

Description of the technology: upadacitinib

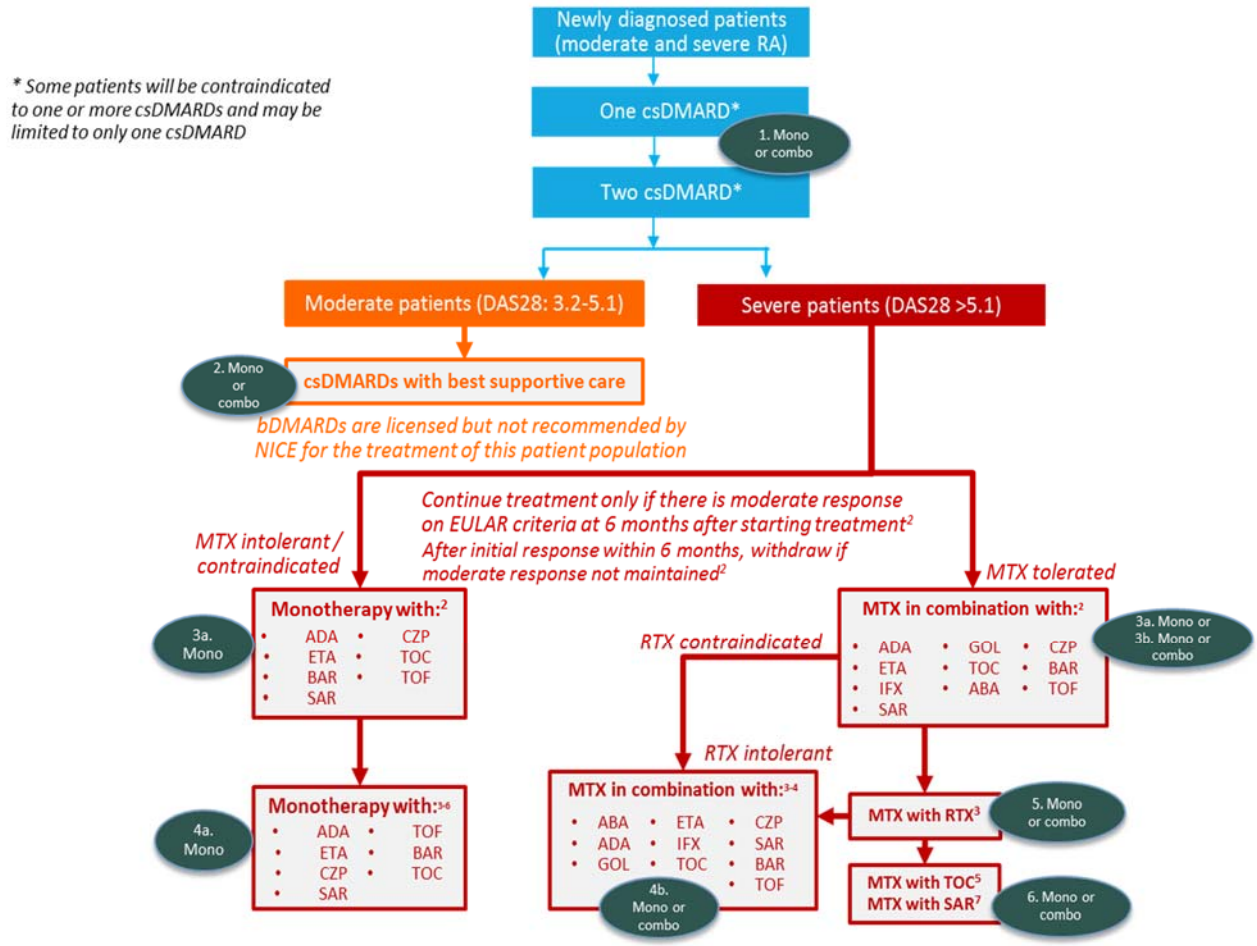
Upadacitinib (brand name unknown, AbbVie) is a Janus-kinase (JAK) 1 inhibitor that blocks the JAK-signal transducer and activator of transcription (STAT) pathway and inflammatory responses. It can be used as a monotherapy or in combination with methotrexate. It is administered orally. Upadacitinib does not currently have a marketing authorisation in the UK for RA. It received a positive opinion from the

Committee for Medicinal Products for Human Use in October 2019, for the treatment of moderate to severe active RA, either on its own or with methotrexate, in adults who have responded inadequately to, or who are intolerant to 1 or more DMARDs.

Potential position of upadacitinib in the clinical pathway

The company proposes to position upadacitinib at various points in the current clinical pathway. These positions cover both moderate and severe RA, both as a monotherapy and in combination with other csDMARDS, including methotrexate (Figure 1).

Figure 1. Company proposed positioning of upadacitinib



Abbreviations: csDMARDs, conventional synthetic disease modifying antirheumatic drugs; UPA, upadacitinib
Source: Company Submission, p.29, Figure 2.

Issue date: January 2020

The company has modelled 10 RA population subgroups in its submission, defined by disease severity, the suitability of methotrexate and rituximab as treatment options, and the number and type of previously failed therapies. These are shown in Table 1.

Table 1. Company RA population subgroups considered

Position ID	Disease severity	Failed treatments	Methotrexate	Rituximab
1a	Moderate	Failed one csDMARD	Intolerant	Tolerant
1b	Moderate	Failed one csDMARD	Tolerant	Tolerant
2a	Moderate	Failed ≥2 csDMARD	Intolerant	Tolerant
2b	Moderate	Failed ≥2 csDMARD	Tolerant	Tolerant
3a	Severe	Failed ≥2 csDMARD	Intolerant	Tolerant
3b	Severe	Failed ≥2 csDMARD	Tolerant	Tolerant
4a	Severe	Failed 1 bDMARD	Intolerant	Tolerant
4b	Severe	Failed 1 bDMARD	Tolerant	Intolerant
5	Severe	Failed 1 bDMARD	Tolerant	Tolerant
6	Severe	Failed rituximab	Tolerant	Tolerant

1.3 Clinical evidence

The clinical trial evidence for upadacitinib comes from four randomised-control trials (RCTs). A brief description of each can be seen in Table 2 (a more detailed description of these trials can be found in the ERG report table 3 pages 48 to 50).

Table 2. Summary of phase III clinical trials

Trial:	SELECT-COMPARE	SELECT-NEXT	SELECT-MONOTHERAPY	SELECT-BEYOND
Description	Phase III RCT	Phase III RCT	Phase III RCT	Phase III RCT
Population	Moderate to severe RA, on MTX and have an inadequate response to MTX	Moderate to severe RA, on csDMARDs and have an inadequate response to csDMARDs	Moderate to severe RA, on MTX and have an inadequate response to MTX	Moderate to severe RA, on a csDMARD and had an inadequate response or intolerance to at least 1 bDMARD

Intervention	UPA 15 mg orally once daily to week 48 (period 1) and thereafter up to 5 years (period 2)	UPA 15 mg or 30 mg orally once daily to week 12 (period 1) and thereafter up to 5 years (period 2)	UPA 15 mg or 30 mg orally once daily to week 14 (period 1) and thereafter up to week 226 (period 2)	UPA 15 mg or 30 mg orally once daily to week 48 (period 1) and thereafter up to week 216 (period 2)
Comparators	PBO to week 26 followed by UPA 15 mg from week 26 to week 48 (period 1) and thereafter up to 5 years (period 2) ADA 40 mg to week 48 (period 1) ad thereafter up to 5 years (period 2)	PBO to week 12 (period 1), followed by UPA 15 mg or 30 mg orally QD (in 2 different randomised groups) at week 12 and thereafter up to 5 years (period 2)	MTX to week 14 (period 1), followed by UPA 15 mg or 30 mg at week 14 and thereafter up to week 226 (period 2)	PBO to week 12, followed by UPA 15 mg or 30 mg (in 2 different randomised groups) at week 12 to week 24 (period 1) and thereafter up to week 216 (period 2)
Treatment key: ADA, adalimumab; MTX, methotrexate; PBO, placebo; UPA, upadacitinib.				

1.4 Key trial results

A brief summary of key clinical trial results is provided in Table 3 (a more detailed commentary on clinical trial results can be found in the ERG report pages 77 to 89).

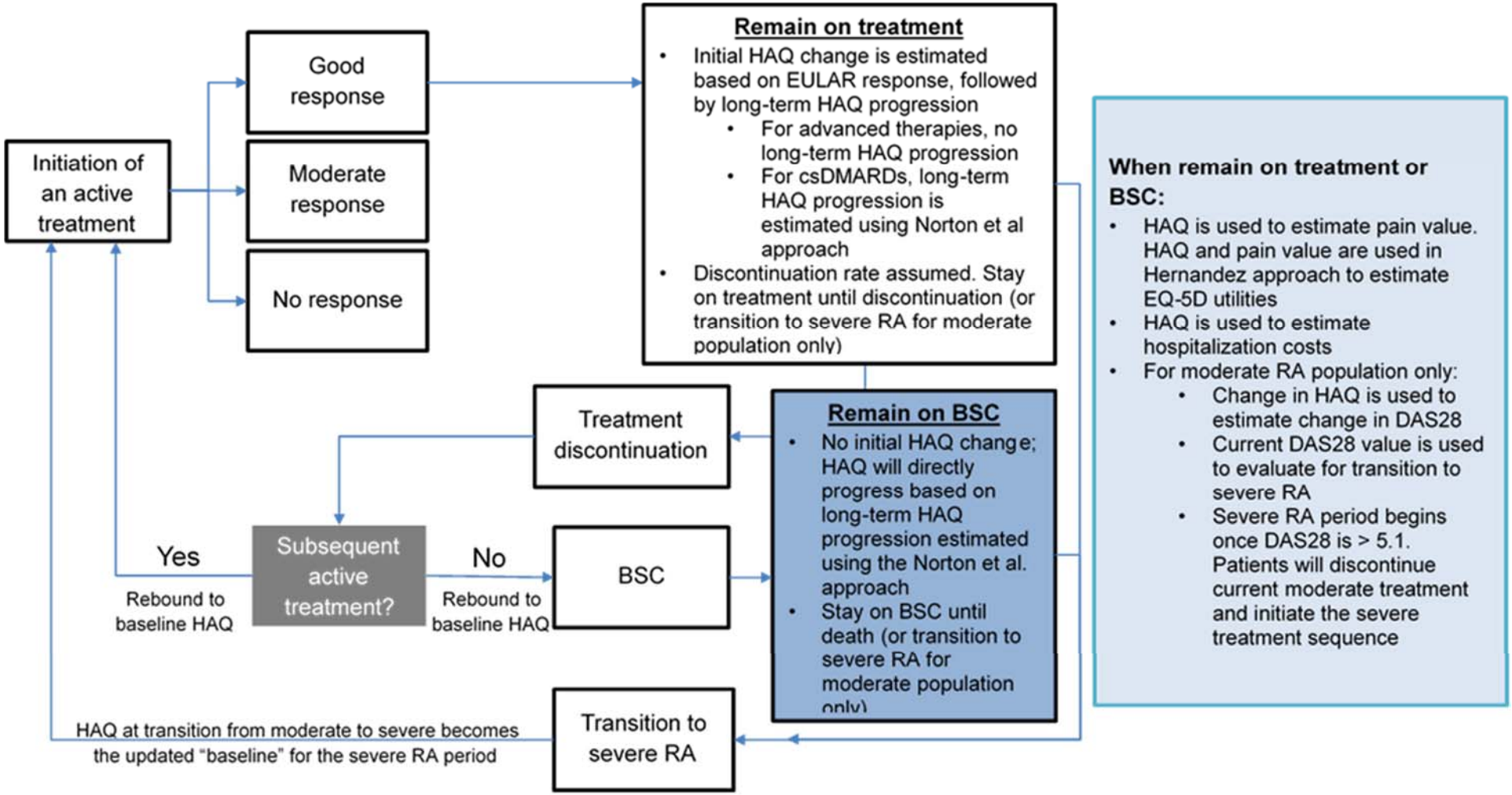
Table 3. Key clinical trial results

Key clinical outcome	**SELECT-COMPARE**	**SELECT-NEXT**	**SELECT-MONOTHERAPY**	**SELECT-BEYOND**
Time point	Week 12	Week 12	Week 14	Week 12
ACR 20 response	UPA+MTX: 71% ADA+MTX: 63% (p≤0.05) PBO: 36% (p≤0.001)	UPA: 64% PBO: 36% (p≤0.001)	UPA: 68% MTX: 41% (p≤0.001)	UPA+csDMARDs: 65% PBO+csDMARDs: 28% (p≤0.001)
ACR 50 response	UPA+MTX: 45% ADA+MTX: 29% (p≤0.001) PBO: 15% (p≤0.001)	UPA: 38% PBO: 15% (p≤0.001)	UPA: 42% MTX: 15% (p≤0.001)	UPA+csDMARDs: 34% PBO+csDMARDs: 12% (p≤0.001)
ACR 70 response	UPA+MTX: 26% ADA+MTX: 13% (p≤0.001) PBO: 5% (p≤0.001)	UPA: 21% PBO: 6% (p≤0.001)	UPA: 23% MTX: 3% (p≤0.001)	UPA+csDMARDs: 12% PBO+csDMARDs: 7% (p≤0.05)

Clinical remission (DAS-28 CRP)	UPA+MTX: 29% ADA+MTX: 18% (p≤0.001) PBO: 6% (p≤0.001)	UPA: 31% PBO: 10% (p≤0.001)	UPA: 28% MTX: 8% (p≤0.001)	UPA+csDMARDs: 29% PBO+csDMARDs: 10% (p≤0.001)
Low disease activity (DAS-28 CRP)	UPA+MTX: 49% ADA+MTX: 29% (p≤0.001) PBO: 14% (p≤0.001)	UPA: 48% PBO: 17% (p≤0.001)	UPA: 45% MTX: 19% (p≤0.001)	UPA+csDMARDs: 43% PBO+csDMARDs: 14% (p≤0.001)
Treatment key: ADA, adalimumab; csDMARDs, conventional synthetic disease-modifying anti-rheumatic drugs; MTX, methotrexate; PBO, placebo; UPA, upadacitinib. Note: p values denote the significance level of the difference between UPA and each comparator. Results are rounded to the nearest percentage point.				

SELECT-COMPARE also reported results at 26 weeks; however, these data include patients who switched treatments from 12 weeks, from PBO to UPA, ADA to UPA or UPA to ADA, and therefore they are not shown above.

1.5 **Company's model structure (reproduced from ERG report, Figure 8 page 161)**



The above figure shows the model structure developed by the company. In the model, people with RA have a first-line treatment for 6 months, and remain on it if they achieve a EULAR response (which is achieving a pre-defined DAS-28 improvement based on the patient's current DAS-28 score) and have a corresponding reduction in their HAQ (health assessment questionnaire – a disease-specific questionnaire for RA). Those not achieving a EULAR response at 6 months go on to have the next treatment in the sequence. The model includes the possibility of patients moving from moderate RA to severe RA; this is a key difference to the model developed as part of TA375, which was a NICE multiple technology appraisal (MTA) and evaluated a range of treatments (ADA, ETN, INF, CTZ, GOL, TOC and ABT) for RA not previously treated with DMARDs or after conventional DMARDs only have failed. The company model is consistent with the model used in TA485 (SRL for moderate to severe RA), where allowing progression between moderate and severe RA was judged to better reflect clinical practice.

1.6 Key model assumptions

The company, in its submission, have taken key modelling assumptions from previous NICE appraisal TA375, which was a multiple technology appraisal (MTA). The assessment group for TA375 developed an individual patient-based discrete event simulation model. The company's model also notably differs from the one developed in TA375 in some areas. The model estimates the relationship between the HAQ scores and the DAS-28 scores to allow patients in the model to progress from moderate to severe RA. This is done from 3- and 6-month data from the SELECT trials and extrapolated over 45 years (see issue 3a). The model also assumes that there is a constant EULAR response by line of treatment (i.e. regardless of severity of RA or previous treatments received (see issue 3c).

1.7 Overview of how quality-adjusted life years accrue in the model

The treatment effectiveness estimates are based upon the EULAR response estimates of the company's two network meta-analyses (NMAs): the csDMARD-IR NMA (IR = inadequate response), and the bDMARD-IR NMA (see issue 4). An

additional “treatment” of BSC is included in the economic model, which is assumed to have a EULAR response rate of zero (see issue 1). The HAQ scores determine quality of life and inpatient costs. EULAR responses are assumed to result in the improvements in patients’ HAQ scores. The EULAR relationship with HAQ changes can be seen in Table 4 (ERG table 51, page 171).

Table 4. Relationship between EULAR response and HAQ change

	HAQ Change			
	Company and ERG Base case (Source: TA375)		**SELECT trials (Company scenario analysis)**	
EULAR response	**Mean**	**(SE)**	**Mean**	**(SE)**
None	0.000	..	-0.123	(0.018)
Moderate	-0.317	(0.048)	-0.481	(0.016)
Good	-0.673	(0.112)	-0.755	(0.019)

Abbreviations: HAQ, health assessment questionnaire; SE, standard error

The base case values are the same as those applied in TA375. HAQ changes are not differentiated by whether a patient has moderate RA or severe RA.

The company’s model maps from a patient’s HAQ score to a pain score, using a mapping function derived from the pooled SELECT trials. In TA375, the mapping function was derived from a large registry dataset (n > 100,000). The company’s model also uses HAQ to determine mortality, by selecting the hazard ratio (HR) should be applied to the background, general population mortality risk. This is the same approach as was used in TA375 (see Table 5).

Table 5. Baseline HAQ and mortality hazard ratios (Table 53 in ERG report, page 174)

Baseline HAQ	**Mortality HR**
0.000	1.0
0.125-0.375	1.4
0.500-0.875	1.5
1.000-1.375	1.8

Baseline HAQ	Mortality HR
1.500-1.875	2.7
2.000-2.375	4.0
2.500-3.000	5.5

Abbreviations: HAQ, health assessment questionnaire; HR, hazard ratio

The time horizon is 45 years in the company's base-case analysis. The ERG notes that the model results are not sensitive to extending its time horizon to 60 years.

2. Summary of the technical report

2.1 After technical engagement, the technical team has collated the comments received and, if relevant, updated the judgement made by the technical team and rationale. Judgements that have been updated after engagement are highlighted in bold below:

Issue 1 BSC response rate. The most relevant comparator for both moderate positions **may be** csDMARDs rather than BSC. **However, if BSC is accepted as the most relevant comparator,** assuming BSC provides no EULAR response is unlikely to be appropriate. **It may be appropriate to apply the placebo response rate to BSC when it is being compared with an active treatment. The appropriateness of the company's "net treatment effect" analysis, and the different assumptions regarding the HAQ trajectory of people who respond to BSC, should be considered in decision making.**

Issue 2 Treatment pathway. When MTX is a suitable treatment option, UPA in combination with MTX **is** likely to be cost effective compared with UPA monotherapy, based on a cost-effectiveness analysis done by the ERG. In the moderate RA population, it will usually be appropriate to consider intensified csDMARDs before UPA. **It may also appropriate to model treatment with csDMARDs after UPA failure if csDMARDs is the relevant comparator, although consideration should be given to whether this moves the placebo effect to a subsequent line of treatment.**

Issue 3 Model inputs

3a. Modelling the transition from moderate to severe RA. In the company's model, **patients seem to progress from moderate to severe RA more slowly than UK data suggests; which likely biases the cost-effectiveness results in favour of UPA**. It is not clear how the relationship between HAQ and DAS-28 is applied in the company's model. It is also uncertain if the relationship between the HAQ and DAS-28 estimated by the company holds in the long-term.

3b. Mapping from HAQ to pain scores. The approach for mapping from HAQ to pain from TA375 (which used a large RA dataset) is preferred to the company's method (which use data from the SELECT trials), **however the company's mapping approach may be an informative alternative**.

3c. Common treatment effect at different points in the treatment pathway. The assumption of constant EULAR response across lines of treatment may be inappropriate. It appears to favour UPA, and favours treatment sequences with more active treatments.

Issue 4 **Network meta-analysis.** There are some uncertainties associated with the company's NMA (such as the strong assumption of the generalisability of effects at different lines of treatment). The ERG's application of the NMA results is more appropriate than the company's approach.

Issue 5 **New issue: Model validation. Compared with the model developed by the assessment group for TA375, the company's model appears to overestimate the quality-adjusted life year (QALY) gains for bDMARD treatments relative to csDMARD treatments. This may bias cost-effectiveness estimates in favour of UPA.**

2.2 The technical team recognised that the following uncertainties would remain in the analyses and could not be resolved:

- The phase III comparative trial evidence for UPA is of a short duration, with most of the trials reporting comparator outcomes at 12 or 14 weeks.
- The company's model has a "black box" element to it, which did not allow the ERG to fully critique and examine the programming accuracy of the model.

2.3 The cost-effectiveness results include a confidential commercial arrangement (simple patient access scheme) for UPA. The cost-

effectiveness results also include non-confidential patient access schemes for CTZ and GOL. Taking these aspects into account, the technical team's preferred assumptions result in an incremental cost-effectiveness ratio (ICER) range of £21,393 to £67,565 per QALY gained in the moderate RA population (position 2) if csDMARDs is the comparator. If best supportive care is the comparator, the technical team's preferred assumptions result in an ICER range of £17,249 to £94,563. For the severe RA population, the technical team's preferred assumptions result in UPA either being the dominant option (that is, cheaper and more effective than its comparators) or dominated (that is more expensive and less effective than its comparators).

2.4 The cost-effectiveness estimates above do not include commercial arrangements for ABT, BRC, SRL and TFC, because these are confidential and cannot be reported here. There are also confidential commercial arrangements for biosimilar versions of ADA, ETN, IFX and RTX (see ERG biosimilars addendum). Including these commercial arrangements would increase the cost-effectiveness estimates. Using the price of Humira for ADA, the commercial arrangements for ABT, BRC, SRL and TFX, and the lowest price following commercial arrangements for each of ETN, IFX and RTX, the technical team considers the plausible ICERs to be:

- Position 1a (moderate RA, failed 1 csDMARD, MTX intolerant, RTX tolerant) and Position 1b (moderate RA, failed 1 csDMARD, MTX tolerant, RTX tolerant): The technical team agree with the ERG that position 2 is more cost-effective than position 1.
- Position 2a (moderate RA, failed ≥2 csDMARDs, MTX intolerant, RTX tolerant): <£30,000 to >£30,000 per QALY gained vs csDMARDs/BSC (fully incremental)
- Position 2b (moderate RA, failed ≥2 csDMARDs, MTX tolerant, RTX tolerant): <£30,000 to >£30,000 per QALY gained vs csDMARDs/BSC (fully incremental)

- Position 3a (severe RA, failed ≥2 csDMARDs, MTX intolerant, RTX tolerant): dominant to <£30,000 per QALY gained vs bDMARDs (fully incremental)
- Position 3b (severe RA failed ≥2 csDMARDs, MTX tolerant, RTX tolerant) dominant to >£30,000 per QALY gained vs bDMARDs (fully incremental)
- Position 4a (severe RA, failed 1 bDMARD, MTX intolerant, RTX tolerant): ERG do not consider this position
- Position 4b (severe RA, failed 1 bDMARD, MTX tolerant, RTX intolerant): dominant to ICER>£30,000 vs bDMARDs (fully incremental)
- Position 5 (severe RA failed 1bDMARD, MTX tolerant, RTX tolerant) dominated vs RTX+MTX
- Position 6 (severe RA, failed RTX) dominant to <£30,000 per QALY gained vs bDMARDs (fully incremental)

2.5 The company considers upadacitinib to be innovative. However, the technical team considers that all relevant benefits associated with the drug are adequately captured in the model (see Table 12).

2.6 No equality issues have been raised by stakeholders.

Issue date: January 2020

3. Key issues for consideration

Issue 1 – Response rate for best supportive care

Questions for engagement	1. What does best supportive care (BSC) consist of in NHS clinical practice? How often is it used in both moderate and severe RA in clinical practice as a last line treatment? 2. Which of the following assumptions is the most appropriate to use in the model for BSC? a) Use the placebo EULAR response rates from the upadacitinib phase III trials or the NMA, for BSC b) Assume that the response rate for BSC is 0% 3. Do people with RA experience a natural recovery of their symptoms? If so what proportion of people experience this and for how long?
Background/ description of issue	In most of the upadacitinib phase III clinical trials, a placebo (PBO) was used in the comparator arm. This placebo was administered either orally (to match UPA) or subcutaneously (to match ADA). The PBO response rates in the SELECT trials were substantially higher than zero. **The company** has assumed in its modelling that treatment with BSC provides no EULAR response (i.e. its response rate is 0%). In its factual accuracy check response, the company states that background csDMARDs may contribute to the control arm responses rates in UPA clinical trials. **The ERG** believes that it is incorrect to dismiss the response rates in the SELECT trials' control arms. It explained that it is not clear whether the control arm response rates were caused by natural recovery of symptoms, a pure PBO effect, or some combination of the two. The ERG states that responses caused by natural recovery or a delayed treatment effect in particular should not be excluded. Even if there were no natural recovery or a delayed treatment effect, the ERG advised that it would expect a PBO effect to be present in both arms of a trial (contributing some proportion of the benefit observed in the upadacitinib arm). Therefore, the cost-effectiveness results should not include the PBO effect in only the intervention arm. The ERG noted that by doing so the company's modelling implies a much larger relative treatment effect for UPA over the control arm than is present in the results from the SELECT trials. Therefore, the ERG preference is to use the PBO rate from the NMA to model the effectiveness of BSC. In exploratory analyses, the ERG applies a control arm treatment effect for BSC

	informed by PBO data from the SELECT trials. The ERG provides an addendum in which they compare their approach, and the company's approach, with that of TA375 (see ERG model validation addendum). The ERG feels that a BSC response should only be modelled where BSC is used at the same line of treatment as an active treatment on the comparator model arm. This is because assumptions about response to BSC may be particularly important in comparisons between model arms with different numbers of active treatments in their pathways. For example, applying a last-line BSC response to patients on a model arm with more treatments would potentially bias model results, because patients on that arm will have more chances to experience a response. Conversely, applying a 0% BSC response rate at a line where an active treatment has a non-zero response rate is subject to the issue described above, whereby a PBO effect is implicitly captured within the active treatment's response rate but not the equivalent BSC response rate. **Clinical expert opinion received by NICE** from 1 clinical expert stated that both the company's and ERG's preferred approaches have some conceptual merit. Firstly, it may be methodologically appropriate to assume that a PBO effect is present in both arms of a clinical trial. However, it is likely to be inappropriate to assume that a PBO response rate observed in a trial should be used to model response to palliative BSC, which is given to patients who are more heavily treated than the position indicated by trials. The clinical expert stated that BSC is not expected to provide good outcomes for people with RA, most of whom would prefer to explore enrolment into clinical trials than to have BSC. The clinical expert also explained that few people with RA (around 5%) would experience a natural recovery of their symptoms, and this is particularly rare in people who have received a number of lines of treatments. Those who do have a natural recovery would only experience this for a short period of time, after which symptoms would return. **The technical team** considers that the response rates for PBO from the clinical trial are higher than zero, and that this is also observed in other clinical trials in RA. The technical team is concerned that applying a 0% response rate to BSC may bias the cost-effectiveness results in favour of UPA.
Why this issue is important	The choice of how to model the BSC response rate has an important effect on the cost-effectiveness estimates. Using the company's approach produces substantially lower cost-effectiveness estimates for UPA than using the approach preferred by the ERG. If the company's approach is appropriate, the cost-effectiveness estimate for UPA in moderate RA is likely to be below the threshold usually considered cost effective by NICE. If the ERG approach

	is appropriate, the cost-effectiveness estimate for UPA is likely to exceed the usual threshold in moderate RA (see Table 7).
Technical team preliminary judgement and rationale	The technical team recognises that the company and ERG methods for modelling response to BSC differ, and that this has a substantial effect on cost-effectiveness estimates. The technical team considers that a response rate of 0% should not be used to model response to BSC. The technical team notes that the ERG model validation addendum suggests that the ERG approach is more consistent with the methods accepted by the committee in TA375, compared to the company's approach (see ERG model validation addendum). The most relevant comparator for position 2 (moderate RA, failed 2 or more csDMARDs) is an important consideration (see issue 2). If more csDMARD treatment is given in practice, then comparisons with BSC are not appropriate. Previous NICE technology appraisal guidance in RA (TA375, TA466, TA480 and TA485) have all considered csDMARDs to be the most relevant comparator for the moderate RA population. In addition, the UPA clinical trials included background treatment (i.e. other treatments could be taken) with csDMARDs in the comparator arms, which suggests that neither BSC nor a 0% response rate is likely to be appropriate. Therefore, in summary, the technical team considers that it is appropriate to compare UPA with active treatment (csDMARDs) in the moderate RA population, and the comparison with BSC may not be appropriate. The technical team also believes that analyses with a different number of treatment lines on different model arms should be have the same number of opportunities for patients to experience a treatment response on all arms, so results are not biased by the differences in sequence length.
Summary of comments	**Comments from the company** Best supportive care (BSC = re-challenge with previously failed csDMARDs and corticosteroids) would be given to patients in the moderate population who have failed recommended treatments options. This is captured in the model where patients, who have exhausted all treatment options after receiving and failing csDMARDs, receive BSC. Clinical expert advice to NICE stated that re-challenging with previously failed csDMARDs and corticosteroids is unlikely to benefit patients and would not result in a disease modifying effect.

	They quote the ERG clinical expert:"…*UPA might be withdrawn and patients placed back on whichever combination of csDMARDs proved best*" (Pg. 211 ERG report) and state that this approach would be taken in clinical practice after the failure of upadacitinib. The most appropriate response rate for BSC is zero. The preliminary NICE preferred approach is not appropriate as: • The model intends to reflect clinical practice; placebo would not constitute clinical practice. • The assumption of placebo equating to natural recovery in untreated patients is not supported by the evidence base which demonstrates progressive decline in functionality. • The inclusion of placebo in the comparator arm to address the issue that the efficacy of upadacitinib seen in in the clinical trials may be inflated because of the trial setting is not methodologically appropriate. The appropriate methodological approach would be to "net off" the inflated efficacy of upadacitinib directly from the upadacitinib arm by using the difference between the placebo rate and the upadacitinib response (company have provided updated analysis using this approach) • The approach of assuming 0% efficacy for BSC is aligned to the approach in TA375. The understanding of the ERG that this approach is not aligned to the approach in TA375 based on the ERG validation exercise of the company model against the TA375 model (as stated in the ERG model validation report addendum) is undermined by analysis carried out by the company (company have provided a critique of the model validation work undertaken by the ERG). **Placebo response in the UPA clinical trials** The company believes that the technical team's preference for the use of a placebo response in the model is due to concerns that UPA efficacy in clinical trials consists of some efficacy which is specific to a trial setting and will not manifest in clinical practice. If this is correct, then the current ERG method is not appropriate, as it requires the UPA arm to have a treatment continuation rate associated with the higher response rate than would be observed in practice, incurring higher drug costs. A more appropriate method would be to "net" the placebo effect in the NMA and apply a reduced efficacy to the UPA arm (the company present ICERs for this approach).

	Natural recovery in RA The company states that applying a response rate greater than zero for BSC implies natural recovery, but previous RA appraisals have used UK observational datasets to map HAQ trajectories for BSC, demonstrating a decrease in functionality over time. The company also states that any natural recovery would be rare and short-lived. The company argues that if a response rate of greater than zero is used: • The csDMARD-IR NMA is a more appropriate source for placebo response as the patients in the control arms of the upadacitinib phase III trials were placed on placebo plus background csDMARD. • The HAQ trajectory associated with those experiencing natural recovery (placebo effect) should have a HAQ trajectory the same as those on csDMARDs or BSC (the company presents ICERs for this approach) • If the assumption of natural recovery is present, this should apply to BSC after UPA failure. (the company present ICERs for this approach) They state that the ERG analysis assumes a response rate higher than 0% for patients initiated on BSC in the comparator arm but a 0% response rate for those initiated on BSC in the UPA arm. **Model validation** In relation to the ERG model validation work (which compares the company's model with the model used in TA375), the company states: • applying a 0% response rate for BSC is consistent with TA375. The assessment group report for TA375 (pg. 347) "*It was assumed that non-biologic therapy would be associated with no initial EULAR response, unlike MTX where the results from the NMA indicated that MTX had a significant EULAR response.....This description is in line with the data on HAQ progression that was presented by Norton et al*". They state that non-biologic therapy in the TA375 report refers to BSC. • the ERG model validation work has errors. These include not including drug monitoring costs (except for BSC) and, some drug costs are underestimated. Correcting these points makes its model output more consistent with TA375. The company suggests that the ICERs produced by its analysis are closer to those in the NICE Technology Appraisal Review Proposal paper: Review of TA375

	(https://www.nice.org.uk/guidance/ta375/evidence/consultation-paper-may-2019-pdf-6779359118) compared with the ERGs ICERs. **Comments from commentators** One commentator stated that they believe that the placebo rate from the NMA is the most appropriate to use to model BSC, and that this method has been accepted by committee in previous RA appraisals. Another commentator stated that BSC would not be used in the moderate setting. Patients with moderate disease would receive csDMARDs, therefore BSC is not a relevant comparator in moderate RA. **ERG comments** All 1st line treatment sequences modelled in TA375 have a 1st line treatment with non-zero EULAR response rates. The ERG still believes that its position is consistent with TA375 in this regard, but states that the company is correct to note that non-biologic treatment (BSC) in TA375 is associated with 0% EULAR response rates. The placebo effect should be retained in both arms of the modelling as there are no estimates available for responses purely attributed to being in a clinical trial. The company's revised NMA, which estimates the 'net' effectiveness of UPA, results in ongoing UPA drug costs incurred only by a subset of those who response to UPA in the model (that is, the costs are only applied to the 'net' UPA responders over the control arm responders). This analysis retains a 0% response rate in the comparator arm, which causes BSC patients to worsen to severe RA and incur the higher cost of the biologic treatments more quickly. Allowing different sequence lengths is similar to the approach of TA375, therefore the ERG's position on this matter is different. However, if treatment sequence lengths can differ in the model for moderate RA, then the approach of the company simply shifts the placebo effect issue to the next line of treatment: on the UPA arm, an active treatment is given after UPA which includes a trial effect within its response rate, whereas the comparator 2nd line treatment is BSC with 0% response. It remains the ERG's view that whenever BSC at the same position in

	a treatment sequence as an active treatment, the effectiveness of BSC should be modelled using the control/placebo response rates (not 0%). The company is correct to note that in TA375 those responding to MTX or intensified csDMARDs have an initial HAQ improvement but from that point onwards, even though remaining on treatment, their HAQ progressively worsens. This differs from those responding to a biologic, who have an initial HAQ improvement and from that point onwards while remaining on treatment have a constant HAQ. The company is also correct to note that in the ERG modelling where UPA is compared with BSC, responders to both UPA and BSC have an initial HAQ response and which remains constant HAQ while the person remains on treatment. The ERG argues that it may be appropriate to model in this way as there is a large PBO response, relative to the UPA response. This makes it difficult to argue that much of the observed response rate in both arms is from the same underlying source (i.e. a trial effect); therefore, it would be less appropriate to make different assumptions about what happens to the response rates in the long term. The ERG provides a scenario analysis which takes the alternative approach, by retaining the constant HAQ for UPA responders but assuming a worsening of HAQ among BSC responders.
Technical team judgement after engagement	The technical team notes that all interventions in NICE technology appraisal TA375 were compared with comparators with a non-zero 1st line response rate in the moderate RA population. There is no direct comparison with BSC, and this is also the case in TA485, TA480 and TA466. The technical team also notes that last-line treatment modelled in TA375 (non-biologic treatment) was assumed not to provide a response rate. The technical team understands that non-biologic treatment defined in TA375 is not the same as BSC defined in this appraisal. Here, BSC appears to be an umbrella term representing all interventions that may be given after failure of 2 or more csDMARDs, which may be re-challenge with previously failed csDMARDs for some patients. For this appraisal, the company has presented results for 2 separate moderate RA populations (positions 1 and 2). For position 2 (failed 2 or more csDMARDs), the company's base case has assumed that BSC is the relevant comparator as patients would have exhausted all treatment options and would be placed on treatments which would have no disease-modifying effect (re-challenging with previously failed csDMARDs). This appears to be a different approach to that taken in TA375, where csDMARDs are considered as the comparator in the moderate population. TA375 did not split the moderate population into failed 1 csDMARD (position 1) and failed 2 or more csDMARD (position 2), and instead considered the moderate population as a single population. This matched the population included in the csDMARD-IR NMA, which was not split by number of failures to csDMARDs. The csDMARD-IR NMA used by the company in this appraisal also does not split this population.

	If UPA is compared with BSC at position 2, then the technical team's preferred approach is to use the PBO rate to model response on the comparator arm. This accounts for the PBO rate being implicitly part of the UPA response rate as well. The technical team also believes that there is not enough evidence to suggest that the PBO response observed in the trial data is linked to natural recovery of symptoms; rather, it is more likely to be a 'pure' placebo effect. Therefore, it is not necessary to model the PBO response rate to subsequent, last-line BSC, including following UPA failure. The company's updated NMA estimated the treatment effect of UPA net of PBO; however, the ERG was concerned that this underestimates the treatment costs of UPA. The technical team believes that it may be reasonable to expect a shorter treatment duration, and therefore lower costs, if the response rate is lower in clinical practice once the placebo/trial effect has been removed. Therefore, it may be appropriate to consider both approaches in decision making. In addition, the technical team believes that if BSC is considered the most relevant comparator, then the ERG scenario analysis (SA06) should be considered for its appropriateness. SA06 in the ERG response to engagement assumes a worsening of HAQ among BSC/PBO responders (similar to that of csDMARD responders) and a constant HAQ for upadacitinib responders. Further to this, the technical team understands the company's 'net effect NMA' scenario analysis, provided in response to technical engagement, implicitly assumes that all of the effect observed on control arms is explained as a trial effect, which would not occur in clinical practice. In contrast, the ERG's preferred analysis of including control arm responses in the model in full implicitly assumes that they are entirely due to a placebo effect. The technical team believes that as neither approach can separate the trial and placebo effects, both should be considered; however, it agrees with the ERG's conclusion that it is important not to underestimate treatment costs. The technical team also concludes that if it is considered appropriate to apply a control arm response rate to BSC, then it may be appropriate to apply the same assumption about the long-term HAQ trajectory on both arms. Again, both the ERG and Company's modelling of PBO responders should be considered. If UPA is compared with further treatment with a csDMARD at position 2, then the technical team believes that is appropriate to consider both: • The company's preferred approach, whereby csDMARDs given following UPA failure should be compared with a BSC treatment response of 0%, as this is consistent with how BSC was modelled in TA375

	• The ERG's concerns that allowing treatment sequence lengths to differ may simply move the placebo effect issue in the UPA arm to occur on a subsequent line, and that this may be exaggerated further by the NMA assuming constant treatment effects regardless of a treatment's position in a sequence.

Issue 2 – Clinical pathway and positioning of upadacitinib

Questions for engagement	Moderate population 4. Would UPA be used before intensified csDMARDs for treating moderate RA in clinical practice (position 1a and 1b)? 5. Would you expect UPA be continued in the moderate RA population if some clinical benefit was achieved, even though the EULAR response criteria had not been met? What clinical benefits would need to be shown? 6. Following the failure of 2 or more csDMARDs (position 2, Table 1, section 1.2), is BSC or csDMARDs used in practice (and therefore, the most relevant comparator)? Severe population 7. Would UPA be considered as a first-line bDMARD for treating severe RA? 8. Is there sufficient evidence to consider the clinical and cost effectiveness of UPA at position 4a (severe RA, failed 1 bDMARD, MTX intolerant, RTX tolerant)? General 9.Would UPA be used as a monotherapy in MTX-tolerant populations, or would it be used only with MTX, in clinical practice? 10. Is MTX monotherapy used as a last-line treatment in MTX-tolerant populations? 11. Are the company's or ERG's treatment sequences the most appropriate (see table 6 section 4 and appendix)?
Background/ description of issue	The company has modelled UPA as a treatment option for a range of clinical pathway positions, which can be seen in Table 2, section 1.2. The treatment pathways modelled by the company and the ERG for both the moderate and severe RA population can be seen in the appendix of this report (and in the ERG report from pages 164-169 and pages 216-222). ERG – moderate RA treatment pathway

	An ERG exploratory analysis, including all confidential treatment prices, suggested that giving UPA before intensification of csDMARDs (position 1) has cost-effectiveness estimates above the range normally considered to be a cost-effective use of NHS resource compared with giving intensified csDMARDs first (position 2). The ERG considers that it would not feasibly be optimal to use UPA prior to the intensification of csDMARDs, largely due to the low cost of csDMARDs, and does not consider UPA at position 1a or 1b for treatment of moderate RA. Further, the ERG states that, in general, UPA+MTX appears to be cost effective relative to UPA monotherapy in situations where both could be used. Therefore, for patients tolerant of MTX, the ERG only considers UPA+MTX (both in the moderate and severe RA populations). The ERG considers that BSC would not be used in routine practice in the moderate population, and they therefore present results for position 2 (see Table 1 and Table 7) with csDMARDs and BSC as comparators. The ERG also believes that MTX monotherapy would be not be used as a last-line treatment option because patients would have failed MTX already by that point in the clinical pathway. The ERG noted that it is important to consider whether UPA, if used as a last-line treatment for moderate RA, would be stopped for a patient who shows some DAS-28 improvement, but does not achieve a EULAR response. The ERG considers that if treatment continues in these circumstances, then the cost effectiveness of UPA for moderate RA patients will be considerably worse that the ERG's ICER estimates. The ERG clinical expert opinion stated that moderate RA patients do not usually have BSC; instead, they tend to have further treatment with the csDMARDs which worked best, possibly as new combinations with steroids also an option. The ERG feels that including this (csDMARD use), rather than last-line BSC, would increase the cost-effectiveness estimates for UPA in moderate RA. Following clinical advice, the ERG made the following changes to its base case sequences for moderate RA patients who progress to severe RA (ERG sequence scenario 1): • ADA as a first-line treatment • RTX (for those tolerant) as a second-line treatment • ABT SC (rather than ABT IV – due to patient preferences) as a third line treatment (for those who received UPA as moderate RA treatment) The ERG also carries out further sequencing scenarios:

	• Scenario 2: UPA used for those with severe disease who did not receive UPA when in moderate RA • Scenario 3: Scenarios 1 and 2 considered together • Scenario 4: Sequences of the ERG base case adding UPA after ADA into the treatment sequence for severe RA in the comparator ERG – severe RA treatment pathway For the modelling of severe RA patients, the ERG broadly follows the treatment sequences proposed by the company but with the following changes: • For patients tolerant of MTX, UPA monotherapy is not considered - only UPA+MTX is modelled. • The use of TCZIV and TCZIV+MTX subsequent to first-line treatment is replaced by SRL and SRL+MTX • A final treatment line of MTX is not considered. • Position 4a is not considered due to the company assuming clinical equivalence between treatments at this line. The ERG states that there is no clinical evidence for this assumption. The bDMARD-IR NMA does not provide estimates for RTX so the ERG applied those of RTX+MTX. The ERG states that this may be optimistic for RTX monotherapy. Clinical expert opinion received by NICE explained that in the moderate RA population, treatment decisions are driven by cost and effectiveness, and current NICE guidance, so intensified csDMARDs are typically given before more advanced treatments in current practice. The expert advised that MTX monotherapy is not typically give as a last-line active treatment option prior to palliative BSC, because patients would have already received MTX during at least 1 prior line of treatment. The clinical expert also stated all treatments are stopped in current practice if they do not provide a EULAR response, and that this would be the case for UPA (the exception being MTX, due to its frequent use as part of a combination treatment). If 2 csDMARDs have failed for a patient, the likelihood of a third csDMARD being effective is also low. The expert also stated that moderate RA patients will consider enrolling in clinical trials at this point; otherwise, palliative BSC is the only option. The clinical expert also stated that UPA monotherapy may be considered over UPA in combination with MTX in MTX tolerant populations, if clinicians wanted to reduce the risk of adverse reactions associated with combination therapy.

	The NICE technical team is concerned that the company's analyses may include some treatment sequences that either do not reflect current NHS practice in England. The technical team notes that in TA466, the committee accepted expert clinical opinion that advanced therapies would not be used before intensive therapy with csDMARDs in the moderate population, and therefore did not consider baricitinib at this position.
Why this issue is important	The positioning of UPA determines the relevant cost-effectiveness estimates and other modelling assumptions. UPA can be used as monotherapy or in combination with MTX, therefore both options should be considered. The modelled treatment sequences should reflect those seen in NHS clinical practice. If they do not, the cost-effectiveness results may not be appropriate for decision-making.
Technical team preliminary judgement and rationale	The technical team considers that the ERG's preferred treatment sequences for both the moderate and severe RA populations are more likely to be appropriate. The technical team welcomes comments on these sequences from consultees and commentators (see appendix). The team considers that the company's position 1a and 1b (use of UPA before intensified csDMARDs) is unlikely to be appropriate based on expert clinical opinion, but would like to see cost-effectiveness analyses for UPA at these positions using the ERG's preferred modelling assumptions. In position 2 (moderate RA, failed 2 or more csDMARDs), the technical team believe that BSC may not be the most relevant comparator, and therefore prefer the ERG's analysis which uses csDMARD as the comparator in this position (see issue 1). The technical team recognises that it is uncertain whether UPA would be continued if no EULAR response occurs in the moderate population. It may be useful to consider cost-effectiveness results with and without continued treatment. The technical team agrees that the evidence presented by the ERG shows that UPA in combination with MTX would be preferred to UPA monotherapy in people for whom MTX is an option in terms of cost-effectiveness. The team would welcome comments on whether UPA monotherapy would be used over UPA in combination with MTX in MTX tolerant populations in clinical practice. The technical team would also like to see cost-effectiveness estimates for UPA at position 4a using the ERG's preferred modelling assumptions.
Summary of comments	**Comments from the company** **Moderate population** <u>Position 1: Failed 1 csDMARD</u> The company believes that upadacitinib could be used before intensified csDMARDs for treating moderate RA in clinical practice, and American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) guidelines suggest that moderate RA patients with poor prognostic factors would benefit from earlier treatment with advanced therapies. The company state that csDMARDs would be used following UPA failure, and that the current ERG modelling in the moderate population only includes csDMARDs as a last line treatment option

	in the comparator arm and not the UPA arm. The inclusion of csDMARDs following intervention failure in the moderate population is consistent with TA466, TA480 and TA485. (The company provide updated ICERs including csDMARDs in the UPA arm following UPA failure). The company also believes that the ERG's decision to not include csDMARDs after UPA failure in the UPA arm may be due to a desire to model the same number of treatments in both arms. The company believes this does not reflect clinical practice with UPA and states that this diverges from previous RA appraisals. (The company provide additional clinical trial data for the full and moderate subgroup.) The company believes that UPA is cost-effective after failure of 1 csDMARD, and notes that the treatment modelled after UPA failure leads to substantially different cost-effectiveness estimates in this population. Position 2: Failed ≥2 csDMARDs Regarding position 2 (after two or more csDMARD failures), the company notes: • This position relates to the situation where patients have tried and failed all existing treatment options in moderate RA. Based on clinical advice, these patients go on a combination of csDMARDs which may have worked best previously. • It is counterintuitive for the ERG to model intensive csDMARDs (and their relatively high efficacy) in this population as clinical expert advice has stated that current treatment is less effective in this population. The company believes that assumptions around what happens after failure of 2 or more csDMARDs – namely whether UPA is compared to a csDMARD or BSC, and the response rate for BSC – substantially affect the estimates of cost effectiveness in this population. The company believes that clinicians should be able to decide whether UPA is suitable after 1 or 2 csDMARD failures. General comments • UPA would be discontinued in the moderate population if response criteria is not met because there is clear guidance on this. • UPA monotherapy should be considered in moderate RA populations who are tolerant to MTX. It is not appropriate to consider UPA as a comparator to UPA+MTX (see ERG sequences 2/3/4 for positions 2a, 2b and 2c), as UPA is the intervention under appraisal.

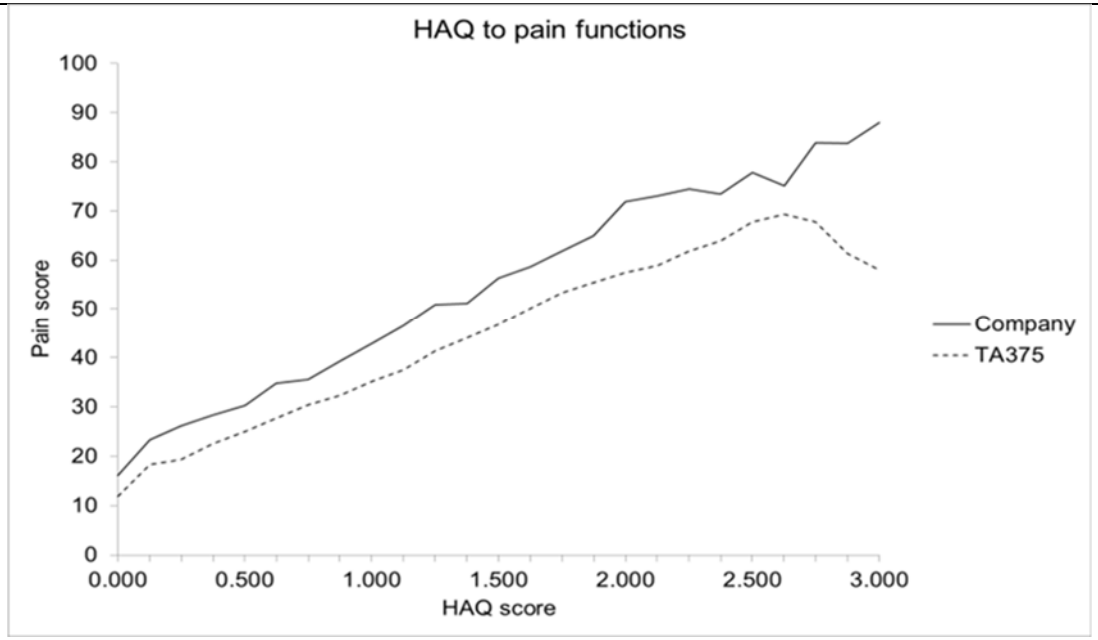
	Severe population The company broadly agrees with the NICE technical team's preferred treatment sequencing in the severe population. The sequences presented by the company and ERG concur for positions 3a, 5 and 6 (apart from MTX as a last-line therapy, discussed below). For positions 3b and 4b, the company agrees with the decision to substitute SRL for TCZ. Regarding position 4a (severe RA, failed 1 bDMARD, MTX intolerant, RTX tolerant), the company states that no advanced therapy to date has clinical data in this specific population, but advanced therapies have previously been recommended in this group. Upadacitinib achieved its primary endpoints in all populations including MTX-intolerant populations, and the efficacy in the MTX-intolerant population was comparable to MTX-tolerant populations. The company states that UPA monotherapy results are comparable to those where UPA was given in combination with MTX, and that modelling MTX as a last line treatment is consistent with TA375. However, it acknowledges that excluding last-line MTX treatment has minimal impact on cost-effectiveness estimates, and therefore accepts the ERG's preference of excluding last line MTX on pragmatic grounds. UPA monotherapy should be considered in severe RA populations who are tolerant to MTX (positions 3b, 4b, 5 and 6). It is not appropriate to consider UPA as a comparator to UPA+MTX, as UPA is the intervention under appraisal. **Commentator comments** One commentator states that there is evidence that some moderate patients would benefit with earlier treatment (after failure of 1 csDMARD). They also stated that MTX would generally not be prescribed last line as it is likely that MTX has been prescribed earlier in the pathway. **ERG comment** To approximate the patients being re-challenged with csDMARDs, the ERG presents a scenario analysis (SA07) that appends MTX to the end of the moderate RA treatment sequences. This is consistent with the treatment sequences in the original company modelling and in TA375, but is subject to the caveats noted in section 5.3.4.12 of the original ERG report, which states that applying the MTX response rates among patients who have previously

	failed on MTX is unlikely to be reliable. The issues highlighted in relation to issue 1 (response rate for BSC) also supports comparing only sequences of the same length.
Technical team judgement after engagement	**Moderate population** It is likely that UPA would be discontinued if the appropriate EULAR response was not achieved in the moderate population. It is also likely that the use of UPA before intensified csDMARDs is unlikely to be cost-effective when compared to UPA use after intensified csDMARDs. The relevant comparator at position 2 is important, this is covered in the technical team's judgement after engagement section in issue 1. The technical team believes it is potentially misleading to apply the effect of placebo in one model arm, but not the other. Therefore, analyses comparing treatment sequences of different lengths should not simply move this potentially misleading approach to modelling the placebo effect to a later line of treatment. The technical team are aware however that past RA appraisals have modelled different treatment lengths, therefore both the company's and ERG's approaches should be considered. **Severe population** The technical team prefers the ERG's treatment sequences for severe RA and noted that the company also accepts this. **UPA + MTX compared with UPA monotherapy** In people for whom MTX is a treatment option, the technical team believes that UPA+MTX is likely to be cost effective compared with UPA as a monotherapy. However, the technical team notes that previous RA appraisal recommendations based on evidence for a technology used combination with MTX have been extended to apply to people for whom MTX is not a treatment option. The technical team notes that this may be appropriate to consider for decision making.

Issue 3 – Model inputs and assumptions

Questions for engagement	**Issue 3a – Modelling the transition from moderate to severe RA** 12. Would you expect the relationship between HAQ and DAS-28 to change over time? 13. Should the intercept term from the company's repeated measures linear mixed effects model be used in the modelling? **Issue 3b – Mapping from HAQ to pain scores** 14. Is the HAQ to pain mapping from TA375 more reliable than the company estimates from the SELECT trials? **Issue 3c – Common treatment effect at different points in the treatment pathway** 15. Would a treatment be expected to provide the same level of EULAR response rate regardless of the line of treatment?
Background/ description of issue	The company model uses a similar structure and inputs to the model developed for TA375. Like previous models, the effect of a treatment (e.g. from the company's NMA) is assumed to be constant, regardless of where that treatment features in the clinical pathway. There are 2 notable differences between this model and the TA375 model: • The company's model permits progression from moderate RA to severe RA • The company uses an alternative mapping function to go from HAQ score to pain score, estimated using data from the SELECT trials. Note: The resulting pain scores are then used to estimate EQ-5D utility values using the same quality of life function as TA375 (see issue 3b). **Issue 3a – Modelling the transition from moderate to severe RA** **The company**'s model includes patients moving from moderate RA to severe RA. To do so, it was necessary to estimate a relationship between the HAQ and the DAS-28. This was because long-term DAS-28 data was not available for patients in the clinical trial, and without this data it is not possible to state whether a patient is in the moderate or severe category over the lifetime of the model. The company estimated this relationship using 3- and

	6-month from the SELECT trials. The company ran a 'repeated measures linear mixed effects' model on the data to estimate the change in DAS-28 from baseline as a function of the change in HAQ from baseline. The relationship between HAQ and DAS-28 is assumed to hold over the full 45-year time horizon of the company's model. **The ERG** has concerns about how the company estimates the relationship between HAQ and DAS-28 over the full model time horizon, because it is based on much shorter-term (3- to 6-month) trial data. During a 6-month trial, both the HAQ and DAS-28 are generally improving, whereas over 45 years it is plausible to assume that a person's HAQ score would worsen. The ERG also noted that the company's model does not use the intercept term from its HAQ-to-DAS mapping function. In an exploratory analysis, the ERG noted that applying the intercept term appears to result in no patients transitioning from moderate to severe RA (because doing so makes the ICERs for these scenarios identical [ERG report tables 70 and 71, page 198 and 199]). The ERG believes that removing the intercept term causes the model to overestimate patients' DAS-28 scores by 1.16, which means the model simulates progression from moderate RA to severe RA too quickly. The ERG states that the company submission contains no detail of how this aspect of the model works, what the parameter inputs are or how these parameters were estimated. **Issue 3b – Mapping from HAQ to pain scores** The second difference between TA375 and this appraisal is associated with how health-related quality of life (HRQL) is modelled. **The company** derives a mapping function to estimate pain scores from HAQ scores using the SELECT trial data, which are subsequently used to estimate health related quality of life. In TA375, the equivalent mapping was based upon the large National Databank for Rheumatic Diseases dataset. The different relationships between HAQ and pain scores implied by the 2 alternative approaches can be seen in **Error! Reference source not found.** (from ERG report, figure 12 page 197). For all HAQ scores, the company's approach predicts a higher pain score (more pain), and the difference between both approaches is more pronounced towards the highest HAQ scores. Figure 2. Difference in ERG and Company's HAQ to Pain estimates

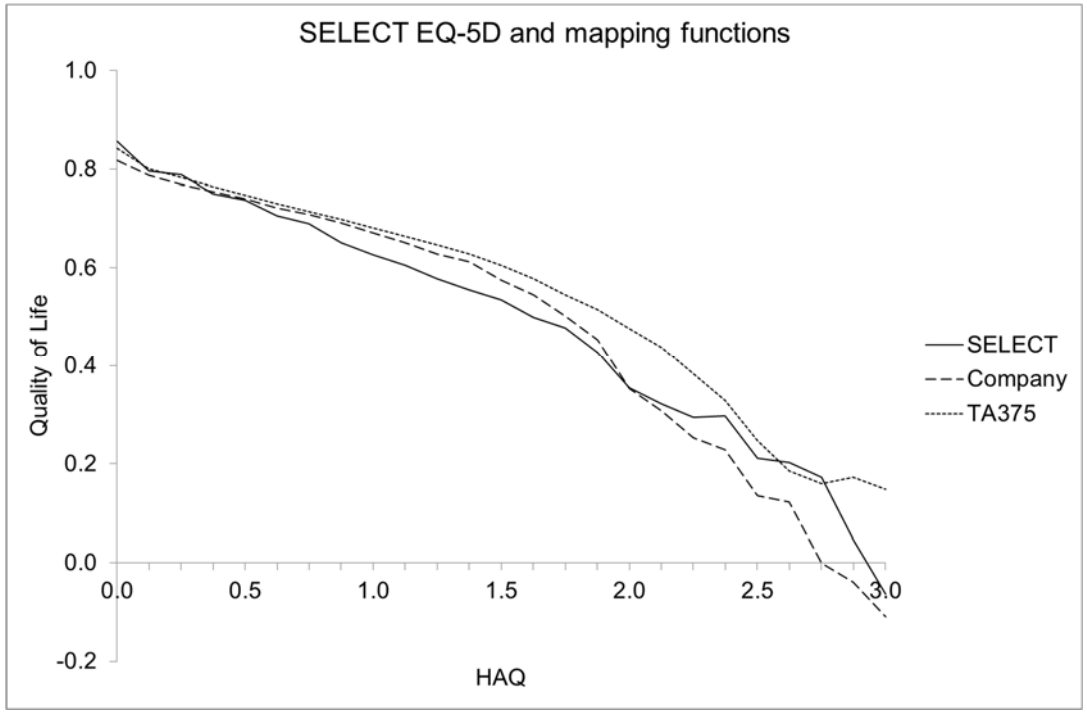


Pain scores estimates from both company and TA375 (ERG preferred) mapping methods

The ERG prefers the HAQ to pain mapping used in TA375 as it is based on a large dataset and is more comparable with the EQ-5D values from the SELECT trials and therefore consider this method in their base case,

but stated that the company's approach may also be valid. The ERG also incorporates a scenario in which the company's mapping method is applied (ERG sensitivity analysis 4 – table 6, section 4).

Figure 3. Company's mapped utility values compared with SELECT trial EQ-5D data and TA375 values



EQ-5D utility values from the SELECT trials and estimated EQ-5D values from both the company and TA375 (ERG preferred) mapping methods

The ERG also corrected some comparator drug and administration costs (see ERG report pages 192 to 194). The ERG also corrected the calculation of inpatient costs to mirror TA375 more closely.

	Issue 3c – Common treatment effect at different points in the treatment pathway In the company's model, EULAR response rates for a treatment do not decline when it is used at a later line of treatment. The ERG states that if the treatment sequences that are being compared are not of equal length, this assumption is likely to bias the analysis in favour of the longer treatment sequence. This may be particularly important when assessing UPA later in the treatment pathway; for example, in the assessment of UPA among people who have failed to respond to RTX therapy. **Clinical expert advice received by NICE** from 1 clinical expert stated that the HAQ score does generally worsen over time. This worsening is in part due to patients getting older; even if you did not have RA, your HAQ score will decrease due to age-related comorbidity. Therefore, other (non-RA) factors begin to play an increasingly important role in a person's HAQ score over time. They explained that this slow HAQ decrease is imperceptible over the typically short duration of a clinical trial, meaning the relationship between HAQ and disease activity observed in trials might not hold in the long term (issue 3a). Regarding the magnitude of benefit a treatment provides at different lines in the treatment pathway, the clinical expert advised that bDMARDs are expected to give a lower response rate with each passing line of therapy (approximately 5% less each time). The clinical expert would expect to see a similar decrease in response rate at each line of therapy for csDMARDs but noted there is less evidence for these treatments (issue 3c). **The NICE technical team** is concerned that the company's model may overestimate the rate at which patients move from moderate to severe RA, by excluding the intercept term. The technical team is also concerned that extrapolating the relationship between HAQ and DAS-28 from short-term trial data is uncertain, as the increasing importance of other factors is likely to weaken his relationship over time. The technical team notes that in TA485, a linear relationship between the HAQ and DAS-28 was not accepted by the appraisal committee (issue 3a). The technical team is aware that in the most recent NICE technology appraisal in RA (TA485), the committee accepted the mapping from HAQ to pain score approach used in TA375 and that preferred by the ERG for this appraisal. The technical team is concerned that the company's HAQ-to-pain model might overestimate pain scores compared with the equivalent mapping used in TA375 (issue 3b).

Why this issue is important	The modelling assumptions presented here could affect cost-effectiveness estimates. In particular, the modelling of moderate RA patients progressing to have severe RA is a key determinant of the estimated cost effectiveness of UPA among moderate RA patients. To do this the company has estimated a relationship between HAQ and DAS-28. Assuming treatments give the same magnitude of benefit regardless of where they feature in a treatment pathway improves the cost effectiveness of longer treatment sequences and may be inconsistent with clinical expert advice. Furthermore, it may be inconsistent with the view that a PBO effect observed in trials should not apply for last-line BSC (see Issue 1).
Technical team preliminary judgement and rationale	The technical team agrees that allowing patients to progress from moderate to severe RA is appropriate (as concluded by the committee for TA485), but is concerned by how this has been implemented in the company's model. The technical team believes that patients in the company's model may progress from moderate to severe disease faster than is observed in clinical practice, because the company did not apply the intercept term from its model of the relationship between the HAQ and DAS-28 over time. The technical team requests further clarity from the company on how the model incorporates the transition from moderate to severe RA, and would like to see further sensitivity analysis surrounding the HAQ to DAS-28 estimation; for example, it may be inappropriate to assume that this relationship holds in the long term (issue 3a). In addition, the technical team would like the company to investigate non-linear models to estimate the relationship between HAQ and DAS-28, as the relationship between these two measures may not be linear. The technical team believes that the ERG's preferred HAQ-to-pain mapping method, used to estimate HRQL, which is also the method used in TA375, is the most appropriate for use. This is because it is based on a large dataset and that it has been accepted for use in several past NICE appraisals (issue 3b). The assumption of constant EULAR response across lines of treatment appear to favour UPA, and certainly favours treatment sequences with more active treatments (issue 3c). The technical team believes that a fixed treatment effect (obtained from trial data) regardless of position in the pathway is inappropriate, if at the same time, a trial-based PBO effect for last-line BSC is not applied (see issue 1). The technical team believes that the ERG's cost corrections are appropriate.

Summary of comments	**Company comments** **Issue 3a** The company believes that its modelling of the HAQ-DAS relationship is appropriate and in line with that accepted by committee in TA485. The company state that the intercept term from the repeated measures linear mixed effects model should not be applied as this represents non-HAQ related changes in DAS. The company adds that without use of the intercept term in the model, 7% of patients transition from moderate to severe at 2 years, whereas data from the UK ERAN dataset suggests this figure is 19%. Therefore, the company state that the model may actually underestimate this transition and to include the intercept term would further underestimate this transition. **Issue 3b** The company prefers its estimates from the SELECT trials to map HAQ onto pain scores than the estimates used in TA375. They state mapping based on trial data was also accepted in TA480, and note that: • Both ERG and company approaches demonstrated similar performance/fit compared with SELECT trials' EQ-5D values, but trial-based mapping showed a slightly better fit. • Root mean squared error was smaller for trial-based mapping (trial-based map RMSE: 0.172, TA375 map RMSE: 0.180). For a subset of data excluding extreme HAQ values (HAQ > 2.5) (trial-based map RMSE: 0.170, TA375 map RMSE: 0.179). • Visually, the trial-based mapping provides a better fit than the TA375 values. Utility values estimated using the TA375 mapping algorithm were consistently higher than the utility observed in the SELECT trials and did not follow the rapid decrease in utility at the tail end of the HAQ spectrum. Utility estimated with the trial-based map was generally closer to SELECT trial values and showed a similar trend throughout the HAQ score spectrum. **Issue 3c** The company accept that EULAR response will vary depending on the line of treatment and therefore it would be better to model efficacy based on the line of therapy. **ERG comments**

	Issue 3a The company in its technical engagement response does not state what it means by "untreated moderate patients". The 7% severe RA patients at year 2 is the result of assuming patients remain untreated. It is notable that the company's base-case model treatment sequence, which is meant to reflect current practice, results in only 1% of patients transitioning to severe RA after 2 years. If the company's HAQ to DAS28 intercept term is applied this results in no moderate RA patients being modelled as worsening to severe RA. Based upon the Kiely et al paper the company is correct to note that its model under predicts the proportion of patients who will progress to severe disease after 2 years. **Issue 3b** It would be surprising if the SELECT trial bespoke mapping function from HAQ to pain did not result in a better fit to the SELECT trials' QoL data than another mapping function from HAQ to pain estimated from a different source. But this does not imply that the SELECT trial bespoke mapping function from HAQ to pain is superior in general. It cannot be definitively determined whether the company's mapping based upon SELECT trial data or the TA375 Assessment Group's mapping based upon National Databank for Rheumatic Diseases data is superior in general. But the very large number of observations contributing to the TA375 mapping is a strong argument in its favour. **Issue 3c** A long treatment sequence which applies the clinical effectiveness estimates of the NMAs at different lines may be optimistic, and may introduce bias, which is likely to be considerably higher if treatment sequences of different lengths are modelled. While it is not uncommon for economic modelling of a new treatment to simply insert the new treatment at the start of the current practice treatment sequence and then compare this with the current practice treatment sequence, the ERG thinks that this is likely to be biased and possibly significantly biased.
Technical team judgement after engagement	The technical team is satisfied that the model appears not to overestimate the transition from moderate to severe RA (Issue 3a) but notes that it may instead underestimate this transition. The technical team still prefers the mapping approach used in TA375, as it was developed using a much larger dataset. However, the company's

	approach may also be appropriate to consider as an alternative analysis, as it was derived from the UPA trial data (issue 3b). The technical team understands the ERG's concerns about the constant effectiveness assumptions at different lines of treatment and considers this to be an unresolvable issue due to the lack of evidence to inform a decline in effectiveness by line of treatment. This issue should be considered to add uncertainty to the cost-effectiveness results, potentially favouring UPA, particularly if the it is modelled as part of a longer treatment sequence that the comparator.

Issue 4 – Clinical effectiveness data

Questions for engagement	16. Is the company or ERG's approach the most appropriate regarding the application of the results of the two NMAs at different points in the treatment pathway? 17. Are the clinical effectiveness estimates applicable to the population who have failed RTX?
Background/ description of issue	**The company** did 2 NMAs as part of its evidence submission, because the UPA clinical trials did not include all of the relevant comparators for this appraisal. The 2 NMAS were: csDMARD-IR, for patients who were csDMARD experienced; and bDMARD-IR, for patients who were bDMARD experienced. **The ERG** stated that the company did not provide a feasibility assessment for the NMAs, which it considers to potentially reduce the credibility of the NMAs. The ERG considered that interpretation of NMA findings was complicated by the need for strong conceptual assumptions relating to the generalisability of effects at different points in the treatment pathway and different disease severities. Moderate and severe RA were not considered separately, and treatment effects are assumed to be equivalent, for example, after 1 bDMARD and after 2 or more bDMARDs. This means that data used to inform comparisons where no head-to-head data exist, borrowing information from the wider network, will include people who might not ever plausibly receive those treatments. The ERG also states that the company applied the incorrect NMA results at various pathway points and made changes in its base case. These errors are highlighted in the ERG report: • Applying csDMARD-IR results for moderate patients at treatment lines beyond 1st line in the UPA treatment arm – the ERG state that csDMARD-IR NMA results should be used in the comparator arm with results from the bDMARD-IR NMA applied to the UPA arm. • Applying results of the bDMARD-IR NMA to the comparator arm for patients who move from moderate to severe RA – the ERG state that this should be taken from the csDMARD-IR NMA results.

	The ERG explained that the company's approach biases the clinical effectiveness in favour of UPA as the results from the csDMARDs are generally better than those of the bDMARD-IR NMA. The ERG also highlight that the cost-effectiveness results may not be as robust for severe patients who have failed RTX, because only 14% of the patients in the SELECT-BEYOND trial being RTX experienced. **Clinical expert opinion received by NICE,** from 1 clinical expert, advised that bDMARDs are expected to give a lower response rate with each passing line of therapy (approximately 5% less each time). The clinical expert would expect to see a similar decrease in response rate at each line of therapy for csDMARDs, but noted there is less evidence for these treatments. The clinical expert explained that failure of a csDMARD does not provide any information about how well a person will respond to subsequent treatment with bDMARDs (or vice versa), as their mechanisms of action are different. Regarding the generalisability of trials used in the NMAs, the clinical expert advised that the key UPA trials are broadly generalisable to NHS clinical practice in England, except the SELECT-SUNRISE trial which might not be generalisable because outcomes in a Japanese population may be very different to the population in England. The expert also stated that they would not consider patients who fail RTX to be clinically distinct from other RA patients in terms of their subsequent outcomes. **The NICE technical team** notes that the exclusion of the SELECT-SUNRISE trial (ERG scenario analysis) did not affect cost-effectiveness estimates by a significant amount.
Why this issue is important	As most of the model inputs for the comparator treatments are based on the company's NMAs, it is important that the results from the NMAs are robust and produce valid estimates. It is also important to understand the extent to which clinical trial evidence for UPA is generalisable to the NHS in England.
Technical team preliminary judgement and rationale	The technical team believes that the company's NMAs broadly appear to include relevant studies for comparison, and that the SELECT trials are relevant to NHS decision-making. The technical team considers that is likely that the treatment effect slightly diminishes as the number of prior treatment failures increases, meaning that the NMA assumption of common effects at different positions in the treatment pathway may not hold. This adds some uncertainty to the cost-effectiveness results, particularly when treatment sequences differ in length. The technical team agrees with the ERG's approach in terms of the most appropriate NMA results to apply at different points in the pathway. The technical team considers that the low proportion of RTX experienced patients in the SELECT-BEYOND trial adds uncertainty to the cost-effectiveness results at position 6; however, the team notes that clinical

	expert advice stated that these patients are unlikely to differ significantly from other RA patients in terms of outcomes.
Summary of comments	**Company comments** The company agrees that the ERG's approach is more appropriate - the results of the csDMARD-IR NMA should be applied to the biologic naïve patients and the results of the bDMARD-IR NMA should be applied for the biologic experienced patients. The company also states that it is appropriate to apply the results of UPA from its base case bDMARD-IR NMA to the corresponding results for tocilizumab and sarilumab, as an estimate of its relative effectiveness compared to the only drugs presently recommended for use in the failed RTX population. In considering whether UPA is cost effective compared with these 2 treatment options, it will be important for NICE to consider the relative drug acquisition costs for the treatments (including their confidential PAS discounts). **ERG comments** The ERG views on this issue remain unchanged.
Technical team judgement after engagement	The technical team considers the ERG's application of the results of the NMAs to be more appropriate than the company's initial approach and note the company has now accepted this position.

New Issue: Issue 5 – Model validation

Background/ description of issue	The **company's** model is based on the model developed by the assessment group in TA375, with the addition of allowing patients to transition from moderate to severe RA once their DAS score reaches at least 5.1. The **ERG** has highlighted concerns that the model has a "black box" element to it, which did not allow the ERG to fully critique and examine the programming accuracy of the model. The ERG carried out model a validation analysis which compared the company's model with that of TA375. This compared the cost and QALY outcomes

	from the 2 models. The ERG acknowledged that its initial model validation addendum analysis used incorrect costs, and that the estimated costs between the two models are comparable. In its response to technical engagement the ERG highlighted that the company's model appears to favour bDMARD treatments when compared to csDMARDs. This is due to the company's model producing higher estimated QALY gains for bDMARDs than those produced in the TA375 model. While the absolute difference in incremental QALYs is small, the relative difference is large, which can have a considerable impact on ICERs.
Why this issue is important	The economic model is central to decision-making. It is therefore important that the model produces appropriate outcomes. The company has based its model largely on TA375. As the ERG has highlighted that the company's model produces higher QALY gains for bDMARDs relative to csDMARDs than expected, this may have implications for decision-making in the moderate RA populations.
Technical team judgement after engagement	The technical team is concerned that the company's model appears to overestimate bDMARD effectiveness. This may bias the cost-effectiveness results in favour of bDMARDs relative to csDMARDs, which has particular implications for the comparison of UPA with csDMARDs in the moderate RA population. The validity of the model should be considered in decision-making, as the model validation analysis has highlighted the uncertainty regarding how closely the company's model performs compared to that of TA375.

4. Issues for information

Table 6 to Table 12 are provided to stakeholders for information only and are not included in the technical report comments table provided.

Table 6. Summary of ERG analyses for moderate and severe RA

Moderate RA population	
ERG analysis	**Description and rationale**

Base case sequences	Same as company's sequences with ERG corrections to costs and model inputs applied (see issue 2)
Alternative sequence 1	Based on ERG expert opinion: • Most progressing from moderate RA to severe RA treated with ADA. • Those tolerant of RTX will tend to receive it next, even if they are intolerant of MTX. Third-line treatment may be an interleukin. But since JAKs and interleukins act through similar pathways, those who received UPA when in moderate RA might tend instead to receive a treatment with a different method of action such as ABT. It will be assumed to be ABT-SC rather than ABT-IV.
Alternative sequence 2	Patients prefer oral over subcutaneous administration, therefore UPA might be used for those with severe disease who did not receive UPA when in moderate RA.
Alternative sequence 3	Scenario 1 and 2 combined.
Alternative sequence 4	Sequences of the ERG base case with the additional insertion of UPA after ADA into the treatment sequence for severe RA in the comparator arm.
Severe RA population	
ERG analysis	ERG broadly follows the company's treatment sequences, with the following changes: • For patients tolerant of MTX, UPA monotherapy is not considered and only UPA+MTX is modelled.

	• The use of TCZ-IV and TCZ-IV+MTX subsequent to first-line treatment is replaced by SRL and SRL+MTX • A final treatment line of MTX is not considered. Position 4a is not considered due to a lack of clinical evidence comparing first-line treatments (the company assumes clinical equivalence).

Note: In situations where UPA and UPA+MTX are treatment options (i.e. in MTX tolerant populations), the ERG considers UPA+MTX only (see issue 2)

Table 7. Technical team preferred assumptions and impact on cost-effectiveness estimates – moderate RA position 1

Position 1: moderate RA, failed 1 csDMARD				
Description	**Comparator**	**Analysis**	**ICER****	**ICER with weighted average ADA price and other biosimilars' lowest prices*****
1a (MTX: no, RTX: yes)	csDMARD	Company base case	UPA: £16,554	ICER ≤ £30,000
		ERG base case*	N/A (see issue 2)	N/A (see issue 2)
1b (MTX: yes, RTX: yes)	csDMARD	Company base case	UPA: £22,659 UPA+MTX: £21,631	ICER ≤ £30,000
		ERG base case*	N/A (see issue 2)	N/A (see issue 2)
* Technical team agrees that intensified csDMARDs are likely to be used before advanced treatments, including UPA, in the moderate RA population (see issue 2). **Note: ICERs presented in this column include the simple patient access scheme for UPA but do not include confidential commercial arrangements for comparator treatments ***ICER information in this column includes all commercial arrangements, including weighted average ADA price and other biosimilars' lowest prices (see ERG biosimilar addendum)				

Table 8. Technical team preferred assumptions and impact on cost-effectiveness estimates – moderate RA position 2

Position 2: moderate RA, failed ≥ 2 csDMARDs				
Description	**Comparator**	**Analysis**	**ICER****	**ICER with weighted average ADA price and other biosimilars' lowest prices *** **
2a (MTX: no, RTX: yes)	BSC	Company base case	UPA: £8,885	ICER ≤ £30,000
		ERG base case*	UPA: £38,432	ICER > £30,000

Position 2: moderate RA, failed ≥ 2 csDMARDs				
		ERG SA1: head-to-head trial data*	UPA: £87,847	ICER > £30,000
		ERG SA2: no BSC response	UPA: £17,506	ICER ≤ £30,000
		ERG SA3: company HAQ-pain mapping	UPA: £32,545	ICER > £30,000
		ERG SA4: HAQ-DAS intercept term	UPA: £41,400	ICER > £30,000
		ERG SA5: Net effects UPA*	UPA: £23,833	ICER ≤ £30,000
		ERG SA6: Comparator worsening HAQ*	UPA: £31,220	ICER > £30,000
		ERG SA7: 2nd line MTX	UPA; £46,101	ICER > £30,000
		ERG SA8: Humira cPAS, other biosimilar lowest cPAS*	ICER > £30,000	-
		ERG SA9: Humira cPAS, other biosimilar highest cPAS*	ICER > £30,000	-
		ERG alternative sequence 1	UPA: £41,991	ICER > £30,000
		ERG alternative sequence 2	UPA: £47,907	ICER > £30,000
		ERG alternative sequence 3*	UPA: £51,466	ICER > £30,000
		ERG alternative sequence 4	UPA: £46,354	ICER > £30,000
	csDMARD	ERG base case*	UPA: £52,990	ICER > £30,000
		ERG SA1: head-to-head trial data	N/A	N/A
		ERG SA2: no BSC response	N/A	N/A
		ERG SA3: company HAQ-pain mapping	UPA: £47,006	ICER > £30,000
		ERG SA4: HAQ-DAS intercept term	UPA: £56,626	ICER > £30,000
		ERG SA5: Net effects UPA*	UPA: £27,627	ICER > £30,000
		ERG SA6: Comparator worsening HAQ*	-	-

Position 2: moderate RA, failed ≥ 2 csDMARDs				
		ERG SA7: 2nd line MTX	UPA: £56,205	ICER > £30,000
		ERG SA8: Humira cPAS, other biosimilar lowest cPAS*	ICER > £30,000	-
		ERG SA9: Humira cPAS, other biosimilar highest cPAS*	ICER > £30,000	-
		ERG alternative sequence 1	UPA: £57,335	ICER > £30,000
		ERG alternative sequence 2	UPA: £63,220	ICER > £30,000
		ERG alternative sequence 3*	UPA: £67,565	ICER > £30,000
		ERG alternative sequence 4	UPA: £66,328	ICER > £30,000
2b (MTX: yes, RTX: yes)	BSC	Company base case	UPA: £13,568 UPA+MTX: £13,434	ICER ≤ £30,000
		Company scenario 1: PBO trajectory same as csDMARDs	UPA+MTX: £49,555	See ERG SA6
		Company scenario 2: PBO (natural recovery) applied after UPA failure	UPA+MTX: £21,295	-
		Company scenario 3: netting UPA effect scenario	UPA+MTX: £18,537	See ERG SA5
		ERG base case*	UPA: N/A (see issue 2) UPA+MTX: £35,958	ICER > £30,000
		ERG SA1: head-to-head trial data*	UPA+MTX: £44,163 to £94,563	ICER > £30,000
		ERG SA2: no BSC response	UPA+MTX: £16,729	ICER ≤ £30,000
		ERG SA3: company HAQ-pain mapping	UPA+MTX: £30,512	ICER > £30,000
		ERG SA4: HAQ-DAS intercept term	UPA+MTX: £38,757	ICER > £30,000
		ERG SA5: Net effects UPA*	UPA+MTX: £17,249	ICER ≤ £30,000

Position 2: moderate RA, failed ≥ 2 csDMARDs				
		ERG SA6: Comparator worsening HAQ*	UPA+MTX: £29,190	ICER > £30,000
		ERG SA7: 2nd line MTX	UPA+MTX: £47,567	ICER > £30,000
		ERG SA8: Humira cPAS, other biosimilar lowest cPAS*	ICER > £30,000	-
		ERG SA9: Humira cPAS, other biosimilar highest cPAS*	ICER > £30,000	-
		ERG alternative sequence 1	UPA+MTX: £39,308	ICER > £30,000
		ERG alternative sequence 2	UPA+MTX: £44,619	ICER > £30,000
		ERG alternative sequence 3*	UPA+MTX: £47,892	ICER > £30,000
		ERG alternative sequence 4	UPA+MTX: £43,507	ICER > £30,000
	csDMARD	Company scenario 4: csDMARDs after UPA failure then BSC v csDMARDs then BSC scenario	UPA+MTX: £21,128 - £24,039	-
		ERG exploratory base case*	UPA+MTX: £47,466	ICER > £30,000
		ERG SA1: head-to-head trial data	N/A	N/A
		ERG SA2: no BSC response	N/A	N/A
		ERG SA3: company HAQ-pain mapping	UPA+MTX: £42,014	ICER > £30,000
		ERG SA4: HAQ-DAS intercept term	UPA+MTX: £50,874	ICER > £30,000
		ERG SA5: Net effects UPA*	UPA+MTX: £21,393	ICER > £30,000
		ERG SA6: Comparator worsening HAQ*	-	-
		ERG SA7: 2nd line MTX	UPA+MTX: £56,133	ICER > £30,000
		ERG SA8: Humira cPAS, other biosimilar lowest cPAS*	ICER > £30,000	-

Position 2: moderate RA, failed ≥ 2 csDMARDs				
		ERG SA9: Humira cPAS, other biosimilar highest cPAS*	ICER > £30,000	-
		ERG alternative sequence 1	UPA+MTX: £51,130	ICER > £30,000
		ERG alternative sequence 2	UPA+MTX: £56,678	ICER > £30,000
		ERG alternative sequence 3*	UPA+MTX: £60,272	ICER > £30,000
		ERG alternative sequence 4	UPA+MTX: £57,703	ICER > £30,000
2c (MTX: no, RTX: no)	BSC	ERG exploratory base case*	UPA: £37,911	ICER > £30,000
		ERG SA1: head-to-head trial data*	UPA: £76,405	ICER > £30,000
		ERG SA2: no BSC response	UPA: £17,114	ICER ≤ £30,000
		ERG SA3: company HAQ-pain mapping	UPA: £31,887	ICER > £30,000
		ERG SA4: HAQ-DAS intercept term	UPA: £41,400	ICER > £30,000
		ERG SA5: Net effects UPA*	UPA: £18,418	ICER ≤ £30,000
		ERG SA6: Comparator worsening HAQ*	UPA: £29,846	ICER > £30,000
		ERG SA7: 2nd line MTX	UPA: £49,158	ICER > £30,000
		ERG SA8: Humira cPAS, other biosimilar lowest cPAS*	ICER > £30,000	-
		ERG SA9: Humira cPAS, other biosimilar highest cPAS*	ICER > £30,000	-
		ERG alternative sequence 1	UPA: £43,378	ICER > £30,000
		ERG alternative sequence 2	UPA: £50,812	ICER > £30,000
		ERG alternative sequence 3*	UPA: £56,199	ICER > £30,000
		ERG alternative sequence 4	UPA: £50,050	ICER > £30,000
	csDMARD	ERG exploratory base case*	UPA: £52,359	ICER > £30,000
		ERG SA1: head-to-head trial data	N/A	N/A

Position 2: moderate RA, failed ≥ 2 csDMARDs				
		ERG SA2: no BSC response	N/A	N/A
		ERG SA3: company HAQ-pain mapping	UPA: £45,755	ICER > £30,000
		ERG SA4: HAQ-DAS intercept term	UPA: £56,626	ICER > £30,000
		ERG SA5: Net effects UPA*	UPA: £18,289	ICER ≤ £30,000
		ERG SA6: Comparator worsening HAQ	-	-
		ERG SA7: 2nd line MTX	UPA: £60,586	ICER > £30,000
		ERG SA8: Humira cPAS, other biosimilar lowest cPAS*	ICER > £30,000	-
		ERG SA9: Humira cPAS, other biosimilar highest cPAS*	ICER > £30,000	-
		ERG alternative sequence 1	UPA: £59,025	ICER > £30,000
		ERG alternative sequence 2	UPA: £66,968	ICER > £30,000
		ERG alternative sequence 3*	UPA: £73,633	ICER > £30,000
		ERG alternative sequence 4	UPA: £70,860	ICER > £30,000

*The technical team believes that the ERG base case, SA1 SA5, SA6, alternative sequence 3, and the alternative biosimilar pricing scenarios should be considered for decision making. If treatment lengths should be allowed to differ, then company scenario analysis 4 should be considered for decision making.

**Note: ICERs presented in this column include the simple patient access scheme for UPA but do not include confidential commercial arrangements for comparator treatments

***ICER information in this column includes all commercial arrangements, including an estimated weighted average price for ADA and the lowest nationally available prices for other biosimilars (see ERG biosimilar addendum):

- ERG SA8 analysis includes the Humira price for ADA and the lowest biosimilar price for the other biosimilar treatments
- ERG SA9 analysis includes the Humira price for ADA and the highest biosimilar price for the other biosimilar treatments

Table 9. Technical team preferred assumptions and impact on the cost-effectiveness estimate – severe RA position 3

Position 3: severe RA, failed ≥ 2 csDMARDs				
Description	**Comparator**	**Analysis**	**ICER*** **[range of head-to-head ICERs]**	**ICER with weighted average ADA price and other biosimilars' lowest prices** [range of head-to-head ICERs]**
3a (MTX: no, RTX: yes)	Advanced treatment	Company base case	UPA: £502k, **S/W ICER** (INMB: £38,294) [dominant to £502k **S/W** ICER]	ICER > £30,000 [dominant to ICER>£30,000]
		ERG base case	UPA: £651k, **S/W ICER** (INMB: £38,695) [dominant to £651 **S/W** ICER]	ICER > £30,000 [dominant to ICER>£30,000]
		ERG SA8	ICER ≤ £30,000 [dominant to ICER ≤ £30,000]	-
		ERG SA9	ICER ≤ £30,000 [dominant to ICER ≤ £30,000]	-
3b (MTX: yes, RTX: yes)	Advanced treatment	Company base case	UPA: Not cost effective vs. UPA+MTX UPA+MTX: £828k, **S/W ICER** (INMB: £23,846) [dominant to £828k **S/W** ICER]	ICER > £30,000 [dominant to ICER>£30,000]
		ERG base case	UPA: N/A (see issue 2) UPA+MTX: £142mn, **S/W ICER** (INMB: £24,589) [dominant to £142mn **S/W** ICER]	ICER > £30,000 [dominant to ICER>£30,000]
		ERG SA8	ICER > £30,000 [dominant to ICER>£30,000]	-
		ERG SA9	ICER > £30,000 [dominant to ICER>£30,000]	-

Position 3: severe RA, failed ≥ 2 csDMARDs	
Note: **S/W ICER** denotes that a comparator produces more QALYs than UPA at a higher cost than UPA. The S/W ICER shows the incremental cost per QALY gained for the comparator compared with UPA. Incremental net monetary benefit (INMB) is shown for these comparisons, where INMB = £20,000 x incremental QALYs – incremental costs. INMB > £0 indicates that UPA is cost effective. Note: Technical team prefers the modelling assumptions of the ERG in the severe RA population and note that the company, in their response to technical engagement, also agree with the ERG modelling. *ICERs presented in this column include the simple patient access scheme for UPA but do not include confidential commercial arrangements for comparator treatments – fully incremental **ICER information in this column includes all commercial arrangements, including an estimated weighted average price for ADA and the lowest nationally available prices for other biosimilars (see ERG biosimilar addendum): • ERG SA8 analysis includes the Humira price for ADA and the lowest biosimilar price for the other biosimilar treatments • ERG SA9 analysis includes the Humira price for ADA and the highest biosimilar price for the other biosimilar treatments	

Table 10. Technical team preferred assumptions and impact on the cost-effectiveness estimate – severe RA positions 4-6

Positions 4, 5 & 6: severe RA, failed 1 bDMARD				
Description	**Comparator**	**Analysis**	**ICER*** **[range of head-to-head ICERs]**	**ICER with weighted average ADA price and other biosimilars' lowest prices**** **[range of head-to-head ICERs]**
4a (MTX: no, RTX: yes)	Advanced treatment	Company base case	UPA: Dominant	ICER > £30,000 [dominant to ICER>£30,000]
		ERG base case	N/A (see issue 2)	N/A
4b (MTX: yes, RTX: no)	Advanced treatment	Company base case	UPA: Dominated	ICER > £30,000 [dominant to ICER>£30,000]

Positions 4, 5 & 6: severe RA, failed 1 bDMARD				
			UPA+MTX: £2mn, **S/W ICER** (INMB: £32,358) [dominant to £2mn **S/W** ICER]	
		ERG base case	UPA: N/A (see issue 2) UPA+MTX: £680k, **S/W ICER** (INMB: £37,250) [dominant to 680k **S/W** ICER]	ICER > £30,000 [dominant to ICER>£30,000]
		ERG SA8	ICER > £30,000 [dominant to ICER>£30,000]	-
		ERG SA9	ICER > £30,000 [dominant to ICER>£30,000]	-
5 (MTX: yes, RTX: yes)	RTX	Company base case	UPA: Dominated UPA+MTX: Dominated	Dominated
		ERG base case	UPA+MTX: Dominated	Dominated
6 (MTX: yes, RTX: failed)	Advanced treatment	Company base case	UPA: £10,000, **S/W ICER** (INMB: -£800) UPA+MTX: £10,000 [dominant to £10,000 **S/W** ICER]	ICER $\leq$ £30,000 [dominant to ICER ≤ £30,000]
		ERG base case	UPA+MTX: £505k, **S/W ICER** (INMB: £37,871) [dominant to £505k **S/W** ICER]	ICER $\leq$ £30,000 [dominant to ICER ≤ £30,000]
Note: **S/W ICER** denotes that a comparator produces more QALYs than UPA at a higher cost than UPA. The S/W ICER shows the incremental cost per QALY gained for the comparator compared with UPA. Incremental net monetary benefit (INMB) is shown for these comparisons, where INMB = £20,000 x incremental QALYs – incremental costs. INMB > £0 indicates that UPA is cost effective.				

Positions 4, 5 & 6: severe RA, failed 1 bDMARD	
Note: Technical team prefers the modelling assumptions of the ERG in the severe RA population and note that the company, in their response to technical engagement, also agree with the ERG modelling. *ICERs presented in this table include the simple patient access scheme for UPA but do not include confidential commercial arrangements for comparator treatments – fully incremental **ICER information in this column includes all commercial arrangements, including an estimated weighted average price for ADA and the lowest nationally available prices for other biosimilars (see ERG biosimilar addendum): • ERG SA8 analysis includes the Humira price for ADA and the lowest biosimilar price for the other biosimilar treatments • ERG SA9 analysis includes the Humira price for ADA and the highest biosimilar price for the other biosimilar treatments	

Table 11. Outstanding uncertainties in the evidence base

Area of uncertainty	**Why this issue is important**	**Likely impact on the cost-effectiveness estimate**
Phase III clinical trials of upadacitinib	The clinical trials took place in various countries. SELECT-MONOTHERPAY clinical trial did not include any UK centers.	Unknown
Black box element to company's model	The ERG was not able to critique the model in extensive detail.	Unknown
Short duration of blinded comparative clinical trial	Many of the UPA clinical trials only reported relevant outcomes for the model at 12 or 14 weeks, therefore NMA data for six months relies on a projections from three-month trial data.	Unknown

Table 12. Other issues for information

Issue	Comments
End-of-life criteria	The technical team agrees with the ERG that the NICE end of life criteria are not met in this appraisal. The company did not make a case for upadacitinib meeting these criteria in its submission.
Innovation	The company considers upadacitinib to be innovative. However, the technical team considers that all relevant benefits associated with the drug are adequately captured in the model.
Equalities considerations	No equalities issues were identified by the company, consultees and their nominated clinical experts and patient experts.

5. Appendix

Table 13. Company and ERG modelled sequences (moderate and severe RA)

Position 1: moderate RA, failed 1 csDMARD							**If transition to severe occurs**					
1a MTX: no, RTX: yes	Analysis	Model arm	**Moderate 1st line**	**2nd**	**3rd**	**4th**	**Severe 1st line**	**2nd**	**3rd**	**4th**	**5th**	**6th**
	Company	UPA	UPA	csDMARD	BSC	-	ADA	SRL	BSC	-	-	-
		Comparator	csDMARD	BSC	-	-	BRC	ADA	SRL	BSC	-	-
	ERG	ERG does not consider this position (see issue 2).										
1b MTX: yes, RTX: yes	Analysis	Model arm	**Moderate 1st line**	**2nd**	**3rd**	**4th**	**Severe 1st line**	**2nd**	**3rd**	**4th**	**5th**	**6th**
	Company	UPA 1	UPA	csDMARD	MTX	BSC	ADA+MTX	RTX+MTX	TCZ_{IV}+MTX	MTX	BSC	-
		UPA 2	UPA+MTX	csDMARD	MTX	BSC	ADA+MTX	RTX+MTX	TCZ_{IV}+MTX	MTX	BSC	-
		Comparator	csDMARD	MTX	BSC	-	BRC+MTX	ADA+MTX	RTX+MTX	TCZ_{IV}+MTX	MTX	BSC
	ERG	ERG does not consider this position (see issue 2).										

Position 2: moderate RA, failed ≥ 2 csDMARDs							**If transition to severe occurs**					
2a MTX: no, RTX: yes	Analysis	Model arm	**Moderate 1st line**	**2nd**	**3rd**	**4th**	**Severe 1st line**	**2nd**	**3rd**	**4th**	**5th**	**6th**
	Company	UPA	UPA	BSC	-	-	ADA	SRL	BSC	-	-	-
		Comparator	BSC	-	-	-	BRC	ADA	SRL	BSC	-	-
	ERG	UPA	UPA	BSC	-	-	ADA	RTX	SRL	BSC	-	-
		Comp 1	PBO/BSC	BSC	-	-	ADA	RTX	SRL	BSC	-	-
		Comp 2	csDMARDs	BSC	-	-	ADA	RTX	SRL	BSC	-	-
	ERG alt seq 1	UPA	As above				ADA	RTX	ABT_{SC}	BSC	-	-
		Comp 1/2	As above				ADA	RTX	SRL	BSC	-	-
	ERG alt seq 2	UPA	As above				ADA	RTX	SRL	BSC	-	-
		Comp 1/2	As above				ADA	RTX	UPA	BSC	-	-
	ERG alt seq 3	UPA	As above				ADA	RTX	ABTsc	BSC	-	-
		Comp 1/2	As above				ADA	RTX	UPA	BSC	-	-
	ERG alt seq 4	UPA	As above				ADA	RTX	SRL	BSC	-	-
		Comp 1/2	As above				ADA	UPA	RTX	SRL	BSC	-
2b MTX: yes, RTX: yes	Analysis	Model arm	**Moderate 1st line**	**2nd**	**3rd**	**4th**	**Severe 1st line**	**2nd**	**3rd**	**4th**	**5th**	**6th**
	Company	UPA 1	UPA	MTX	BSC	-	ADA+MTX	RTX+MTX	TCZ_{IV}+MTX	MTX	BSC	-
		UPA 2	UPA+MTX	MTX	BSC	-	ADA+MTX	RTX+MTX	TCZ_{IV}+MTX	MTX	BSC	-
		Comparator	MTX	BSC	-	-	BRC+MTX	ADA+MTX	RTX+MTX	TCZ_{IV}+MTX	MTX	BSC
	ERG	UPA	UPA+MTX	BSC	-	-	ADA+MTX	RTX+MTX	SRL+MTX	BSC	-	-
		Comp 1	csDMARD	BSC	-	-	ADA+MTX	RTX+MTX	SRL+MTX	BSC	-	-
		Comp 2	PBO / BSC	BSC	-	-	ADA+MTX	RTX+MTX	SRL+MTX	BSC	-	-
	ERG alt seq 1	UPA	As above				ADA+MTX	RTX+MTX	ABT_{SC}+MTX	BSC	-	-
		Comp 1/2	As above				ADA+MTX	RTX+MTX	SRL+MTX	BSC	-	-
	ERG alt seq 2	UPA	As above				ADA+MTX	RTX+MTX	SRL+MTX	BSC	-	-
		Comp 1/2	As above				ADA+MTX	RTX+MTX	UPA+MTX	BSC	-	-

	ERG alt seq 3	UPA	As above				ADA+MTX	RTX+MTX	ABTsc+MTX	BSC	-	-
		Comp 1/2	As above				ADA+MTX	RTX+MTX	UPA+MTX	BSC	-	-
	ERG alt seq 4	UPA	As above				ADA+MTX	RTX+MTX	SRL+MTX	BSC	-	-
		Comp 1/2	As above				ADA+MTX	UPA+MTX	RTX+MTX	SRL+MTX	BSC	-
2c MTX: no, RTX: no	Analysis	Model arm	**Moderate 1st line**	**2nd**	**3rd**	**4th**	**Severe 1st line**	**2nd**	**3rd**	**4th**	**5th**	**6th**
	Company	Company did not include this position in its analyses.										
	ERG	UPA	UPA	BSC	-	-	ADA	SRL	BSC	-	-	-
		Comp 1	csDMARD	BSC	-	-	ADA	SRL	BSC	-	-	-
		Comp 2	PBO/BSC	BSC	-	-	ADA	SRL	BSC	-	-	-
	ERG alt seq 1	UPA	As above				ADA	ABT_{SC}	BSC	-	-	-
		Comp 1/2	As above				ADA	SRL	BSC	-	-	-
	ERG alt seq 2	UPA	As above				ADA	SRL	BSC	-	-	-
		Comp 1/2	As above				ADA	UPA	BSC	-	-	-
	ERG alt seq 3	UPA	As above				ADA	SRL	ABTsc	BSC	-	-
		Comp 1/2	As above				ADA	SRL	UPA	BSC	-	-
	ERG alt seq 4	UPA	As above				ADA	SRL	BSC	-	-	-
		Comp 1/2	As above				ADA	UPA	SRL	BSC	-	-

Position 3: severe RA, failed ≥ 2 csDMARDs								
3a MTX: no, RTX: yes	Analysis	Model arm	**Severe 1st line**	**2nd**	**3rd**	**4th**	**5th**	**6th**
	Company	UPA	UPA	SRL	BSC	-	-	-
		Comparator	bDMARD	SRL	BSC	-	-	-
	ERG	UPA	UPA	SRL	BSC	-	-	-
		Comparator	bDMARD	SRL	BSC	-	-	-
3b MTX:	Analysis	Model arm	**Severe 1st line**	**2nd**	**3rd**	**4th**	**5th**	**6th**
	Company	UPA 1	UPA	RTX+MTX	TCZ_{IV}+MTX	MTX	BSC	-

yes, RTX: yes		UPA 2	UPA+MTX	RTX+MTX	TCZ_{IV}+MTX	MTX	BSC	-
		Comparator	bDMARD+MTX	RTX+MTX	TCZ_{IV}+MTX	MTX	BSC	-
	ERG	UPA	UPA+MTX	RTX+MTX	SRL+MTX	BSC	-	-
		Comparator	bDMARD+MTX	RTX+MTX	SRL+MTX	BSC	-	-
Position 4, 5 & 6: severe RA, failed 1 bDMARD								
4a MTX: no, RTX: yes	Analysis	Model arm	**Severe 1st line**	**2nd**	**3rd**	**4th**	**5th**	**6th**
	Company	UPA	UPA	BSC	-	-	-	-
		Comparator	bDMARD	BSC	-	-	-	-
	ERG	ERG does not consider this position (see issue 2).						
4b MTX: yes, RTX: no	Analysis	Model arm	**Severe 1st line**	**2nd**	**3rd**	**4th**	**5th**	**6th**
	Company	UPA 1	UPA	TCZ_{IV}+MTX	MTX	BSC	-	-
		UPA 2	UPA+MTX	TCZ_{IV}+MTX	MTX	BSC	-	-
		Comparator	bDMARD+MTX	TCZ_{IV}+MTX	MTX	BSC	-	-
	ERG	UPA	UPA+MTX	SRL+MTX	BSC	-	-	-
		Comparator	bDMARD+MTX	SRL+MTX	BSC	-	-	-
5 MTX: yes, RTX: yes	Analysis	Model arm	**Severe 1st line**	**2nd**	**3rd**	**4th**	**5th**	**6th**
	Company	UPA 1	UPA	TCZ_{IV}+MTX	MTX	BSC	-	-
		UPA 2	UPA+MTX	TCZ_{IV}+MTX	MTX	BSC	-	-
		Comparator	RTX+MTX	TCZ_{IV}+MTX	MTX	BSC	-	-
	ERG	UPA	UPA+MTX	SRL+MTX	BSC	-	-	-
		Comparator	RTX+MTX	SRL+MTX	BSC	-	-	-
6 MTX: yes, RTX: **failed**	Analysis	Model arm	**Severe 1st line**	**2nd**	**3rd**	**4th**	**5th**	**6th**
	Company	UPA 1	UPA	MTX	BSC	-	-	-
		UPA 2	UPA+MTX	MTX	BSC	-	-	-
		Comp 1	SRL+MTX	MTX	BSC	-	-	-
		Comp 2	TCZ_{IV}+MTX	MTX	BSC	-	-	-

	ERG	UPA	UPA+MTX	BSC	-	-	-	-
		Comp 1	SRL+MTX	BSC	-	-	-	-
		Comp 2	TCZ_{IV}+MTX	BSC	-	-	-	-

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