NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Sarilumab for previously treated moderate to severe active rheumatoid arthritis [ID994]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Sarilumab for previously treated moderate to severe active rheumatoid arthritis [ID994]

Contents:

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

Pre-meeting briefing

Sarilumab for treating moderate-to-severe rheumatoid arthritis

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting

1

Abbreviations (shaded rows contain comparator technologies)

ABT	Abatacept
ACR20/50/70	20%/50%/70% improvement in American College of Rheumatology Criteria
ADA	Adalimumab
BAR	Baricitinib
bDMARD	Biological DMARD
cDMARD	Conventional DMARD
CTZ	Certolizumab pegol
DAS28/44	Disease activity score in 28/44 Joints
DMARD	Disease-modifying anti-rheumatic drug
ETN	Etanercept
EULAR	European League against Rheumatism
GOL	Golimumab
HAQ-DI	Health Assessment Questionnaire–Disability Index

IFX	Infliximab
mTSS	Modified Total Sharp Score
MTX	Methotrexate
Q2W	Every 2 weeks
NRI	Non-responder imputation
QD	Once daily
QW	Weekly
RA	Rheumatoid arthritis
RTX	Rituximab
SAR	Sarilumab
SSZ	Sulfasalazine
TCZ	Tocilizumab
TNF	Tumour necrosis factor
TNFi	Tumour necrosis factor inhibitor
TOFA	Tofacitinib

2

Note: Throughout the presentation the term '+ cDMARDs' includes '+ MTX'

Key issues: Clinical effectiveness

- Is SAR comparable to the bDMARDs in clinical effectiveness in moderate and severe RA?
- Is SAR effective as a monotherapy in TNFi-IR patients?
- Are the Committee comfortable with the conclusion that the company NMA results are unlikely to change?

3

Key issues: Cost effectiveness

- Do the Committee accept the ERG's changes to the company model:
  - Using a non-linear approach (Norton et al) for HAQ trajectory
  - Including the option for patients to receive treatment for severe disease when in the moderate state and their DAS28 score reaches 5.1.
- Is SAR comparable to the bDMARDs in both clinical and cost effectiveness?
- Is SAR monotherapy cost-effective?

4

Background to rheumatoid arthritis

- Autoimmune disease characterised by chronic systemic inflammation and progressive inflammation of the synovial joints resulting in pain and stiffness. Can lead to joint damage, deformities and loss of function
  - Hands, wrists and feet most commonly affected
- Initial symptoms are reversible but joint damage is not
- Disease severity measured using the composite disease activity score (DAS28), includes assessment of 28 joints for swelling/tenderness, the patient's assessment of health and erythrocyte sedimentation rate or C-reactive protein
  - DAS28 <3.2 indicates low disease activity, DAS28 ≥3.2 and ≤5.1 indicates moderate activity, and DAS28 >5.1 indicates high activity
- For the majority of patients, disease remains mild with occasional flare-ups of higher disease activity. However, for some patients the disease may be active and progressive, significantly compromising quality of life
- Management of RA aims to suppress disease activity and induce remission, prevent the development of irreversible joint damage and, in more severe disease, maintain quality of life and address comorbidities associated with the condition
- Affects ~450,000 people in the UK, with a prevalence of 0.86% and incidence of 0.47 per 1,000 person-years. Around 12,000 new cases are diagnosed each year. The National Rheumatoid Arthritis Society estimates up to 690,000 people are living with RA in the UK
  - In the UK, approximately 15% (~60,000) of RA patients have severe disease
  - More prevalent in women than men, with 2–3 times as many cases in women
  - Can develop at any age but the typical age of onset in the UK is approximately 40–70 years, with most diagnoses made when people are in their 70s

5

Relevant NICE technology appraisals		
TA	**Treatment**	**Population**
415 2016	CTZ + MTX	Adults whose disease has responded inadequately to, or who cannot tolerate, other DMARDs including at least 1 TNF inhibitor, only if: • disease activity is severe and RTX is contraindicated or not tolerated
	CTZ monotherapy	As above but only if: • RTX therapy cannot be given because MTX is contraindicated or not tolerated
375 2016	ADA, ETN, IFX, CTZ, GOL, TCZ, ABA (all + MTX)	Disease is severe (disease activity score [DAS28] >5.1) and has not responded to intensive therapy with a combination of cDMARDs
	ADA, ETN, CTZ, TCZ monotherapy	As above but for people who cannot have MTX because of contraindications or intolerance
247 2012	TCZ + MTX	Disease has responded inadequately to DMARDs and a TNF inhibitor and the person cannot have RTX because it is contraindicated or not tolerated, and TCZ is used as described for TNF inhibitor treatments in TA195, specifically the recommendations on disease activity or the disease has responded inadequately to 1 or more TNF inhibitor treatments and to RTX
225 2011	GOL + MTX	Adults whose RA has responded inadequately to other DMARDs, including a TNF inhibitor, if it is used as described for other TNF inhibitor treatments in TA195
195 2010	RTX + MTX	Adults with severe active RA with an inadequate response to, or are intolerant of, other DMARDs, including at least 1 TNF inhibitor.
	ADA, ETN, IFX, ABT (all + MTX)	As for RTX + MTX but for people who cannot have RTX because of contraindications or intolerance
	ADA, ETN monotherapy	As for RTX + MTX but for people who cannot have RTX because they have a contraindication to, or intolerance of MTX

6

Stopping rules

TA415 - Continue treatment only if there is at least a moderate response measured using EULAR criteria at 6 months. After an initial response within 6 months, withdraw treatment if at least a moderate EULAR response is not maintained.

TA375 - Continue treatment only if there is a moderate response measured using EULAR criteria at 6 months after starting therapy.

TA247 - As described for TA195

TA225 - GOL + MTX – As described for TA195

TA195 – RTX + MTX - Treatment with rituximab in combination with methotrexate should be continued only if there is an adequate response following initiation of therapy and if an adequate response is maintained following retreatment with a dosing interval of at least 6 months. An adequate response is defined as an improvement in DAS8 of 1.2 points or more.

TA195 - ADA, ETN, IFX, ABA (all + MTX) - Treatment with adalimumab, etanercept, infliximab and abatacept should be continued only if there is an adequate response (an improvement in DAS28 of 1.2 points or more) 6 months after initiation of therapy. Treatment should be monitored, with assessment of DAS28, at least every 6 months and continued only if an adequate response is maintained.

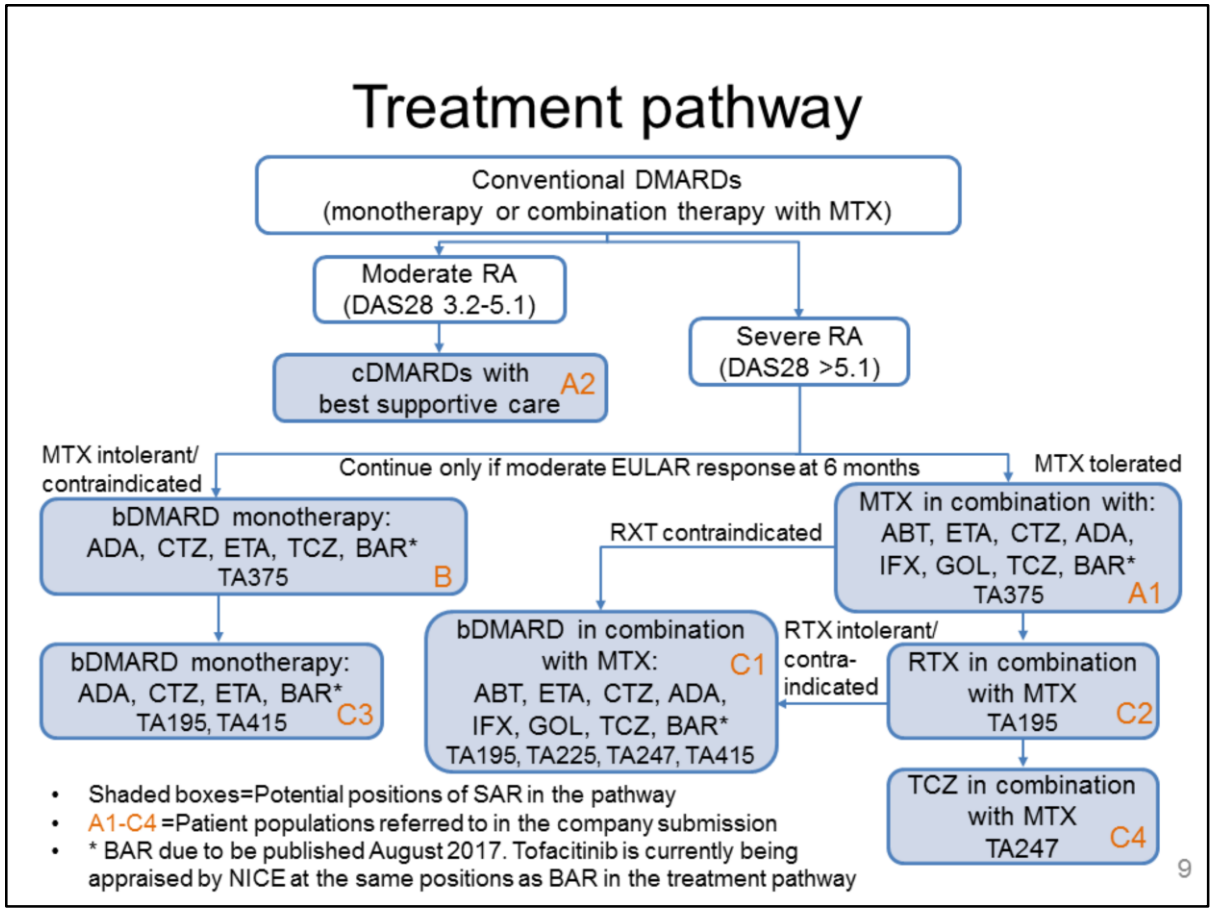
Details of the technology	
Technology	Sarilumab (Kevzara; Sanofi)
Marketing authorisation	Treatment of moderate to severe active RA in adult patients • who have responded inadequately to, or • who are intolerant to one or more DMARDs – used as monotherapy or in combination with MTX
Mechanism of action	interleukin-6 inhibitor
Administration	Subcutaneous injection: once every 2 weeks. 2 doses available (as a single use pre-filled pen [PFP] or pre-filled syringe [PFS]):150 mg and 200 mg
Acquisition cost	List price per PFS/PFP: 150 mg or 200 mg: £457.69 Annual cost per patient: £11,900 Company have agreed a confidential PAS with a simple discount on the list price

7

Innovation

- Only IL-6 receptor inhibitor available as an auto-injectable pre-filled pen, administered subcutaneously every other week by the patient at home
- 2 doses available (200 mg and 150 mg) enabling dose reduction as needed. It is also stable out of the fridge for up to 14 days
  - TCZ is currently the only other IL-6 receptor inhibitor available. It is administered by IV infusion every 4 weeks or by SC injection once a week.
  - Once removed from the refrigerator, TCZ must be administered within 8 hours

8



Source: Adapted from BAR appraisal slides and Figure 3.2 page 50 of company submission.

EULAR response criteria

- Good EULAR response=change of >1.2 in DAS28 from baseline AND a DAS28 of ≤3.2 at endpoint
- Moderate EULAR response=change >0.6 and ≤1.2 in DAS28 from baseline AND DAS28 >3.2 and ≤5.1 or DAS2 ≤3.2 at endpoint OR if change of >1.2 in DAS28 from baseline AND DAS28 >3.2 at baseline
- No EULAR response=change ≤0.6 in DAS28 from baseline OR if change of >0.6 and ≤1.2 in DAS28 from baseline AND DAS28 >5.1 at baseline

Decision problem: Population & intervention

	Final scope issued by NICE	ERG comments
Population	Adults with moderate-to-severe, active RA, whose disease has not responded adequately to, or who are intolerant of cDMARDs or bDMARDs	None.
Intervention	Sarilumab monotherapy or in combination with cDMARDs	None.

10

Source: Adapted from table 1.1, page 16 of the company submission and section 3 of the ERG report

Decision problem: Comparators

	Final scope issued by NICE	ERG comments
Comparators	People with moderate active RA that has not responded adequately to, or who are intolerant of therapy with cDMARDs • Best supportive care People with severely active RA that has not responded adequately to therapy with cDMARDs only • Biologic DMARDs in combination with MTX (ADA, ETN, IFX, CTZ, GOL, TCZ, ABT) • ADA, ETN, CTZ, or TCZ (each as monotherapy) People with severely active RA that has not responded adequately to therapy with DMARDs including at least 1 TNF inhibitor • RTX in combination with MTX • When RTX is contraindicated or withdrawn due to adverse events: o ABT, ADA, CTZ, ETN, IFX, TCZ, or GOL, each in combination with MTX o ADA, ETN or CTZ (each as monotherapy) People with severe, active disease despite treatment with bDMARDs: o TCZ in combination with MTX, best supportive care	Company did not consider biosimilars for ADA and RTX.

11

Source: Adapted from table 1.1 page 16 of the company submission and section 3 of the ERG report

Decision problem: Outcomes and economic analyses

	Final scope issued by NICE		ERG comment
Outcomes	The outcome measures to be considered include:		No data identified on extra-articular manifestations related to sarilumab
	• disease activity • physical function • joint damage • pain • mortality	• fatigue • radiological progression • extra-articular manifestations • adverse effects of treatment • health-related quality of life	
Economic analysis	• Cost-effectiveness should be expressed in terms of incremental cost per QALY • 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 • Patient access schemes for the intervention or comparator technologies will be taken into account • Availability and cost of biosimilar products should be taken into account		None.

12

Source: Adapted from table 1.1 of the company submission and section 3 of the ERG report

Decision problem: Subgroups

	Final scope issued by NICE	ERG comment
Subgroups to be considered	If evidence allows, the appraisal will consider subgroups of people identified as: • Having had primary or secondary failure of response to the first TNFi; or • Having seronegative or seropositive antibody status • People with moderate disease activity (DAS28 between 3.2 and 5.1) and severe active disease (DAS28 greater than 5.1)	No data were identified to enable a comparison on previous TNF inhibitor failure or seropositive/seronegative antibody status

13

Source: Adapted from table 1.1 of the company submission and section 3 of the ERG report

Submissions from patient/carer organisation (National Rheumatoid Arthritis Society and patient expert)

- Being diagnosed RA can be extremely distressing as it is life-changing, affects physical and emotional wellbeing, and impacts the whole family
- People can be diagnosed at any age over 16 years so it can have a major impact on life plans and expectations, dreams and aspirations affecting:
  - Personal confidence and future relationships in younger people
  - Working life and job security, and caring for young children
  - Retirement plans
- People simply want their life back. They want a reduction in pain and fatigue, to prevent permanent disability, and to maintain independence and ability to work
- The side effects of some drugs can be debilitating. Even with all the new treatments available, the heterogeneity of RA means that there remains unmet need
- Sarilumab offers an additional therapy for people with moderate or severe disease which has not responded to cDMARDs or a TNFi.
- Sarilumab is self-administered which means people do not have to travel to hospital for treatment.

14

Submissions from clinical experts

- Current evidence suggests that IL-6 inhibitors (SAR, TCZ) appear to have similar clinical effectiveness and adverse effect profiles
- Compared with some other bDMARDs, SAR is licensed as a monotherapy in people where co-administration of methotrexate is contraindicated or not tolerated
- Differences in injection device and dosing means people may find it easier to administer the drug.

15

Clinical effectiveness – included studies overview

Trial name	Population and number enrolled	Intervention	Comparators	Primary outcome
MOBILITY A	MTX-IR, N=306	• SAR + MTX • SAR doses: 100mg QW, 150mg QW, 100mg Q2W, 150mg Q2W, 200mg Q2W	• PBO + MTX	• ACR20 response at week 12
MOBILITY B	MTX-IR, N=1197	• SAR + MTX • SAR doses: 150mg Q2W, 200mg Q2W	•PBO + MTX	• ACR20 response at Week 24 • Change in HAQ-DI from baseline to Week 16 • Change in mTSS from baseline to Week 52
MONARCH	MTX-IR, N=369	• SAR monotherapy • dose 200mg Q2W	• ADA monotherapy • ADA dose 40mg Q2W	• DAS28-ESR at week 24
TARGET	TNFi-IR, N=546	• SAR + cDMARD • SAR doses: 150mg Q2W, 200mg Q2W	• PBO + cDMARD	• ACR20 response at Week 24 • Change in HAQ-DI from baseline to Week 12
ASCERTAIN	TNFi-IR, N=202	• SAR + cDMARD • SAR doses: 150mg Q2W, 200mg Q2W	• TCZ + cDMARD • TCZ dose 4mg/kg	• Safety
EXTEND	cDMARD/TNFi-IR, N=2023	• SAR + cDMARD, • SAR monotherapy	• NA, Extension study	• Safety

16

Adapted from table 6 page 39 of ERG report
ERG report page 40 - There were no imbalances within trials between treatment groups at baseline

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Clinical effectiveness Results: ACR 20

- SAR+MTX (both licenced doses) showed a statistically significant improvement in ACR20 compared with PBO+MTX in MOBILITY-A (at week 12) and MOBILITY-B (at week 24)
- SAR 200mg Q2W showed a statistically significant improvement in ACR20 compared with ADA 40mg Q2W in MONARCH (at week 24)
- SAR+MTX (both licenced doses) showed a statistically significant improvement in ACR20 compared with PBO+ cDMARD in TARGET (at week 24)
- The company did not report comparative statistics for ASCERTAIN as the study was powered for safety not effectiveness. However it noted that [redacted]

17

See tables 10-14 pages 44-45 of ERG report for full ACR 20 response results.

Results for other outcomes including EULAR and HAQ-DI on page 47 of ERG report.

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Clinical effectiveness Results: adverse events

cDMARD-IR trials

- Adverse event rates reported in MOBILITY-A and B were higher in SAR groups (53%-78%) compared with PBO (47%-61%).
- In the MONARCH trial, ADA and SAR had similar AE rates (63.6% and 64.1% respectively).

TNFI-IR trials

- [redacted]
- [redacted]

18

Company NMA overview

- No direct evidence for all comparators.
- Company performed NMA separately for:
  - cDMARD-IR (further separated into combination therapy and monotherapy)
  - bDMARDs-IR
- Efficacy outcome measures included:
  - ACR response
  - HAQ-DI
  - EULAR
  - DAS28
  - mTSS

19

Health Assessment Questionnaire Disability Index (HAQ-DI),
European League Against Rheumatism (EULAR) responses,
Disease Activity Score 28 (DAS28)
remission and modified Total Sharp Score (mTSS)

Company NMA results for the cDMARD-IR population

	ACR at week 24	EULAR good response at Week 24	EULAR moderate-to-good response at Week 24
SAR 200 mg combination vs cDMARDs combination	statistically superior	statistically superior	statistically superior
SAR 200 mg combination vs bDMARDs combination	Comparable efficacy	statistically superior to ABT, IFX, TCZ 4mg IV, RTX, SAR 150mg combinations Comparable efficacy to GOL, TCZ 8mg IV combinations	statistically inferior to CTZ Comparable efficacy to GOL, IFX, TCZ 4mg IV and 8mg IV, RTX and SAR 150mg combinations
SAR 200 mg monotherapy vs cDMARDs monotherapy	statistically superior	statistically superior	statistically superior
SAR 200 mg monotherapy vs bDMARDs monotherapy	statistically superior to ADA, sirukumab 50 mg** Comparable efficacy to CTZ, ETN, sirukumab 100mg, TCZ 8mg and tofacitinib	statistically superior to ADA Comparable efficacy to TCZ 8mg	statistically superior to ADA Comparable efficacy to TCZ 8mg

*excluded TCZ SC combination
**ACR20/50 only

20

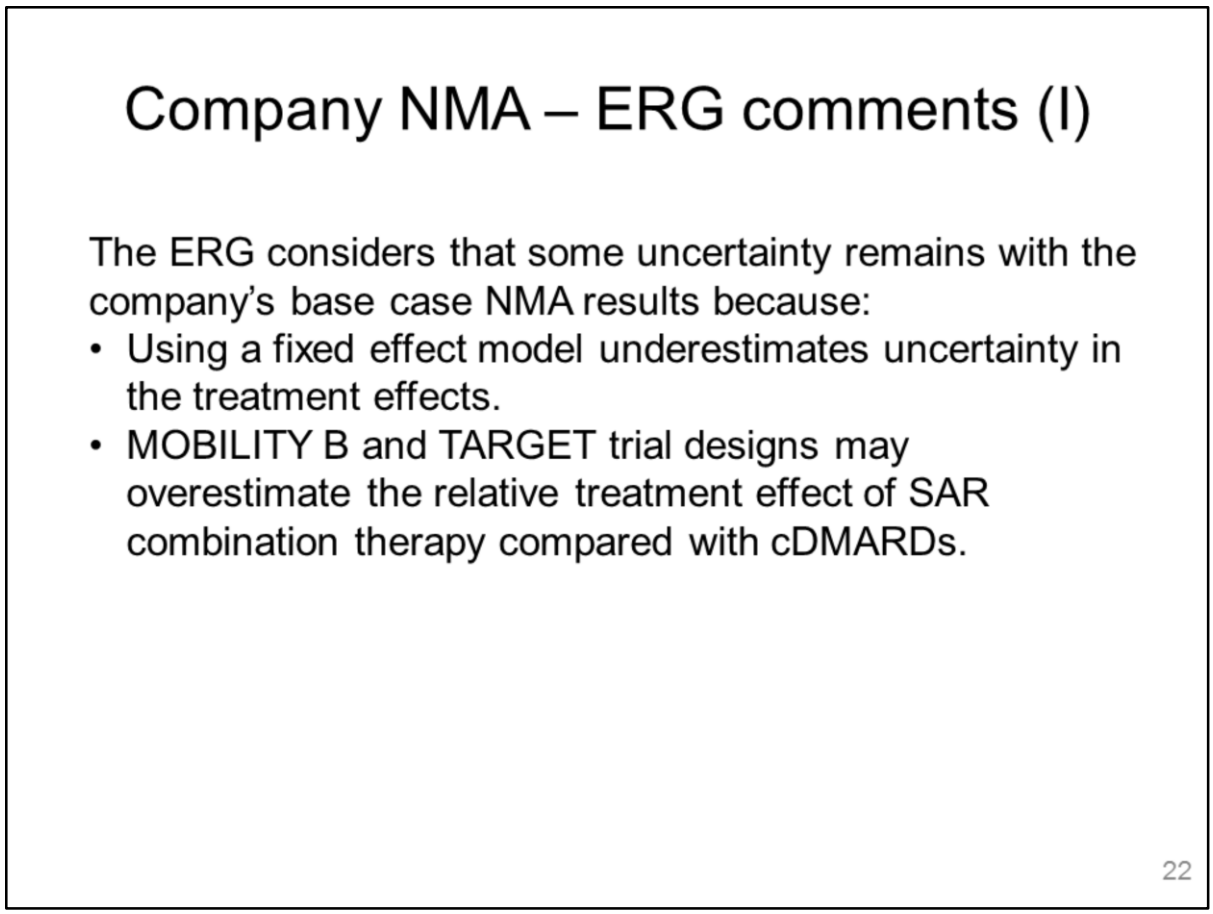
See page 71 of ERG report

Company NMA results for the TNFi-IR population

	ACR at week 24	EULAR good response at week 24	EULAR moderate-to-good response at week 24
SAR 200mg combination vs cDMARDs *combination*	statistically superior	statistically superior	statistically superior
SAR 200mg combination vs bDMARDs *combination*	statistically superior to baricitinib 2mg combination, sirukumab 50mg combination on ACR50 only. Comparable efficacy to other bDMARD combinations on all ACR outcomes	statistically superior to RTX combination Comparable efficacy to ABT, SAR 150mg combinations	statistically inferior to TCZ 8mg, RTX combinations Comparable efficacy to ABT, GOL, SAR 150mg combinations

- The company did not identify any evidence for SAR monotherapy in the TNFi-IR population.

21



The ERG noted that the statistically significant results of SAR 200mg compared with other bDMARD treatments (both as combination therapy and monotherapy) may be as a result of using a fixed effect model, which underestimates uncertainty in the treatment effects.

The MOBILITY B and TARGET trial designs allowed patients who did not achieve a ≥20% improvement from baseline in the swollen joint count or tender joint count at two consecutive assessments to switch to open-label SAR 200mg at 16 and 12 weeks, respectively. Non-responder imputation was carried out for the control arm, assuming none of the non-responders in the cDMARD control group would become responders at 24 weeks; this may overestimate the relative treatment effect of SAR combination therapy versus cDMARD

Further, the ordered categorical ACR response and EULAR response data were dichotomised in the NMA. The ERG noted that this ignored the natural ordering and correlations between the categories within the outcome measure. When a risk difference model was used for binary data, the probability was not constrained to be below 1.0.

Company NMA – ERG comments (II)

- The ERG requested a number of changes to the company NMA :
  - See page 72-73 of ERG report.
- The company provided the results for the cDMARD-IR population on ACR responses only.
- Company concluded that the updated results were in line with the original analysis and the conclusion that SAR 200mg in combination with cDMARD showed comparable efficacy to other bDMARDs was unchanged.
- ERG agreed but noted that the results from the requested NMA may be numerically different from the original NMA in the CS

23

The ERG requested that the company perform additional analysis for ACR and EULAR response in both populations (with the following settings:

- Using a random effects probit model with an informative prior for the between-study variance (log normal with mean -2.56 and variance of 1.74*1.74, which is proposed by Turner *et al* 2012. The log normal is truncated so that the odds ratio in one study would not be ≥50 times than in another, and re-scaled to match the probit scale).
- Keeping all treatments separate.
- Including combination therapy and monotherapy in a single network in order that trials comparing both regimens can provide evidence.
- Including the studies which were excluded due to small sample size
- Including the previously excluded studies that were included in TA375.
- Including the studies assuming that ETN 50mg once weekly was equivalent to ETN 25mg twice weekly.
- Incorporate the KAKEHASI study for consistency with the main network, which includes studies in Asian patients.

Key issues: Clinical effectiveness

- Is SAR comparable to the bDMARDs in clinical effectiveness in moderate and severe RA?
- Is SAR effective as a monotherapy in TNFi-IR patients?
- Are the Committee comfortable with the conclusion that the company NMA results are unlikely to change?

24

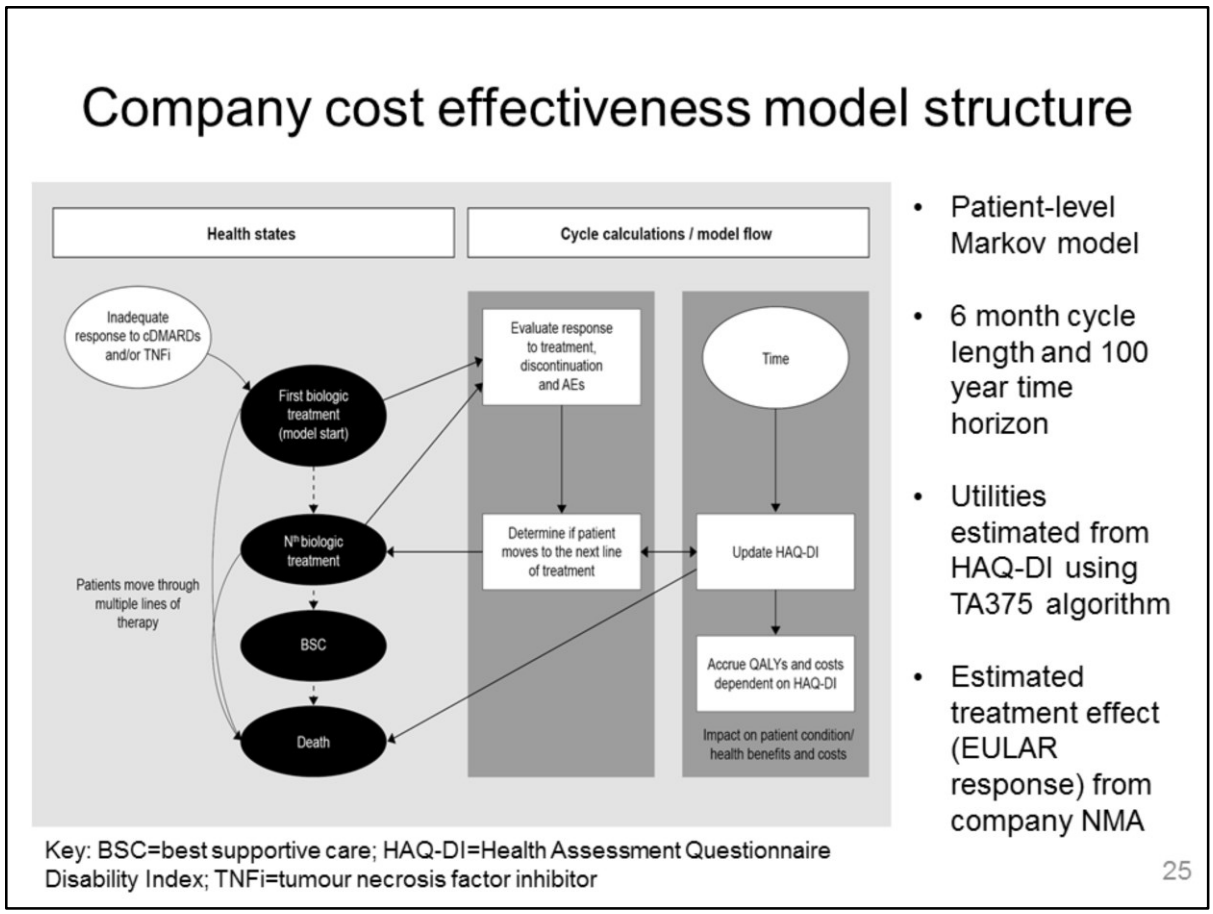


Figure from company submission page 206 figure 5.5

Within the model a clinical response in terms of EULAR (good, moderate or none) is estimated at six months.
Patients who experience either a good or moderate EULAR response remain on treatment; those who experience no response have their treatment withdrawn and move on to the next treatment in the sequence, unless the patient was already receiving BSC.

Throughout the model, the costs incurred and the utility of the patient were assumed to be related to HAQ score

See table 39 page 84 of ERG report for a summary of the company's adherence to the NICE reference case.

Treatment sequences

- Different treatment sequences were evaluated for each of the populations.
- The model treatment sequences included a 'TNFi bundle' in the base case. The 'TNFi bundle' used the pooled efficacy of TNFis with the price weighted according to the estimated market share of each TNFi.
- The ERG noted that sequences were not consistent with those accepted in TA375 and at clarification the company updated these sequences as requested by the ERG
  - The ERG noted that for the TNFi-IR RTX-ineligible population the company had mistakenly added a second line of biologics.
  - In the ERG exploratory analyses these have been corrected
  - Full treatment sequences on page 87-89, tables 42-48 of ERG report

26

The ERG noted that the TNFi bundle were estimated from a freedom of information request to all UK hospital trusts asking for the number of RA patients treated with each named bDMARD between September and December 2016. The ERG noted that these data are likely to change as based on clinical advice provided to the ERG, clinicians are advised to start people requiring bDMARDs on a biosimilar (page 86 ERG report)

Following clarification, the company updated their set of sequences as requested by the ERG. Full details of these sequences are provided on page 87, tables 42 - 48 of the ERG report.

According to the ERG the sequences first presented by the company had 2 issues:
1. Omission of 1 cDMARD treatment (MTX or SSZ) after biologics and before BSC.
2. Inclusion of ABT+MTX after RTX+MTX in cDMARD-IR patients or after SAR+MTX in TNFi-IR patients who are RTX-eligible

The ERG noted that in its updated sequences the company erroneously included a second line of biologics in some sequences for the TNFi-IR RTX-ineligible population as indicated in Table 45 of ERG report. These sequences have been used in the company's analyses but have been amended in the ERG's exploratory analyses.

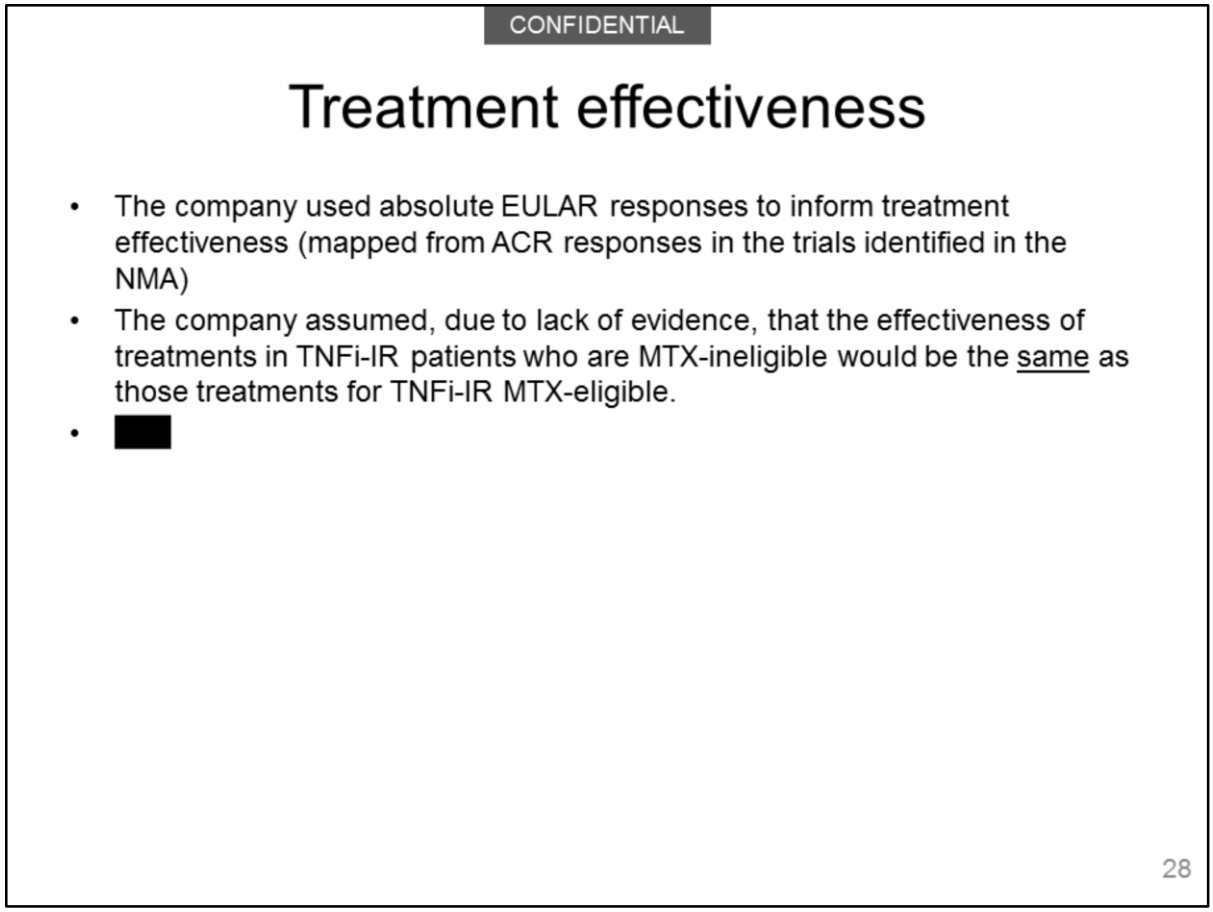
Company cost effectiveness model: Resources and costs

- Company model included costs associated with drug acquisition, administration and monitoring, and hospitalisation and serious infection
- SAR has a confidential PAS
- PASs for CTZ and GOL were incorporated (not confidential)
- Biosimilars for RTX and ADA were not included in the company's analyses
- Administration costs based on TA375 and inflated to 2015/16 prices

27

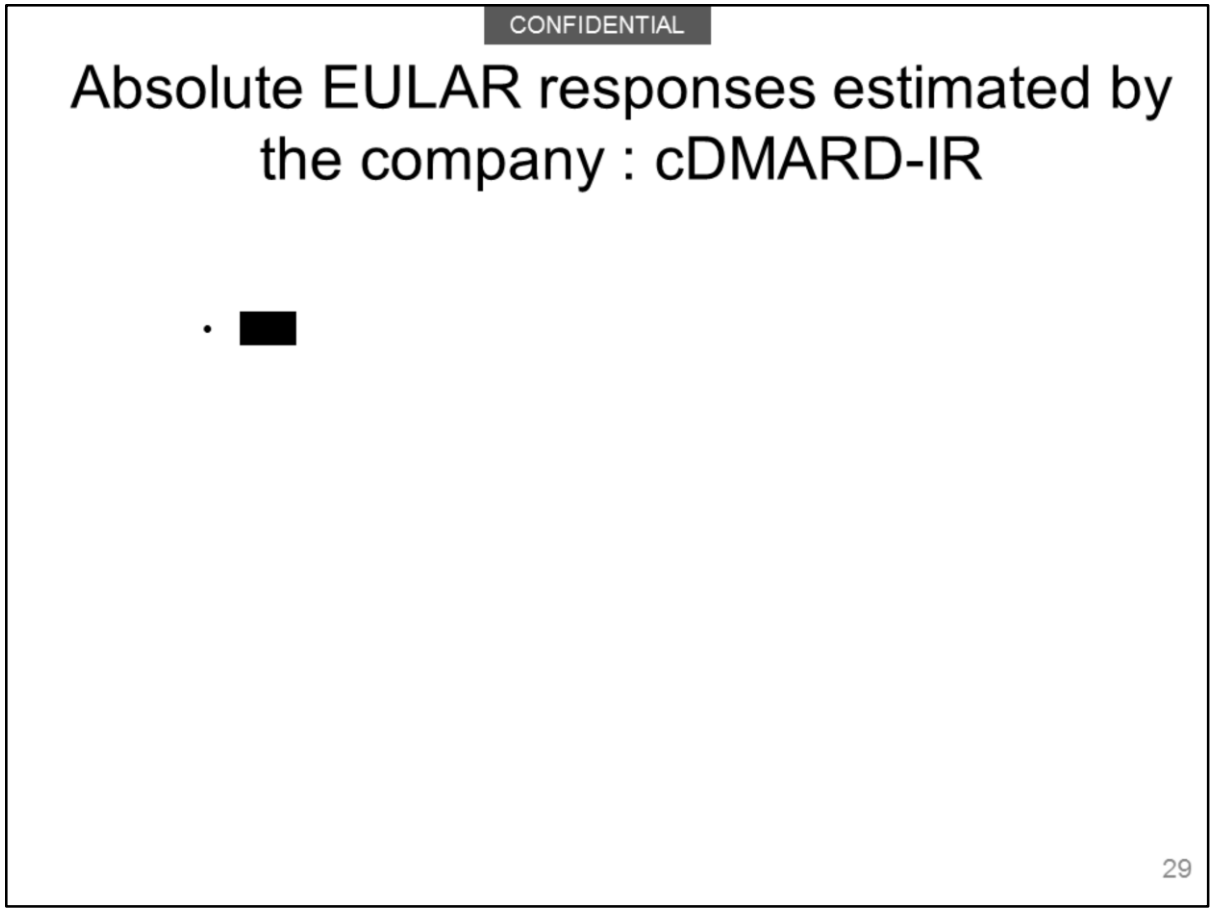
There is a PAS for CTZ that provides the first 12 weeks of treatment free of charge; this was incorporated into the first year's acquisition costs.

The confidential PAS for ABT and TCZ were not excluded, as recommended by NICE, but were assumed to be equal to 15%. Following a request at clarification the company removed this assumption.



The ERG noted that the company had assumed that the efficacy of SAR + MTX in TNFi-IR patients would apply before and after treatment with RTX + MTX.

The ERG noted that the efficacy of SAR+MTX is reduced in TNFi-IR patients compared with cDMARD-IR patients. It therefore predicted that its efficacy could be further reduced after subsequent treatment lines. The ERG acknowledged that this is unlikely to have an effect on the cost-effectiveness analysis as this effect would also apply to its comparators.



Adapted from page 95 table 49 of ERG report.

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Absolute EULAR responses estimated by the company: cDMARD-IR – MTX ineligible

- [redacted]

30

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Absolute EULAR responses estimated by the company: TNFi-IR

- [redacted]

31

Treatment effectiveness: HAQ score

- In the company model, after 6 months, patients are assumed to be assessed for response to treatment.
- Patients who achieved a moderate or good EULAR response were assumed to have an associated reduction in HAQ score which is assumed independent of treatment.
- The ERG noted that the company have used a linear approach to HAQ score progression
- The Appraisal Committee in TA375 favoured a non-linear approach advocated by the AG
- ERG concluded that a linear approach would have a significant favourable effect for SAR when compared with cDMARDs.
- The ERG further noted that the linear method is not likely to significantly affect the conclusions in the comparison of SAR with bDMARDs, due to similar efficacy levels

32

Company cost effectiveness model: Utilities

- EQ-5D utility data was not available for all comparators across all patient populations. Company used literature review to inform health-related quality of life (HRQoL).
- The ERG noted that Hernandez *et al.*, which estimated EQ-5D based on patient characteristics used in TA375 was not included in the company's analysis.
- The company used Malottki et al because they were concerned that the method used in TA375 may double count the effects of pain since the HAQ-DI assessment already includes pain.
- Following a request at clarification by the ERG the company implemented the mapping of Hernandez *et al*
- The rates of serious infections for SAR and BSC were taken from the pivotal studies MOBILITY-B for cDMARD-IR + MTX, MONARCH for cDMARD-IR MTX-IR and TARGET for the remaining populations.

33

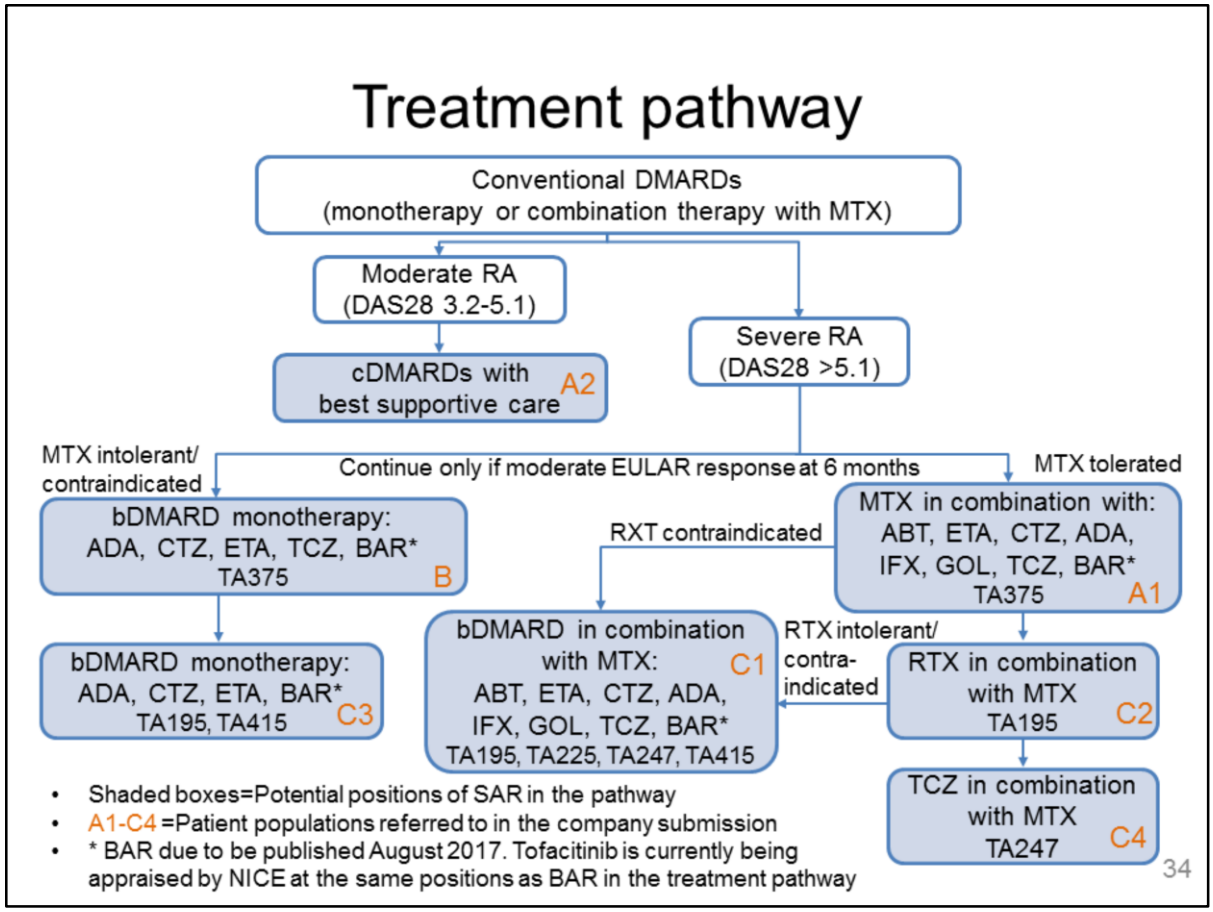
The rates of serious infections for SAR and BSC were taken from the pivotal studies:

MOBILITY-B for cDMARD-IR patients who could receive MTX (4.0% and 2.3% per cycle respectively);

MONARCH for cDMARD-IR patients who could not receive MTX (1.1% and 2.3% per cycle respectively);

TARGET for the remaining patients (1.1% and 1.1% per cycle respectively). The company assumed that the rates for SAR were applicable to other bDMARDs

QALYs losses due to serious infections were stated to have been estimated based on the method used in the AG model for TA375 whereby serious infections were assumed to be of 28 days' duration and incur a disutility of 0.156, both taken from Oppong *et al*. The company have translated this into a QALY loss of 0.024 per cycle.


Treatment pathway
Conventional DMARDs
(monotherapy or combination therapy with MTX)
Moderate RA
(DAS28 3.2-5.1)
cDMARDs with
best supportive care
A2
Severe RA
(DAS28 >5.1)
MTX intolerant/
contraindicated
Continue only if moderate EULAR response at 6 months
MTX tolerated
bDMARD monotherapy:
ADA, CTZ, ETA, TCZ, BAR*
TA375
B
RXT contraindicated
MTX in combination with:
ABT, ETA, CTZ, ADA,
IFX, GOL, TCZ, BAR*
TA375
A1
bDMARD monotherapy:
ADA, CTZ, ETA, BAR*
TA195, TA415
C3
bDMARD in combination
with MTX:
C1
ABT, ETA, CTZ, ADA,
IFX, GOL, TCZ, BAR*
TA195, TA225, TA247, TA415
RTX intolerant/
contra-
indicated
RTX in combination
with MTX
TA195
C2
TCZ in combination
with MTX
TA247
C4
• Shaded boxes=Potential positions of SAR in the pathway
• A1-C4 =Patient populations referred to in the company submission
• * BAR due to be published August 2017. Tofacitinib is currently being appraised by NICE at the same positions as BAR in the treatment pathway
34

Base-case results

- The company undertook analyses on the following groups:
  - cDMARD-IR patients with severe RA who can tolerate MTX (A1)
  - cDMARD-IR patients with severe RA who cannot tolerate MTX (B)
  - TNFi-IR patients with severe RA who can tolerate RTX and MTX (C2)
  - TNFi-IR patients with severe RA who cannot tolerate RTX (C1)
  - TNFi-IR patients with severe RA who cannot tolerate MTX (C3)
  - TNFi-IR patients who have received RTX and MTX (C4)
  - cDMARD-IR patients with moderate RA and DAS28 between 4.0 and 5.1 who can tolerate MTX (A2).
- In the company's original base case SAR+MTX was estimated to either dominate all its comparators or result in ICERs lower than £20,000 per QALY in all populations except in:
  - cDMARD-IR patients with moderate RA and a DAS28 score higher than 4.0 **(£22,275 per QALY gained)**
  - TNFi-IR patients for whom RTX was an option **(£104,012 per QALY gained)**
- The ERG identified a number of issues which the company resolved at clarification (see section 5.3 pages 104-105 of ERG report).

35

ERG exploratory analyses

1) ***Progression of HAQ score for patients on cDMARDs and BSC:***

- The ERG implemented a non-linear HAQ progression based on the latent classes' approach (Norton et al.) which was also implemented in the model developed by the AG in TA375

2) ***Transition from moderate to severe RA***

- At clarification the company updated its model to assume that those with moderate disease would progress to severe disease. The ERG noted that this progression would provide a more accurate representation of clinical practice although it acknowledged this assumption was not included by the AG in TA375
- The ERG identified 2 issues with the company's methods which it corrected in the exploratory analyses:
  - Calculating the DAS28 score of the patient at each cycle based on their DAS28 score at baseline, the change in HAQ score from baseline and the coefficient for HAQ score calculated by the company in their regression and used in their amended model
  - Assuming patients would transition to the severe state at the point when their DAS28 score increases above 5.1 without waiting until they have reached the end of the moderate sequence

36

The ERG noted that the company had assumed patients would go through the moderate sequences first and then transition to the sequences recommended for patients with severe RA, only if their HAQ progression score was above a certain threshold. This was calculated through a regression related to a DAS28 score of 5.1. The ERG noted that the changes in HAQ and DAS28 scores should have been calculated instead of the absolute scores. The relationship between these scores is not linear and by applying it to the changes in these scores instead of the absolute values, the error in the extrapolation is minimised. The company acknowledged that their regression resulted in a DAS28 score of 5.1 being predictive of an implausibly low HAQ score of 0.375.

Impact of the confidential PASs

- CTZ and GOL have non-confidential PASs
  - Incorporated into the previous analyses
- ABA and TCZ have confidential simple discount PASs
- ERG updated the company and ERG exploratory analyses to incorporate these discounts
  - Population C3 not included in confidential appendix as results do not change (TCZ and ABA not relevant comparators for this population)
- All results are deterministic, ERG noted that probabilistic unlikely to change conclusion.

37

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cDMARD-IR patients with severe RA who can tolerate MTX (A1)

Sequences*	Total QALYs	Total costs	Incr. QALYs	Incr. costs	ICER (per QALY)	Pairwise vs SAR (per QALY)
Company results following clarification						
TCZ (SC) + MTX#	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	**Dominated**
TCZ (IV) + MTX#	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	**Dominated**
SAR + MTX	[redacted]	[redacted]	[redacted]	[redacted]	-	-
TNFi bundle + MTX	[redacted]	[redacted]	[redacted]	[redacted]	£79,199	**£79,199**
ABT (SC) + MTX#	[redacted]	[redacted]	[redacted]	[redacted]	£206,188	**£126,110†**
ERG exploratory analyses						
TCZ (SC) + MTX#	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	**Dominated**
TCZ (IV) + MTX#	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	**Dominated**
SAR + MTX	[redacted]	[redacted]	[redacted]	[redacted]	-	
TNFi bundle + MTX	[redacted]	[redacted]	[redacted]	[redacted]	£151,563	**£151,563**
ABT (SC) + MTX#	[redacted]	[redacted]	[redacted]	[redacted]	£311,453	**£214,071**

*Sequences as defined in Table 42 of ERG report
#Does not include confidential PAS
†Approximate ICER calculated by the ERG based on incrementals

38

Company results: table 55 page 100 of ERG report
ERG results: table 63 page 110 of ERG report

ABT: abatacept; MTX: methotrexate; TCZ: tocilizumab; TNFi: tumour alpha necrosis inhibitor; SAR: sarilumab; IV: intravenous; SC: subcutaneous

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cDMARD-IR patients with severe RA who cannot tolerate MTX (B)

Sequences*	Total QALYs	Total costs	Incr. QALYs	Incr. costs	ICER (per QALY)	Pairwise vs SAR (per QALY)
Company results following clarification						
TNFi bundle	[redacted]	[redacted]	[redacted]	[redacted]	-	**£17,123‡**
SAR	[redacted]	[redacted]	[redacted]	[redacted]	£17,123	-
TCZ (SC) #	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	**£2,596,000†**
TCZ (IV) #	[redacted]	[redacted]	[redacted]	[redacted]	£1,578,976	**£1,578,976**
ERG exploratory analyses						
TNFi bundle	[redacted]	[redacted]	[redacted]	[redacted]	-	**£34,422‡**
SAR	[redacted]	[redacted]	[redacted]	[redacted]	£34,422	-
TCZ (SC) #	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dom.	**£2,541,618**
TCZ (IV) #	[redacted]	[redacted]	[redacted]	[redacted]	£1,676,280	**£1,676,280**

*Sequences as defined in Table 43 of ERG report
#Does not include confidential PAS
†Approximate ICER calculated by the ERG based on incrementals
‡ICER in the south western quadrant representing cost savings per QALY lost

39

Company results: table 57 page 101 of ERG report
ERG results: table 64 page 110 of ERG report

Ext. dom: extendedly dominated, TCZ: tocilizumab; TNFi: tumour alpha necrosis inhibitor; SAR: sarilumab; IV: intravenous; SC: subcutaneous

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TNFi-IR patients with severe RA who can tolerate RTX & MTX (C2)

Sequences*	Total QALYs	Total costs	Incr. QALYs	Incr. costs	ICER (per QALY)
Company results following clarification					
RTX	[redacted]	[redacted]	[redacted]	[redacted]	-
SAR	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dom.
RTX,TCZ‡#	[redacted]	[redacted]	[redacted]	[redacted]	£39,994
SAR,TCZ#	[redacted]	[redacted]	[redacted]	[redacted]	£130,691
ERG exploratory analyses					
RTX	[redacted]	[redacted]	[redacted]	[redacted]	
SAR	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dom.
RTX,TCZ‡#	[redacted]	[redacted]	[redacted]	[redacted]	£69,947
SAR,TCZ#	[redacted]	[redacted]	[redacted]	[redacted]	£171,466

*Sequences as defined in Table 44 of ERG report
#Does not include confidential PAS for TCZ
†Approximate ICER calculated by the ERG based on incrementals
‡Currently recommended sequence

40

Company results: table 58 page 102 of ERG report
ERG results: table 65 page 111 of ERG report

Ext. dom: extendedly dominated, RTX: rituximab; SAR: sarilumab

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TNFi-IR patients with severe RA who cannot tolerate RTX (C1)

Sequences*	Total QALYs	Total costs	Incr. QALYs	Incr. costs	ICER (per QALY)	Pairwise vs SAR (per QALY)
Company results following clarification						
SAR + MTX	[redacted]	[redacted]	[redacted]	[redacted]	-	
TCZ (IV) + MTX#	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dom.	**£141,995†**
TNFi Bundle + MTX	[redacted]	[redacted]	[redacted]	[redacted]	£64,602	**£64,602**
ABT (SC) + MTX#	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	**£80,889†**
TCZ (SC) + MTX#	[redacted]	[redacted]	[redacted]	[redacted]	£69,306	**£69,306**
ERG exploratory analyses						
TNFi bundle+ MTX	[redacted]	[redacted]	[redacted]	[redacted]	-	**£34,979‡**
ABT (SC) + MTX#	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	**Dominated**
SAR + MTX	[redacted]	[redacted]	[redacted]	[redacted]	£34,979	**-**
TCZ (IV) + MTX#	[redacted]	[redacted]	[redacted]	[redacted]	£198,863	**£198,863**
TCZ (SC)+MTX#	[redacted]	[redacted]	[redacted]	[redacted]	£777,770	**£205,638**

*Sequences as defined in Table 45 of ERG report
#Does not include confidential PAS
†Approximate ICER calculated by the ERG based on incrementals
‡ICER in the south western quadrant representing cost savings per QALY lost

1

The ERG noted that their sequences differ from those used by the company because the company had included bDMARDs in the second line of their treatment sequence. The ERG noted that this sequence is not in line with those recommended by NICE (see table 45 page 88 of ERG report).

Company results; Table 59 page 102 of ERG report
ERG results: Table 66 page 111 of ERG report

ABT: abatacept; Ext. dom,: Extendedly dominated, MTX: methotrexate; TCZ: tocilizumab; TNFi: tumour alpha necrosis inhibitor; SAR: sarilumab; IV: intravenous; SC: subcutaneous

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TNFi-IR patients with severe RA who cannot tolerate MTX (C3)

Sequences*	Total QALYs	Total costs	Incr. QALYs	Incr. costs	ICER (per QALY)
Company results following clarification					
TNFi Bundle	[redacted]	[redacted]	[redacted]	[redacted]	-
SAR	[redacted]	[redacted]	[redacted]	[redacted]	£17,794
ERG exploratory analyses					
TNFi Bundle	[redacted]	[redacted]	[redacted]	[redacted]	
SAR	[redacted]	[redacted]	[redacted]	[redacted]	£31,433

*Sequences as defined in Table 46 of ERG report

42

The ERG noted that this analysis is subject to considerable uncertainty given that the effectiveness estimates for the monotherapies were assumed to be equal to those in combination with MTX due to lack of evidence. The ERG also noted that TCZ, the only other IL-6 recommended by NICE for severe RA, is not recommended in this population.

The ERG further noted that the difference between the ICERs can be explained by the comparatively lower long-term HAQ progression whilst on cDMARDs based on the non-linear HAQ progression.

Company results: Table 60 page 103 of ERG report
ERG results: Table 67 page 112 of ERG report

TNFi: tumour alpha necrosis inhibitor; SAR: sarilumab

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TNFi-IR patients with severe RA who have received RTX + MTX (C4)

Sequences*	Total QALYs	Total costs	Incr. QALYs	Incr. costs	ICER (per QALY)	Pairwise vs SAR (per QALY)
Company results following clarification						
SAR + MTX	[redacted]	[redacted]	[redacted]	[redacted]	-	
TCZ (IV) + MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	**£141,995†**
TCZ (SC) + MTX	[redacted]	[redacted]	[redacted]	[redacted]	£133,548	**£133,548**
ERG exploratory analyses						
SAR + MTX	[redacted]	[redacted]	[redacted]	[redacted]	-	-
TCZ (IV) + MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	**£245,465**
TCZ (SC) + MTX	[redacted]	[redacted]	[redacted]	[redacted]	£219,153	**£219,153**

*Sequences as defined in Table 47 of ERG report
#Does not include confidential PAS
†Approximate ICER calculated by the ERG based on incrementals

43

Company results: table 61 page 103 of ERG report
ERG results: table 68 page 112 of ERG report

MTX: methotrexate; TCZ: tocilizumab; SAR: sarilumab; IV: intravenous; SC: subcutaneous

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cDMARD-IR patients with moderate RA (DAS28 between 4.0 and 5.1) who can tolerate MTX (A2)

Sequences*	Total QALYs	Total costs	Incr. QALYs	Incr. costs	ICER (per QALY)
Company results following clarification					
MTX	[redacted]	[redacted]	[redacted]	[redacted]	-
SAR + MTX	[redacted]	[redacted]	[redacted]	[redacted]	£38,254
ERG exploratory analyses					
MTX	[redacted]	[redacted]	[redacted]	[redacted]	
SAR + MTX	[redacted]	[redacted]	[redacted]	[redacted]	£63,438
*Sequences as defined in Table 48 of ERG report					

44

Company results: table 62 page 104 of ERG report
ERG results: Table 69 page 113 of ERG report

MTX: methotrexate; SAR: sarilumab;

Key issues: Cost effectiveness

- Do the Committee accept the ERG's changes to the company model:
  - Using a non-linear approach (Norton et al) for HAQ trajectory
  - Including the option for patients to receive treatment for severe disease when in the moderate state and their DAS28 score reaches 5.1.
- Is SAR comparable to the bDMARDs in both clinical and cost effectiveness?
- Is SAR monotherapy cost-effective?

45

Authors

- **Victoria Kelly**
  Technical Lead
- **Alexandra Filby**
  Technical Adviser
- with input from the Lead Team - **Andrew Renehan, Nigel Langford and David Chandler**

46

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Sarilumab for treating moderate-to-severe rheumatoid arthritis [ID994]

Company evidence submission

May 2017

File name	Version	Contains confidential information	Date
	1	**Yes**	**15 May 2017**

Contents

Tables

Figures

List of Abbreviations

ABT	Abatacept
ACR	American College of Rheumatology
ADA	Anti-drug antibody
AE	Adverse events
AESI	Adverse events of special interest
AG	Assessment Group
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
BID	Twice a day
BL	Baseline
BMI	Body mass index
BSC	Best Supportive Care
BSRBR	British Society for Rheumatology Biologics Register
BUN	Blood urea nitrogen
CADTH	Canadian Agency for Drugs and Technologies in Health
CBA	Cost-benefit analysis
CDAI	Clinical Disease Activity Index
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curves
CFB	Change from baseline
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CrI	Credible interval
CRP	C-reactive protein
CSR	Clinical study report
CUA	Cost-utility analysis
CVD	Cardiovascular disease
CXR	Chest X-ray
DAS	Disease activity
DMARD	Disease-modifying anti-rheumatic drugs
EMA	European Medicines Agency
EPAR	European public assessment report
ERAS	Early Rheumatoid Arthritis Study
ES	Erosion score
ESR	Erythrocyte sedimentation rate
ETN	Etanercept
EULAR	European League Against Rheumatism
FBC	Full blood count
FDA	US Food and Drug Administration
FOI	Freedom of information
HAQ	Health Assessment Questionnaire
HCQ	Hydroxychloroquine
HDL	High density lipoprotein
HEED	Health Economic Evaluation Database
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
INB	Incremental net monetary benefit
IR	Irresponsive
ITT	Intention-to-treat
JAK	Janus kinase
JSN	joint space narrowing
LDL	Low density lipoprotein
LMS	Least mean squares
LOCF	Last observation carried forward
LoE	Lack of efficacy

LS	Least squares
LSM	Least squares mean
LY	Life years
LYG	Life years gained
MCID	Minimal clinically important difference
MCS	Mental component summary
MH	Mantel-Haenszel
MHAQ	Modified Health Assessment Questionnaire
MMRM	Mixed model for repeated measures
MoA	Mode of Action
MTX	Methotrexate
NCPE	National Centre for Pharmacoeconomics
NCT	National Clinical Trial Identifier
NMA	Network meta-analysis
NNT	Number need to treat
NOAR	Norfolk Arthritis Register
OD	Once daily
OLE	Open-label extension
OMA	Other modes of action
OR	Odds ratio
ORv	Original review
PAS	Patient access scheme
PCS	Physical component summary
PFP	Pre-filled pen
PFS	Pre-filled syringe
PRO	Patient-reported outcome
PSSRU	Personal Social Services Research Unit
PT	Prothrombin time
PtGA	Patient global assessment of disease activity
QALY	Quality-adjusted life year
QoL	Quality of life
RA	Rheumatoid arthritis
RAQoL	Rheumatoid Arthritis Quality of Life
RCT	Randomised controlled trials
RD	Risk Difference
RF	Rheumatoid factor
RR	Response rate
RTX	Rituximab
SAE	Serious adverse events
SC	Subcutaneous
SD	Standard deviation
SDAI	Simplified Disease Activity Index
SI	Serious infections
SJC	Swollen joint count
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
TCZ	Tocilizumab
TEAE	Treatment-emergent adverse event
TFC	Tofacitinib
TJC	Tender joint count
VAS	Visual analogue scale

1 Executive summary

Key Points

Rheumatoid arthritis (RA) is a chronic autoimmune disease that imposes significant clinical and economic burden on patients, the NHS and society. If left untreated, or sub optimally treated, RA causes progressive and irreversible joint damage with increased functional disability over time.

Sarilumab, a new IL-6 pathway inhibitor, is a valuable addition to the current treatment options for RA, a chronic, and difficult to manage condition. It has demonstrated consistent improvement in disease activity and disability in multiple patient populations. The addition of sarilumab to the current RA treatment pathway for the NHS in England and Wales will provide the following clinical, patient, and economic benefits.

Sarilumab:

- Has a different mechanism of action to commonly used Tumour Necrosis Factor-alpha inhibitors (TNFis). In clinical trials, it has demonstrated consistent improvements in disease activity, and it inhibits progression of joint damage and improves physical functioning in different difficult-to-treat-patient populations, such as patients failing TNFis. The TARGET randomised controlled trial is the first trial demonstrating efficacy with a subcutaneous IL-6 inhibitor following failure or inadequate response to first biological disease-modifying anti-rheumatic drugs (bDMARD) treatment with TNFi
- As monotherapy demonstrates statistically superior clinical efficacy versus adalimumab (globally the most widely used biological disease-modifying anti-rheumatic drug (bDMARD)) monotherapy in MONARCH, a head-to-head study of patients intolerant to methotrexate (MTX)[1].
- Demonstrates similar efficacy and safety versus tocilizumab, the only other IL-6 pathway inhibitor recommended in the UK. At the price proposed in the simple patient access scheme it will result in cost savings compared with tocilizumab
- Demonstrates clinical and cost-effectiveness against all relevant comparators in a subgroup of patients with moderate disease at risk of rapid progression (disease activity score (DAS) >4.0 ≤5.1)
- Is a subcutaneous (SC) injection that offers an improved dosing schedule and stability compared to the other IL-6 on the market: every two weeks (Q2W) dosing rather than every week (QW) dosing; a second dose is available should patients

need it (200 mg Q2W and 150 mg Q2W); stable out of the fridge for 14 days rather than eight hours. These features offer patients convenience and give patients and clinicians more choice, in order to tailor therapies to specific patient needs.

Based on the results of a network meta-analysis, sarilumab in combination with MTX or as monotherapy, is shown to be a cost-effective option compared with all treatments in all patient groups identified in the NICE scope, with the exception of patients able to receive rituximab after TNFi failure.

The base-case incremental cost-effectiveness ratio (ICER) for sarilumab compared with current treatment options ranges from £7,583 to £22,275 per quality-adjusted life year (QALY) gained, depending upon place in therapy and/or comparator. Sensitivity analyses demonstrate these results to be stable under alternative assumptions. The marginal QALY differences between comparators and the non-statistically significant differences in NMA results mean that the cost-effectiveness estimates are only part of treatment decision making, alongside cost savings to the NHS and patient and clinician preference.

As a chronic lifelong disease, several therapeutic options are needed to effectively manage RA and reduce the burden on patients and the economic burden to the NHS. The availability of sarilumab, as combination therapy or monotherapy, gives more choice to patients in whom current treatments do not provide adequate disease control while offering ease and flexibility of use, with no additional economic burden on the NHS: Over the five years following the introduction of sarilumab, the range of expected savings for the NHS will be [redacted] to [redacted] in 2017 rising to [redacted] to [redacted] in 2021 under varying plausible assumptions for sarilumab uptake and comparator displacement.

1.1 Statement of decision problem

1.1.1 Disease background

Rheumatoid arthritis (RA) is a chronic, debilitating, irreversible autoimmune disease involving progressive destruction of the joints and a range of systemic manifestations, all of which contribute to the burden of this disease. If left untreated or treated suboptimally, RA can progress resulting in a wide range of complications, including irreversible joint damage, functional impairment and increased risk of cardiovascular disease. Both moderate and severe RA represent a substantial health burden both in terms of numbers of patients affected and the considerable economic impact in direct and indirect healthcare cost[2-7].

There is estimated to be approximately 400,000 people with RA in the UK[8]. Of these, around 10–15% have severe disease requiring biologic treatment[9]. Within two years of onset approximately one-third of people with RA stop work because of the disease. In 2009, direct healthcare costs to the NHS have been estimated at £560 million. The total costs of RA in the UK, including indirect costs and work-related disability, have been estimated at around £2.4 billion per year[10].

There is significant personal impact for people suffering with RA, their families and carers. Half of all RA patients report pain which interferes significantly with their daily lives — consequently patients often require help from family or friends or need their living space to be adapted[11]. As a result, patients report feeling depressed, having low self-esteem and being fearful about the impact of RA on their future life[12].

Considering the substantial burden of the disease, commissioning services that enable RA patients to be identified, assessed and diagnosed, and to start treatment as quickly as possible is vital to improve quality of life and prevent long-term disability[13].

1.1.2 Current treatment options

MTX is an effective cDMARD often recommended as first-line treatment in early RA. MTX can be used as monotherapy or, because of its additive efficacy benefits, it is typically used in combination with bDMARDs. However, various published studies report suboptimal adherence and persistence. A recent systematic review reported rates of MTX persistence ranged from 50% to 94% at 1 year and 25% to 79% at 5 years. The two-main reasons for discontinuation were lack of tolerability (23%–79%) and lack of efficacy (6%–72%)[14]. Other published studies report MTX intolerance/discontinuation ranging from 6%–21%[15,16]. Despite the highly variable reports of adherence, it is accepted that there is a cohort of patients that cannot be treated with MTX and require biologic monotherapy[17].

TNFis, introduced in the 1990s, have been a valuable addition to the management options for RA and are the most commonly used bDMARDs. Biological treatments are generally used in combination with MTX, but approximately 30% of patients use bDMARDs as monotherapy due to inadequate response or intolerance to MTX[18-20]. However, TNFis do not meet every patients' needs whether used as monotherapy or combination therapy:

- For patients that require a monotherapy, only etanercept, adalimumab and certolizumab are licensed for use in these patients[21-23], however, poorer outcomes are reported for patients treated with TNFi monotherapy compared with patients treated with combination TNFi; and MTX therapy: lower American College of

Rheumatology 20%, 50% and 70% (ACR20/50/70) response rates and radiographic outcomes[19]. Therefore, there is a need for further licensed, efficacious monotherapy treatment options that have advantages over TNFis used as monotherapy.

- A proportion of patients discontinue TNFi therapy due to an inadequate response, loss of response, or intolerance. Reported discontinuation rates are on average approximately 30% at 1 year and up to 50% at 2 years after initiation of treatment[24]. Switching to another TNFi following TNFi failure — a common practise known as 'TNFi cycling' — is associated with poorer outcomes, however switching to a bDMARD with an alternative mode of action provides a more effective treatment option[25-28].

Rituximab is a B-cell-depleting bDMARD with an alternative MoA to TNFi and is recommend by NICE in combination with MTX in adults with severe active RA who have had an inadequate response to, or are intolerant of other disease-modifying anti-rheumatic drugs (DMARDs) including at least one TNFi[9]. Rituximab demonstrates robust efficacy and cost-effectiveness in appropriate patients[17], but as with other current RA treatments, rituximab may not be a clinically optimal choice for some patients.

Rituximab is effective primarily in seropositive RA but alternate treatment options are needed in seronegative RA[29]. Some patients may not be suitable for treatment with rituximab due to comorbidities, concomitant medication, or intolerance associated with adverse events. Infusion-related reaction, the most common reported adverse event, is seen in 30–35% of patients at first infusion with fewer for the second. These reactions are generally mild (low grade fever; hypotension) but in rare cases reactions can be moderate-to-severe/fatal (fever >38.5ºC; chills; mucosal swelling; shortness of breath; hypotension). Risk of subsequent reaction can be reduced with concomitant glucocorticosteroids. Furthermore, rituximab has a slow onset of action and a response (i.e., some degree of improvement in disease activity) is usually seen in most patients by 16 weeks after the first infusion and re-treatment[29-32].

IL-6 receptor inhibitors are another RA treatment option with an alternative MoA to TNFis as they modulate both the innate and adaptive immune response implicated in RA pathogenesis[1,33,34]. Tocilizumab is an IL-6 receptor inhibitor recommended by NICE. It is administered by intravenous (IV) infusion every 4 weeks or by SC injection once a week. Once removed from the refrigerator, tocilizumab SC must be administered within 8 hours[35].

1.1.3 Unmet clinical needs

Current strategies focus on treatment with cDMARDs and bDMARDs with the aim of achieving a sustained clinical remission and thereby preventing disease progression, improving patients' function and quality of life and reducing the clinical and economic impact of RA[4,36-40].

As RA is a chronic, lifelong disease with multiple pathways implicated in the pathophysiology, several therapeutic options are needed to effectively treat and control RA over the course of the disease. Several efficacious and effective therapies are licensed and recommended by NICE, however, despite the availability of multiple cDMARDs and bDMARDs, lack of disease control remains a significant clinical issue and only a minority of RA patients achieve sustained clinical remission or low disease activity[41-47].

Overall there is a need for additional treatment options, both for monotherapy and for combination therapy, which offer clinical, cost and patient benefits for those patients in whom current treatments do not provide adequate disease control[7,41,48-52].

1.1.4 Moderate RA

Patients with moderate RA are an important but often poorly studied subgroup. There is a lack of NICE-recommended bDMARDs for moderate RA patients despite recommendations for clinical remission or low disease activity as key treatment targets[53]. Patients with moderate RA disease activity (DAS28 >3.2 to ≤5.1) may remain on cDMARDs rather than switching to more aggressive treatment strategies and thus are at risk of disease and radiographic progression[54]. According to UK clinicians, moderate patients with DAS28 >4 are those whose disease may be rapidly progressing; therefore, this subgroup of patients may benefit from bDMARD treatment.

1.1.5 Population

This submission considers sarilumab for the treatment of adults with moderate-to-severe active RA in combination with MTX or as monotherapy for patients who:

- Are inadequate responders to one or more cDMARDs (including MTX)
- Are intolerant to or inadequately respond to one or more bDMARDs (TNFi or other mode of action)
- Are intolerant to MTX or for whom continued MTX is inappropriate

In considering sarilumab in these populations, the NICE final scope for this appraisal is addressed.

Table 1.1 The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with moderate-to-severe, active RA, whose disease has not responded adequately to, or who are intolerant of cDMARDs or bDMARDs	As per final scope issued by NICE	N/A
Intervention	Sarilumab monotherapy or in combination with cDMARDs	As per final scope issued by NICE	N/A
Comparator(s)	People with moderate active RA that has not responded adequately to, or who are intolerant of therapy with cDMARDs: 1. Best supportive care *(A2)* People with severe active RA that has not responded adequately or who are intolerant to therapy with cDMARDs: 2. bDMARDs in combination with MTX (adalimumab (Humira®), etanercept (Enbrel®), infliximab (Remicade®), certolizumab pegol (Cimzia®), golimumab (Simponi®), tocilizumab (RoActemra®), abatacept (Orencia®)) *(A1)* 3. Adalimumab, etanercept, certolizumab pegol or tocilizumab (each as monotherapy) *(B)* People with severe active RA that has not responded adequately to, or who are intolerant of therapy with DMARDs including at least one TNFi: • Rituximab (MabThera®) in combination with MTX *(C2)* • When rituximab is contraindicated or withdrawn due to adverse events: o Abatacept, adalimumab, certolizumab pegol, etanercept, infliximab, tocilizumab, or golimumab, each in combination with MTX *(C1)* o Adalimumab, etanercept or certolizumab pegol (each as monotherapy) *(C3)* People with severe, active disease despite treatment with bDMARDs recommended according to NICE guidance: • Tocilizumab in combination with MTX, best supportive care *(C4)*	As per final scope issued by NICE	N/A
Outcomes	The outcome measures to be considered include:	As per final scope issued by	No data were identified to

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• Disease activity • Physical function • Joint damage • Pain • Mortality • Fatigue • Radiological progression • Extra-articular manifestations of the disease • Adverse effects of treatment • Health-related quality of life	NICE	incorporate extra-articular manifestations of the disease related to sarilumab
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 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	As per final scope issued by NICE	N/A
Subgroups to be considered	If evidence allows, the appraisal will consider subgroups of people identified as: • Having had primary or secondary failure of response to the first TNFi; or • Having seronegative or seropositive antibody status • People with moderate disease activity (DAS28 between 3.2 and 5.1) and severe active disease (DAS28 greater than 5.1)	The moderate patient subgroup is considered as part of the base-case set of analyses (see Comparators above)	No data was identified to enable robust comparative analysis based on previous TNF inhibitor failure or seropositive/sero negative antibody status
Special considerations including issues related to equity or equality	N/A	N/A	N/A

ACR20/50/70=American College of Rheumatology 20%/50%/70% improvement; AE=adverse event; bDMARD=biologic disease-modifying anti-rheumatic drugs; cDMARD=conventional disease-modifying anti-rheumatic drugs; DMARD=disease-modifying anti-rheumatic drugs;DAS28=28 joint count disease activity score; EULAR= European League Against Rheumatism; HAQ-DI=Health Assessment Questionnaire Disability Index; mTSS=modified Total Sharp Score; MTX=methotrexate; NA=not applicable; RA=rheumatoid arthritis; TNFi=tumour necrosis factor inhibitor; Q2W=once every 2 weeks

1.2 Description of the technology being appraised

Table 1.2 Technology being appraised

UK approved name and brand name	Sarilumab (brand name Kevzara®)
Mechanism of action	Sarilumab is a human immunoglobulin G1 (IgG1) monoclonal antibody that binds specifically to both soluble and membrane-bound interleukin-6 receptors (sIL-6Rα and mIL-6Rα) with high affinity thereby inhibiting IL-6-mediated signalling
Marketing authorisation/CE mark status	Marketing authorisation application for sarilumab was submitted on 14 July 2016. The CHMP issued a positive opinion on 21st April 2017. An EMA decision on marketing authorisation is expected in late June 2017
Indications and any restriction(s) as described in the Summary of Product Characteristics	Kevzara in combination with MTX 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 DMARDs. Kevzara can be given as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate (see Section 5.1 of SmPC)"
Method of administration and dosage	Sarilumab is administered as a SC injection once every 2 weeks. It is available as two doses, 150 mg and 200 mg, as a single use pre-filled pen or pre-filled syringe. Sarilumab is stable for 14 days after removal from the fridge.
Drug acquisition cost	[redacted] (200 mg or 150 mg pre-filled pen or pre-filled syringe), or, [redacted] (annual cost per patient) with the PAS

CHMP= Committee for Medicinal Products for Human Use; DMARD = disease-modifying anti-rheumatic drugs; EMA= European Medicines Agency; MTX=methotrexate; PAS=patient access scheme; RA=rheumatoid arthritis; SC=subcutaneous; SmPC= Summary of Product Characteristics; TNFi=tumour necrosis factor inhibitor

1.3 Summary of the clinical effectiveness of sarilumab

1.3.1 Summary of randomised controlled trials

The large, global, multicentre, clinical trial programme for sarilumab included nine Phase II and III, randomised controlled trials (RCTs), six of which are considered relevant to this appraisal based on the patient population and therapies assessed (Table 1.3).

MOBILITY (A/B), TARGET and MONARCH were primary efficacy trials[1,55-57]. ASCERTAIN is a safety trial (with efficacy as secondary endpoint) and EXTEND is an extension trial designed to determine long-term safety (primary endpoint) and efficacy of sarilumab (secondary endpoints)[58,59]. The TARGET trial was the first RCT demonstrating efficacy with a subcutaneous IL-6 pathway inhibitor following failure or inadequate response with a TNFi. The MONARCH trial is the only RCT of a subcutaneous IL-6 pathway inhibitor as monotherapy compared with adalimumab, globally the most widely used TNFi.

Table 1.3 Overview of relevant Phase II and Phase III sarilumab trials

Study	Study population	Intervention	Comparator	Reference
MOBILITY A	MTX-IR	Sarilumab + MTX	Placebo + MTX	*Huizinga 2014*[55], *Sanofi Genzyme Data on File*[60]
MOBILITY B	MTX-IR	Sarilumab + MTX	Placebo + MTX	*Genovese 2015*[56], *Sanofi Genzyme Data on File*[61]
TARGET	TNFi-IR/ intolerant	Sarilumab + cDMARD	Placebo + cDMARD	*Fleischmann 2017*[57], *Sanofi Genzyme Data on File*[62]
MONARCH	MTX-IR/ intolerant	Sarilumab	Adalimumab	*Burmester 2016*[1], *Sanofi Genzyme Data on File*[63]
ASCERTAIN (safety study)	TNFi-IR/ intolerant	Sarilumab + cDMARD	Tocilizumab + cDMARD	*Sanofi Genzyme Data on File*[58]
EXTEND (Long-term/ extension safety study)	cDMARD/TNFi-IR/ intolerant	Sarilumab + cDMARD, Sarilumab monotherapy	NA, Extension study	*Sanofi Genzyme Data on File*[59]

cDMARD=conventional disease-modifying anti-rheumatic drugs; cDMARD-IR = conventional disease-modifying anti-rheumatic drug irresponsive; MTX=methotrexate; MTX-IR=methotrexate-irresponsive; NA=not applicable; TNFi-IR=tumour necrosis factor inhibitor irresponsive.

Evidence from the sarilumab clinical trials programme demonstrated that, in addition to being well tolerated with a safety profile consistent with IL-6 blockade, sarilumab (in combination with MTX or as monotherapy) is an appropriate and effective treatment for patients who are unsuitable candidates for continued treatment with cDMARD/TNFi due to intolerance or an inadequate response, thus providing sustained efficacy regardless of patient treatment history[1,55-59].

1.3.1.1 Impact on signs and symptoms of RA

- MOBILITY B: Statistically significant improvements in ACR20 achieved in 66% of patients receiving sarilumab 200 mg Q2W and 58% of patients receiving sarilumab 150 mg Q2W at Week 24 compared to 33% of patients receiving placebo ($p<0.0001$). These improvements were observed as early as 2 weeks after initiation of sarilumab treatment and maintained to 52 weeks[56].

- TARGET: Similar improvements in ACR20 reported. At 24 weeks, ACR20 was achieved in 61% and 56% of patients receiving sarilumab 200 mg Q2W and 150 mg Q2W, respectively, compared with 34% for placebo ($p<0.0001$)[57].

1.3.1.2 Improvement in physical function

- MOBILITY B: Sarilumab significantly improves physical function as measured by changes in Health Assessment Questionnaire Disability Index (HAQ-DI) from

baseline: Sarilumab 200 mg Q2W and 150 mg Q2W (+MTX) versus placebo (+MTX) in HAQ-DI at 16 weeks (−0.55, −0.53, vs. −0.29; p<0.0001), and a greater proportion of patients achieving a clinically meaningful HAQ-DI response (change from baseline ≥0.3; p<0.0001 for 200 mg and p=0.0012 for 150 mg). These improvements in HAQ-DI were maintained to 52 weeks[56].

- TARGET: Sarilumab 150 mg Q2W and sarilumab 200 mg Q2W (+cDMARDs) resulted in statistically significant improvements versus placebo (+cDMARDs) in least squares mean (LSM) change from baseline in HAQ-DI at Week 12 (−0.46 and −0.47, vs. −0.26; p<0.001 vs. placebo for both comparisons), and a significantly greater proportion of patients achieved a clinically meaningful HAQ-DI response ≥0.3 (43.1% and 47.3% vs. 31.5%; p<0.05 for 150 mg and p<0.01 for 200 mg sarilumab[57].

1.3.1.3 Impact on radiographic disease progression

- MOBILTY: Sarilumab Q2W (+ MTX) significantly reduces progression of joint damage at 52 weeks compared to MTX alone (0.9, 0.25, and 2.78 with sarilumab 150 mg, sarilumab 200 mg, and placebo, respectively [p<0.0001 for each dose group versus placebo])[56].

- MOBIILTY: A statistically significantly greater percentage of patients receiving sarilumab 150 mg Q2W (48%) or 200 mg Q2W (56%) had no radiographic progression at Week 52 versus patients receiving placebo (38.7%; p<0.01 for sarilumab 150 mg versus placebo, and p<0.0001 for sarilumab 200 mg versus placebo)[56].

- Inhibition of radiographic progression is maintained at [redacted][59].

1.3.1.4 Sarilumab monotherapy

- MONARCH: Sarilumab 200 mg Q2W administered as monotherapy was superior to adalimumab 40 mg Q2W monotherapy as demonstrated by the primary endpoint of change from baseline in 28-joint disease activity score (DAS28)-erythrocyte sedimentation rate (ESR) (LSM difference: −1.077; p <0.0001), with no unexpected safety signals[1].

1.3.1.5 Sarilumab vs. tocilizumab

- The ASCERTAIN study (versus tocilizumab) evaluated safety as the primary endpoint and efficacy as an exploratory endpoint. The study demonstrated that sarilumab safety is [redacted] to that of tocilizumab in patients with

intolerance/inadequate response to TNFi and that sarilumab [redacted] with that of tocilizumab, only descriptive statistics are available for this study[58].

1.3.1.6 Summary quality of life results from the trials

- Sarilumab demonstrated statistically significant and clinically meaningful improvements across a broad range of patient-reported outcomes (PROs), e.g. physical components of Short Form-36 (SF-36) (MOBILITY; TARGET) mental components of SF-36 (MOBILITY), patient global assessment of disease activity (PtGA) (MOBILITY) as well as health-related quality of life (HRQoL) such as physical function, pain, fatigue, sleep, morning stiffness and participation in activities of daily living[1,55-57,64,65].

1.3.2 Network meta-analysis comparing sarilumab with other therapies

Summary conclusions from a network meta-analysis (NMA) evaluating the comparative efficacy and safety of sarilumab (150 mg and 200 mg Q2W) vs. licensed treatments demonstrates [redacted] (Table 1.4 and Table 1.5).

Table 1.4 Network meta-analysis comparing sarilumab with other therapies

cDMARD-IR population (combination therapy)	
ACR (20/50/70) responses (24 weeks)	[redacted]
DAS28 Remission (24 weeks)	[redacted]
Change in HAQ-DI (24 weeks)	[redacted]
EULAR good response (24 weeks)	[redacted]
EULAR moderate-to-good response (24 weeks)	[redacted]
mTSS (52 weeks)	[redacted]
Safety (52 weeks)	[redacted]
cDMARD-IR population (monotherapy)	
ACR (20/50/70) responses (24 weeks)	[redacted]
DAS28 Remission (24 weeks)	[redacted]
Change in HAQ-DI (24 weeks)	[redacted]
EULAR good and moderate-to-good	[redacted]

response (24 weeks)	
Safety	[redacted]
TNFi-IR population (combination therapy)	
ACR (20/50/70) responses (24 weeks)	[redacted]
DAS28 Remission (24 weeks)	[redacted]
Change in HAQ-DI (24 weeks)	[redacted]
EULAR good response (24 weeks)	[redacted]
EULAR moderate-to-good response (24 weeks)	[redacted]
Safety (24 weeks)	[redacted]

ACR20/50/70= American College of Rheumatology 20%, 50%, 70% improvement; cDMARD=conventional disease-modifying anti-rheumatic drug; DAS28=Disease Activity Score 28; ESR=erythrocyte sedimentation rate; EULAR=European League Against Rheumatism; HAQ-DI=Health Assessment Questionnaire Disability Index; IV=intravenous; IR=irresponsive; IT=intolerant; mTSS= modified Total Sharp Score; TNFi=tumour necrosis factor inhibitor

Table 1.5 Summary ACR20 response at 24 weeks for sarilumab 200 mg Q2W vs. comparators

cDMARD-IR population (combination therapy) - Median OR (95% CrI) sarilumab 200 mg combination vs. other combinations					
	vs. cDMARDs	**vs. TNFis**	**vs. tocilizumab IV (8 mg/kg)**	**vs. tocilizumab SC**	**vs. abatacept**
Odds ratio (OR)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
cDMARD-IR population (monotherapy) - Median OR (95% CrI) sarilumab 200 mg monotherapy vs. other monotherapies					
	vs. placebo	**vs. TNFis**	**vs. tocilizumab IV (8 mg/kg)**	**vs. tocilizumab SC**	**vs. abatacept**
Odds ratio (OR)	[redacted]	[redacted]	[redacted]	-	-
95% CI	[redacted]	[redacted]	[redacted]	-	-
TNFi-IR population (combination therapy) - sarilumab 200mg combinations vs. other combinations					
	vs. cDMARDs/MTX	**vs. golimumab (TNFis)**	**vs. tocilizumab IV (8 mg/kg)**	**vs. tocilizumab SC**	**vs. abatacept**
Risk Difference (RD)	[redacted]	[redacted]	[redacted]	-	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	-	[redacted]

ACR20= American College of Rheumatology 20% improvement; cDMARD=conventional disease-modifying anti-rheumatic drug; CI=confidence interval; CrI=credible interval; MTX=methotrexate; IR=irresponsive; IV=intravenous; OR=odds ratio; Q2W=once every 2 weeks; SC=subcutaneous; TNFi=tumour necrosis factor inhibitor
– =no data

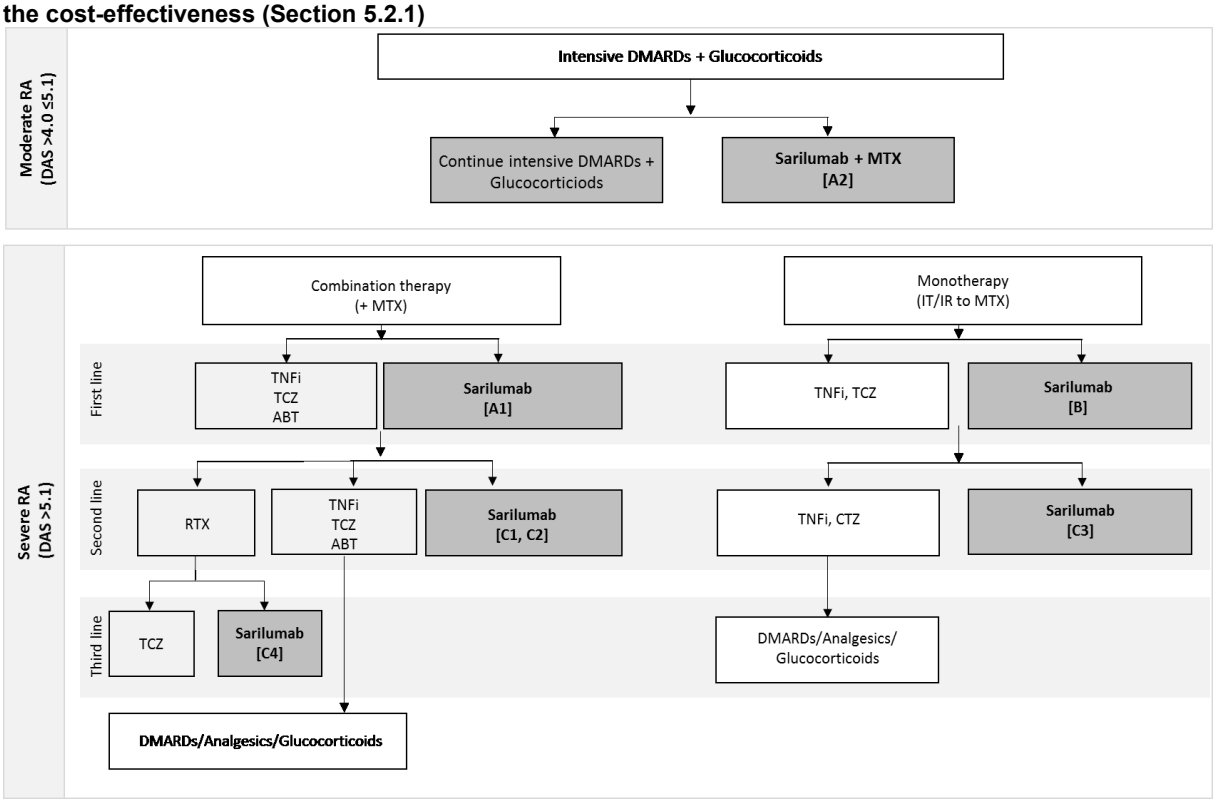
1.4 Anticipated place in therapy

Sarilumab is the second biological IL-6 inhibitor to be approved for the treatment of adult patients with moderate-to-severe active RA who have had inadequate response to, or intolerance to, one or more bDMARD or cDMARD[66]. The first IL-6 inhibitor approved and recommended by NICE for the treatment of RA, is tocilizumab.

Based on its mechanism of action, license indication and UK expert opinion, sarilumab would be considered for utilisation in the same patient populations and at the same point in NICE RA treatment pathway as tocilizumab (Figure 1.1). Currently, tocilizumab IV and SC usages constitutes [redacted] of the UK biologic market (see Section 6). For this submission, tocilizumab is regarded as the most relevant comparator for sarilumab in severe disease. As shown below (Figure 1.1), sarilumab may also be an option in a subset of patients with moderate disease most at risk of progression (defined, for the purpose of this submission, as DAS >4 ≤5.1).

A1/A2, B, C1-C4 are based on the populations defined for the economic model discussed below in Section 1.5.

Figure 1.1 Anticipated place in therapy for sarilumab within the UK showing population assessed within the cost-effectiveness (Section 5.2.1)



ABT=abatacept; ADA=adalimumab; DMARD=disease-modifying anti-rheumatic drug; CTZ=certolizumab; DAS=disease activity score; ETN=etanercept; GC=glucocorticoids; GOL=golimumab; IR=irresponsive; IT=intolerant; MTX=methotrexate; RA=rheumatoid arthritis; RTX=rituximab; TCZ=tocilizumab; TNFi=tumour necrosis factor inhibitor

1.5 Summary of the cost-effectiveness analysis

A cost-effectiveness analysis was undertaken comparing sarilumab with current standard of care bDMARDs across a range of places in therapy (see Figure 1.1 above) from the perspective of the NHS in England and Wales, over a lifetime time horizon. The analysis utilised an economic model which was in line with the majority of models identified in the systematic literature review (SLR), most notably the assessment group models in TA375 and TA195, which have been used and accepted by NICE[67,68.]

1.5.1 Model structure

A de novo patient-level state transition model was developed to assess the cost-effectiveness of sarilumab in patients with moderate-to-severe RA after failure or intolerance to cDMARDs or after failure of at least one TNFi. The model evaluates severe, active RA (defined by baseline DAS28 >5.1) and a subset of moderate, active RA who are at risk of rapid progression. Based on clinical expert feedback this population is defined as those with a baseline DAS28 >4.0 ≤5.1. The full range of comparators included in this scope and recommended by NICE are considered but with a particular focus on the comparison with tocilizumab.

1.5.1.1 Cycle 1 of each treatment

In the first cycle, the model uses a decision tree/'tunnel state' structure to assign one of three possible outcomes:

i. Response/continuation: patients achieve at least moderate European League Against Rheumatism (EULAR) response and continue with the initial treatment
ii. Non-response: patients who do not achieve at least a moderate EULAR response start the subsequent-line of treatment
iii. Death: patients can die

1.5.1.2 Cycles 2+ of each treatment

If response is achieved after the initial six months, for every following cycle patients have either:

i. Continued response: patients stay on treatment
ii. Loss of response: move to subsequent-line of treatment, or,
iii. Loss of response: move to Best Supportive Care (BSC) consisting of cDMARD/non-biologic treatment
iv. Death

1.5.1.3 Patient population

The population considered in the model are patients with moderate-to-severe RA who have failed or are intolerant to cDMARDs or who have failed at least one TNFi.

Given the complexity of the RA treatment pathway we have named populations based on the place in the treatment pathway and whether they can tolerate MTX and/or rituximab in line with the scope, see Table 1.6**.** The patient population is informed by individual patient-level data from the sarilumab trials as shown in Table 1.6**.**

Table 1.6 Populations assessed in the de novo analysis

Population label	Description	Patient profile source
A1	Patients with severe active RA that has not responded adequately to, or are intolerant of therapy with cDMARDs (combination with MTX)	MOBILITY B
A2	Patients with moderate active RA that has not responded adequately to, or are intolerant of therapy with cDMARDs (combination with MTX), at risk of rapid progression	MOBILITY B
B	Patients with severe active RA that has not responded adequately to, or are intolerant of therapy with cDMARDs (monotherapy)	MONARCH
C1	Patients with severe active RA that has not responded adequately to, or are intolerant of therapy with DMARDs including at least one TNFi (RTX intolerant in combination with MTX)	TARGET
C2	Patients with severe active RA that has not responded adequately to, or are intolerant of therapy with DMARDs including at least one TNFi (RTX tolerant in combination with MTX)	TARGET
C3	Patients with severe active RA that has not responded adequately to, or are intolerant of therapy with DMARDs including at least one TNFi (RTX intolerant in monotherapy)	TARGET
C4	Patients with severe, active disease despite treatment with bDMARDs recommended according to NICE guidance (combination with MTX)	TARGET

bDMARD=biological disease-modifying anti-rheumatic drugs; cDMARD=conventional disease-modifying anti-rheumatic drugs; DMARD=disease-modifying anti-rheumatic drugs; MTX=methotrexate; RA=rheumatoid arthritis; RTX=rituximab; TNFi=tumour necrosis factor inhibitor;

1.5.1.4 Model inputs

Clinical parameters included EULAR-based treatment response, HAQ-DI changes and trajectory following response, time to discontinuation, mortality and serious infection (only adverse events included - similar rate applied to all bDMARDs). Utilities were estimated from patient HAQ-DI using the algorithm developed by the assessment group in TA195 (NICE TA195). Costs and resource use included drug acquisition and administration, serious infection as an adverse event, routine costs defined by HAQ-DI scores, and monitoring costs associated with treatment and the disease.

1.5.1.5 Model results

Results from the economic analysis are presented in Table 1.7. In line with convention for presenting fully incremental cost-effectiveness results, the anchor comparator for each analysis is given first in the table. Sarilumab is highlighted in the table. The value in the incremental cost per QALY gained (£) column is the result of the incremental analysis where only the comparators that represent efficient resource allocation have numerical values. The value 'dominated' signifies that the product in the corresponding row does not represent an efficient resource allocation due to comparators in the preceding rows having an equivalent or greater QALY benefit at lower cost. Therefore, in population A1 below, sarilumab has an estimated incremental cost per QALY gained of £9,631 compared with a TNFi bundle meanwhile tocilizumab SC, tocilizumab IV, and abatacept SC are all dominated by sarilumab i.e., sarilumab is less costly and more effective and therefore more efficient. Whilst interpreting the results, it is important to recognise the [redacted] and the non-statistically significant differences in response from the NMA that contribute to these.

Table 1.7 Incremental cost-effectiveness results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY gained (£)
Population A1: Patients with severe active RA that has not responded adequately to, or are intolerant of therapy with cDMARDs (combination with MTX)					
TNFi + MTX	[redacted]	[redacted]	-	-	-
Sarilumab + MTX	[redacted]	[redacted]	[redacted]	[redacted]	**£9,631**
TCZ SC + MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
TCZ IV + MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
ABT SC + MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Population A2: Patients with moderate active RA that has not responded adequately to, or are intolerant of therapy with cDMARDs (combination with MTX), at risk of rapid progression					
BSC	[redacted]	[redacted]	-	-	-
Sarilumab	[redacted]	[redacted]	[redacted]	[redacted]	**£22,275**
Population B: Patients with severe active RA that has not responded adequately to, or intolerant of therapy with cDMARDs (monotherapy)					
TNFi	[redacted]	[redacted]	-	-	-
Sarilumab	[redacted]	[redacted]	[redacted]	[redacted]	**£12,995**
TCZ IV	[redacted]	[redacted]	[redacted]	[redacted]	£1,013,528
TCZ SC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Population C1: Patients with severe active RA that have not responded adequately to, or are intolerant of therapy with DMARDs including at least one TNFi (RTX intolerant in combination with MTX)					
TNFi + MTX	[redacted]	[redacted]	-	-	-
Sarilumab + MTX	[redacted]	[redacted]	[redacted]	[redacted]	**£7,583**
TCZ SC + MTX	[redacted]	[redacted]	[redacted]	[redacted]	£77,024
TCZ IV + MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
ABT SC + MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Population C2: Patients with severe active RA that have not responded adequately to, or are					

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY gained (£)
intolerant of therapy with DMARDs including at least one TNFi (RTX tolerant in combination with MTX)					
RTX IV + MTX	[redacted]	[redacted]	-	-	-
Sarilumab + MTX	[redacted]	[redacted]	[redacted]	[redacted]	**£104,012**
Population C3: Patients with severe active RA that have not responded adequately to, or are intolerant of therapy with DMARDs including at least one TNFi (RTX intolerant in monotherapy)					
TNFi + MTX	[redacted]	[redacted]	-	-	-
Sarilumab + MTX	[redacted]	[redacted]	[redacted]	[redacted]	**£13,878**
Population C4: Patients with severe, active disease despite treatment with bDMARDs recommended according to NICE guidance (combination with MTX)					
BSC	[redacted]	[redacted]	-	-	-
Sarilumab + MTX	[redacted]	[redacted]	[redacted]	[redacted]	**£18,394**
TCZ SC + MTX	[redacted]	[redacted]	[redacted]	[redacted]	£63,276
TCZ IV + MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

ABT=abatacept; BSC=best standard of care; DMARD-disease-modifying anti-rheumatic drug; ICER=incremental cost-effectiveness ratio; IV=intravenous; MTX=methotrexate; QALYs=quality-adjusted life years; RA=rheumatoid arthritis; SC=subcutaneous; RTX=rituximab; TCZ=tocilizumab; TNFi=tumour necrosis factor inhibitor

1.5.2 Discussion of results and sensitivity analysis

Sarilumab was shown to be cost-effective at willingness-to-pay thresholds of £20K to £30K per QALY gained in all populations evaluated, with ICERs ranging from £7,583 to £22,275 per QALY gained, with the exception of rituximab-tolerant patients in the TNFi inadequate responder (TNF-IR) population where the ICER was £104,012 per QALY gained.

In sensitivity analyses, the results suggest sarilumab remains cost-effective at willingness-to-pay thresholds of £20K to £30K per QALY gained in all populations. In the probabilistic sensitivity analysis, sarilumab is associated with ICERs of £7,948, £13,586 and £6,222 per QALY gained from incremental analysis in the following populations of patients with severe, active disease respectively:

- A1: cDMARD-IR, combination therapy, compared with bDMARDs
- B: cDMARD-IR, monotherapy, compared with bDMARDs
- C1 TNF-IR (RTX intolerant) combination therapy, compared with bDMARDs

The NMA reports overlapping credible intervals for many of the outcomes for sarilumab compared with all comparators, specifically tocilizumab. Based on this, a cost-minimisation scenario analysis assuming no clinically meaningful differences between sarilumab and tocilizumab SC was undertaken. This demonstrates that sarilumab offers cost savings to the NHS of approximately [redacted] per patient across all relevant RA populations over 12 months, compared with tocilizumab SC.

1.6 Conclusion

RA is a chronic progressive disease which requires long-term treatment. There have been advances in the treatment of RA in recent years; however, not all available therapies work for every patient and there remains an unmet need for new therapeutic options.

Sarilumab is an IL-6 receptor antagonist, with a different MoA to that of the commonly used TNFis. The extensive clinical trial programme, in different patient populations demonstrates sarilumab has proven efficacy in patients with an inadequate response to both cDMARDs and TNFis, and has demonstrated superior efficacy versus a widely prescribed TNFi (adalimumab) in monotherapy. With the exception of rituximab-tolerant patients, the evidence presented in this submission demonstrates that sarilumab, in combination with MTX and as monotherapy, is a cost-effective option compared with standard of care bDMARDs and best supportive care for all patient groups identified in this NICE scope.

Sarilumab is the only IL-6 pathway inhibitor available as an auto-injectable pre-filled pen administered SC fortnightly with two doses (200 mg and 150mg) enabling dose reduction as needed and is stable out of the fridge for up to 14 days; thus, the formulation offers practical advantages over tocilizumab. Like tocilizumab SC, sarilumab will be offered with a homecare service. UK clinical opinion suggests sarilumab is likely to be used in place of tocilizumab in severe RA patients who do not adequately respond to TNFis or who are intolerant to MTX, and that the addition of biologics as an option for treating patients with moderate disease activity would be welcomed.

In addition to being cost-effective versus tocilizumab, the uptake of sarilumab among patients eligible for biologic treatment is expected to generate considerable savings to the NHS ranging from [redacted] (in a scenario where [redacted] of projected uptake is from [redacted]and[redacted] from [redacted]) to [redacted] (in a scenario where [redacted] of projected uptake is from [redacted]) from118 patients in 2017. In 2021 the expected savings range from [redacted] to [redacted]from 2,017 patients in the same scenarios.

Sarilumab offers practical benefits for patients and can help reduce the economic burden of RA to the NHS via a simple PAS. A positive recommendation from NICE, based on the clinical and cost-effectiveness for sarilumab, will facilitate greater choice for patients and clinicians.

2 The technology

2.1 Description of the technology

Brand Name: KEVZARA®

Approved name: Sarilumab

Therapeutic class: IL-6 receptor inhibitor

Wider class: Biologic disease-modifying anti-rheumatic drug (bDMARD)

Sarilumab is the first fully human immunoglobulin G1 (IgG1) monoclonal antibody that binds specifically and with high affinity to both soluble and membrane-bound interleukin-6 receptors (sIL-6Rα and mIL-6Rα) thereby inhibiting interleukin-6 (IL-6)-mediated signalling by blocking the alpha subunit. Sarilumab blocks these dual signalling pathways and effects the innate and adaptive arms of the immune system and as a consequence, sarilumab impacts both the articular and systemic manifestations of Rheumatoid Arthritis (RA)[52,69-71].

Sarilumab (Kevzara®), is the only IL-6 receptor inhibitor available as an auto-injectable pre-filled pen administered subcutaneously (SC) every other week, has two doses (200 mg and 150 mg) enabling dose reduction as needed and is stable out of the fridge for up to 14 days.

It is an effective, well tolerated bDMARD and the latest IL-6 inhibitor to be approved as combination therapy or monotherapy for patients with moderate-to-severe RA[72]. In clinical trials, sarilumab has been shown to inhibit progression of joint damage and to improve physical function[1,55-59]. The sarilumab Phase III clinical trial programme involved more than 2,500 adults with moderate-to-severe active RA who had an inadequate response to previous treatment regimens[1,55-58,60-63].

It is now well established that cytokines such as tumour necrosis factor α (TNFα) and IL-6 play a critical role in the pathophysiology of RA (Section 2.5.1)[7,52,71]. In patients with RA, elevated levels of the pro-inflammatory cytokine IL-6 in the serum and synovial fluid are closely associated with synovitis, systemic inflammation, bone metabolism, fatigue and joint destruction[69]. Studies have demonstrated that IL-6 has multiple roles in the initiation and maintenance of the RA inflammatory pathway. It is involved in the shift from acute to chronic inflammation, contributes to bone destruction and is a key mediator in maintaining established disease. IL-6 is therefore one of the key therapeutic targets to control RA[7,52,71,73].

2.2 Marketing authorisation/CE marking and health technology assessment

2.2.1 European marketing authorisation

The marketing authorisation application for sarilumab was submitted on 24th June 2016. The CHMP issued a positive opinion on 21st April 2017[72]. An EMA decision on marketing authorisation is expected in June 2017.

The confirmed indication in the UK is as follows:

- Kevzara in combination with methotrexate (MTX) is indicated for the treatment of moderately to severely active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs. Kevzara can be given as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate.

The contraindications in the draft Summary of Product Characteristics are hypersensitivity to the active substance or any of the excipients—histidine, arginine, polysorbate 20 and sucrose.

The draft SmPC and the European public assessment report (EPAR) are provided in Appendix 1.

Sarilumab will be available in the UK following marketing authorisation (expected late June 2017). It is currently approved and available in Canada and will subsequently be made available in the US, continental Europe, Asia, Australasia, South America, Africa and the Middle East.

Sarilumab is anticipated to be reviewed by the Scottish Medicines Consortium (SMC) in Q3 2017, and the National Centre for Pharmacoeconomics (NCPE) in Ireland in Q4 2017.

2.3 Administration and costs of the technology

Table 2.1 Costs of the technology being appraised

	Cost	Source
Pharmaceutical formulation	Solution for injection in a pre-filled pen (PFP) and pre-filled syringe (PFS) containing 150 mg or 200 mg sarilumab in 1.14 mL solution (131.6 mg/mL or 175 mg/mL) respectively.	SmPC
Acquisition cost (excluding VAT)	The list price per pack excluding VAT is £457.69 for one PFS or PFP. The prices for both the 150mg and 200 mg doses are the same. A simple PAS has been agreed with the Department of Health under which sarilumab will be available to the NHS at a cost of [redacted]	Sanofi Genzyme confidential information
Method of administration	Subcutaneous (SC) injection.	SmPC
Doses	150 mg and 200 mg as a single use PFP or PFS.	SmPC
Dosing frequency	Once every 2 weeks (Q2W).	SmPC
Average length of a course of treatment	Treatment continues for as long as patients are adequately responding to treatment.	NICE Pathways*
Average cost of a course of treatment	No average length of treatment with sarilumab has been determined as patients are expected to be treated for as long as response is adequately maintained and in line with NICE guidance. The annual cost of sarilumab is £11,900. [redacted]	NICE Pathways* / Sanofi Genzyme confidential information
Anticipated average interval between courses of treatments	NA — continuous treatment for as long as response is adequately maintained in line with NICE guidance.	NICE Pathways*
Anticipated number of repeat courses of treatments	NA — continuous treatment for as long as response is adequately maintained in line with NICE guidance.	NICE Pathways*
Dose adjustments	The recommended dose of sarilumab is 200 mg Q2W • Reduction of dose from 200 mg Q2W to 150 mg Q2W is recommended for management of neutropenia, thrombocytopenia, and liver enzyme elevations • No dose adjustment is required in patients with mild to moderate renal impairment (note: no data is available for patients with severe renal impairment) • The efficacy and safety of sarilumab has not been studied in patients with hepatic impairment • No dosage adjustment is required in patients over 65 years of age • The efficacy and safety of sarilumab has not yet been established in children up to 18 years of age. Paediatric studies are ongoing.	SmPC
Anticipated care setting	Sarilumab treatment should be initiated and supervised by an experienced physician/rheumatologist. It is anticipated that sarilumab maintenance treatment would be provided in a home care setting, with self-administration of fortnightly maintenance injections. A home care service is provided and funded by Sanofi Genzyme	Sanofi Genzyme

*NICE Pathways – Drug treatment for rheumatoid arthritis[74]
NA=not applicable; PFP=pre-filled pen; PFS=pre-filled syringe; Q2W=once every 2 weeks; SC=subcutaneous, SmPC=Summary of Product Characteristics

2.4 Changes in service provision and management

Sarilumab is anticipated to be initiated in secondary care by healthcare professionals experienced in the diagnosis and treatment of RA (SmPC)[66]. Sarilumab is self-administered or administered by a caregiver once every 2 weeks (Q2W) via a pre-filled syringe or pre-filled pen (Appendix 2.1 and 2.2). It is likely to offer a reduced use of NHS resources compared with intravenously (IV) administered or more frequently administered SC products.

The eligible population for sarilumab is likely to be those patients eligible for bDMARD treatment under current NICE guidance; as such this is a well recognised patient population that is managed in specialist rheumatology centres.

The following monitoring schedules are stated in the SmPC and these do not represent a change in requirements to the currently available bDMARDs:

- Neutrophil count should be monitored 4–8 weeks after start of therapy and according to clinical judgement thereafter
- Platelets should be monitored 4–8 weeks after the start of therapy and according to clinical judgement thereafter
- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) should be monitored 4–8 weeks after start of therapy and every 3 months thereafter
- Lipid parameters should be monitored 4–8 weeks after the start of therapy and at approximately 6-month intervals thereafter.

2.5 Innovations

Adequate disease control in RA patients leads to decreased healthcare utilisation — patients have fewer inpatient admissions/inpatient days, fewer visits to accident and emergency departments and less use of other medical services[4,36-40,53,75]. However, despite existing treatments, many patients do not achieve adequate disease control which adds to the cumulative clinical and economic burden of disease severity[41-47,76].

Sarilumab is the first, human IgG1 monoclonal antibody directed against the alpha subunit of the IL-6 receptor to be made available. Sarilumab blocks binding of IL-6 to its receptor interrupting the cytokine-mediated inflammatory signalling cascade that is central in disease pathophysiology. In patients with moderate-to-severe RA, sarilumab offers an alternative

mode of action to the more commonly used tumour necrosis factor inhibitors (TNFi), and is offered to the NHS at a lower cost than the current IL-6 treatment available (Section 5.1.2).

In moderate-to-severe RA sarilumab is a valuable addition to the currently available therapies.

2.5.1 In moderate-to-severe RA sarilumab is a valuable addition to the currently available therapies Sarilumab targets multiple steps in the rheumatoid arthritis pathway

The pivotal roles of IL-6 and tumour necrosis factor-alpha (TNFα) in the regulation of the innate immune response in RA are well defined[7,52,71]. Cytokines IL-6, IL-21, IL-23, and IL-17 drive adaptive immune activation/differentiation and loss of tolerance in preclinical or early RA, and IL-6 and TNFα dominate the transition to chronicity or the maintenance of established disease. (Figure 2.1)[52,71].

Persistently elevated IL-6 levels contribute to the disruption of homeostasis in many cell types and physiologic processes throughout the body[69]. The widespread effects of IL-6 stem from its versatile signalling, which allows it to interact with a broad range of cells and tissues[52,69,71].

IL-6 signals through both membrane-bound and soluble receptor and differentiates IL-6 signalling from that associated with other cytokines such as TNFα. This dual signalling mechanism means IL-6 contributes to both the articular and systemic manifestations of RA[52,69-71].

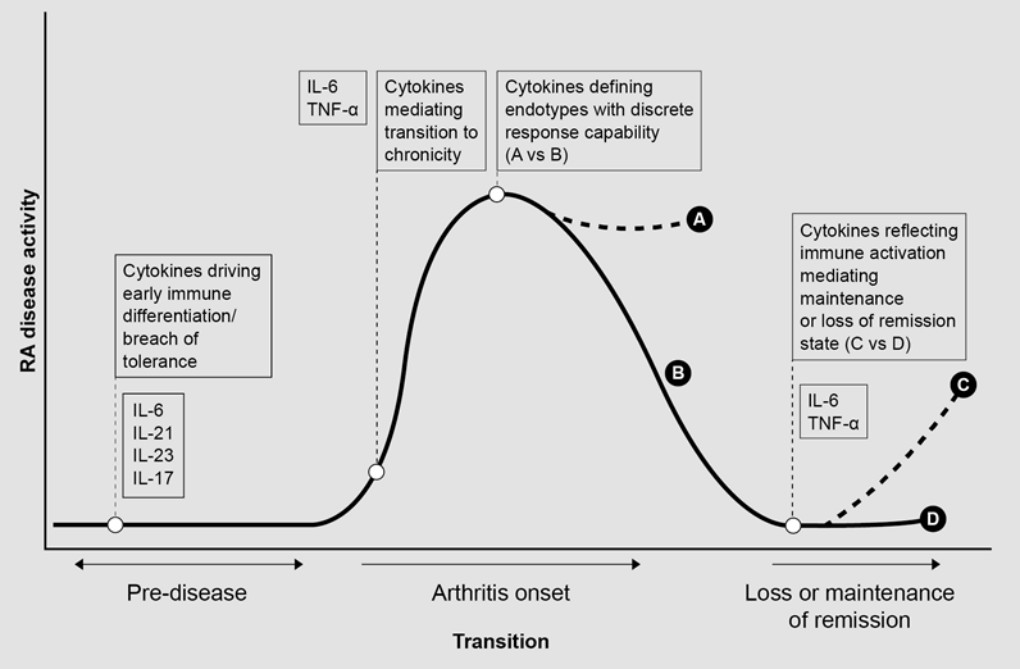
IL-6 promotes chronic inflammation by stimulating interactions between both the innate and adaptive arms of the immune system[52,69-71]:

- IL-6 is first released by neutrophils and other infiltrating cells of the innate immune system
- IL-6 also facilitates generation of the adaptive immune response by stimulating B cells and T cells and fostering interactions between the two cell types

Cytokine profiles may provide novel insights into the application of cytokine-targeting therapies. For example, cytokine signatures could separate those patients likely to fail or respond to a given intervention, and once in remission those patients likely to flare or remain in a low disease activity state. While IL-6 has similar effects to TNFα in the local synovial

environment, IL-6 also enters the circulation to mediate systemic aspects of the innate response, including induction of the acute phase and febrile responses (Figure 2.1)[71].

Figure 2.1 Cytokine profiles at discrete phases of the rheumatoid arthritis disease process[71]



Patients destined to fail (A) or respond to (B) a given intervention, and once in remission those patients destined to flare (C) or remain in a low disease activity state (D).
IL=interleukin; RA=rheumatoid arthritis; TNF=tumour necrosis factor

2.5.2 Sarilumab posology—subcutaneous dosing (once every 2 weeks) with pre-filled pen or pre-filled syringe and the flexibility of two doses

Tocilizumab is currently the only NICE-recommended IL-6 receptor inhibitor available in the UK. It is administered by intravenous (IV) infusion every 4 weeks (Q4W) or by subcutaneous (SC) injection once a week (QW). Once removed from the refrigerator, tocilizumab SC must be administered within 8 hours[77].

Sarilumab is administered SC once every 2 weeks (Q2W) via a pre-filled syringe or innovative, ergonomic, pre-filled pen designed with patients input (Appendix 2.1 and 2.2). Design of the pre-filled pen was informed directly from [redacted] in-depth interviews with patients and their carers across France [redacted], Germany [redacted], UK [redacted] and the USA [redacted], further details are provided in Appendix 3. The pre-filled pen has demonstrated [redacted] when used in RA patients in an [redacted] setting[78]. Dose flexibility can increase patient choice and provide tailored treatment for a patient's individual needs. Sarilumab combines flexibility and ease with two SC doses (a 200 mg dose and a lower 150 mg dose for managing laboratory abnormalities in patients who experience issues while taking the 200 mg dose) via a pre-filled pen or pre-filled syringe[66].

3 Health condition and position of the technology in the treatment pathway

Key points

- Rheumatoid arthritis (RA) is a chronic, debilitating, irreversible autoimmune disease involving progressive destruction of the joints and a range of systemic manifestations, all of which contribute to the burden of this disease[2-7].
- National and international treatment strategies focus on early, aggressive, disease-modifying therapies aiming to achieve sustained clinical remission or low disease activity and thereby preventing disease progression, improving quality of life and reducing the clinical and economic impact of RA and the disability it can cause[4,36-40,79].
- Despite treatment advances there remains a considerable unmet need in RA as treatment failure/loss of response, intolerance and toxicity limit disease control and impact clinical and patient outcomes[41-47].
- After tumour necrosis factor inhibitor (TNFi) failure, patients may switch to an alternative TNFi (TNFi cycling) or switch to a biological disease-modifying anti-rheumatic drug (bDMARD) with an alternative mode of action.
    - TNFi cycling is associated with poorer outcomes than switching to a different mode of action: clinically significant responses were observed in fewer than 50% of patients with RA who cycle to a second TNFi and the likelihood of response to a subsequent TNFi decreases with increasing number of previous TNFi treatments[80]. Patients who switch to a different mode of action following TNFi failure have better outcomes (greater clinical efficacy in terms of change in disease activity score [DAS28] and European League Against Rheumatism [EULAR] response) and are significantly more likely to continue therapy than TNFi cyclers[25-28,81].
- Sarilumab (Kevzara®) in combination with methotrexate (MTX) 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). Sarilumab can be given as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate.

3.1 Disease overview

Rheumatoid arthritis (RA) is a chronic, debilitating, progressive and irreversible inflammatory autoimmune disease. As such, it is a recognised long-term condition within the NHS. RA primarily affects those joints that are lined with synovium — tissue that is responsible for the nutrition and lubrication of the joints. Inflammation of the joints — usually hands and feet — leads to bone erosions, cartilage destruction and joint deformity — causing widespread pain and severe disability[3-7].

RA is a systemic disease and does not just affect the musculoskeletal system, but can affect the whole body, including the cardiovascular system, lungs, heart, eyes and small blood vessels (vasculitis)[82]. Results of a recent nationwide population-based cohort study in 2014 estimate that around 400,000 people in the UK have RA with around 26,000 new diagnoses occurring each year[8]. Of these approximately 15% of people will have severe disease[9,17].

The disease course for RA is highly variable[83]. Generally, there is no evidence of joint destruction in early RA (stage I) disease, although there may be swelling of soft tissue and perhaps some evidence of bone erosion[84]. Moderate (stage II) RA is characterised by evidence of joint destruction, and a narrowing of the joint space and adjacent muscle atrophy may limit mobility. Patients with severe RA (stage III) typically have a loss of joint cartilage, and symptoms including joint pain, swelling, limited range of motion, stiffness, weakness and fatigue. Patients with end-stage disease have similar symptoms to those with severe RA, but there is a formation of fibrous tissue and/or fusing of bone. Patients with end-stage RA may be considered for joint replacement[4].

Although no specific data for the UK are available, global prevalence data suggest that patients with moderate RA represent a substantial proportion of patients within clinical practice. Additionally, a considerable number of patients present with severe disease (Table 3.1)[2]. Thus, both moderate and severe RA represent a substantial burden both in terms of numbers of patients affected and clinical impact.

Table 3.1 Proportions of patients by severity levels[2]

	Female Mean (95%CI)	Male Mean (95%CI)
Mild	41% (39–43)	60% (56–63)
Moderate	31% (28–34)	41% (39–44)
Severe	18% (16–19)	9% (8–11)

CI=confidence interval

3.2 Morbidity and mortality

RA is associated with increased mortality, multiple comorbidities, decreased health-related quality of life (HRQoL), reduced ability to work and reduced ability to participate in usual activities[85,86].

More than 50% of patients with RA have at least one comorbid condition at diagnosis and 40% will develop an additional comorbidity within five years of diagnosis[87]. Depression (around 15% of RA patients), asthma (6.6%), cardiovascular disease (CVD) (6%), solid malignancies (4.5%) and chronic obstructive pulmonary disease (3.5%) are the most frequently reported comorbidities[88].

In RA, physical functioning is the major outcome of interest given the impact impairment has on the patient and society. Specific instruments have been developed to assess disability and its consequences on quality of life, including the Health Assessment Questionnaire Disability Index (HAQ-DI) and the Short Form-36 (SF-36). However, disability is a complex measure comprising of an activity-related component that is reversible and a destruction-related component that is irreversible[89].

The relationship between structural involvement and physical function is influenced by disease duration. In patients with early RA, inflammation and disease activity drive joint damage leading to disability but effective treatment may reverse joint damage and improve physical function. However, as the disease duration increases, the ability to reverse joint damage progressively decreases and loss of function is increasingly related to structural damage[90].

Various groups, including EULAR, American College of Rheumatology (ACR) and the Outcome Measures in Rheumatology Clinical Trials group, recognise that patient-reported outcome (PRO) measures are fundamentally important in RA disease assessment. These measures enable clinicians to develop an understanding of the patients' experience of their disease[91]. For example, responsiveness of PROs decreases dramatically with repeated failure of prior biological disease-modifying anti-rheumatic drugs (bDMARDs) and increasing disease duration[92].

The wide range of complications associated with RA has significant personal impact for people with the disease and their families and carers. While the physical disability caused by RA is usually evident at a clinical level, the psychological and social morbidities may be more difficult to quantify. HRQoL as indicated by physical, mental, and social functioning is

significantly reduced in patients with RA compared with the general population with pain, functional disability and depression being the main predictors of HRQoL[93-96].

In the UK, people with RA continue to have higher mortality rates than the general population, and these rates have not improved since 1990[97]. The risk of death in patients with RA is almost 50% higher than in the general population — matched for age and sex — and patients with highly active disease (28 joint disease activity score [DAS28] >5.1) have a significantly lower survival rate than patients with low disease activity[50,98]. Causes of death in RA populations are similar to those in the wider population, with CVD being the most common cause[97].

3.3 Social and economic impact

RA represents a significant and substantial financial burden at an individual and societal level resulting from direct and indirect costs[99].

Approximately one-third of RA patients stop work because of their condition within 1 year of diagnosis, and over half (59%) within 6 years[100]. While direct healthcare costs to the NHS have been estimated at £560 million in 2009, the total costs of RA in the UK, including indirect costs and work-related disability, have been estimated at around £2.4 billion per year[10].

There is also significant personal impact for people with the disease and their families and carers. [redacted] of RA patients report pain that interferes [redacted] with their daily lives, [redacted] and [redacted][11]. As a result, patients report feeling depressed, having low self-esteem and fearful about the impact of the disease on their future[12].

3.4 Importance of disease control with effective treatment - the NICE clinical guidelines and guidance

Lack of disease control is associated with progression of radiographic joint damage and persistent systemic manifestations including CVD, fatigue, pain, anaemia, and psychosocial impairment, and an increased mortality risk[50,86]. Effective treatment of RA with bDMARDs has been shown to decrease mortality[50]. As a result, treatment strategies in the UK, Europe and the US focus on providing early, aggressive, disease-modifying therapies with the aim of achieving a sustained clinical remission or low disease activity thereby preventing irreversible disease progression and reducing the clinical and economic impact of RA (Section 3.3)[4,36-40].

Within the UK, treatment of RA is based on NICE clinical guidelines (Figure 3.1)[4]. These emphasise timely access to assessment, diagnosis and treatment. The NICE RA Commissioning Guide recommends that treatment with DMARDs starts within six weeks of referral from a GP to prevent functional impairment and disability[82]. Drug management includes DMARDs (conventional [cDMARDs], biological [bDMARDs]) and glucocorticoids[9,17,101,102]. Recommended bDMARDs include tumour necrosis factor inhibitors (TNFi) (adalimumab, certolizumab pegol, etanercept, golimumab [Simponi®], and infliximab [Remicade®]), IL-6 receptor inhibitor (tocilizumab), T-cell co-stimulation inhibitor (abatacept), and B-cell depletion (rituximab)[9,17,101,102].

NICE recommend disease activity is measured by composite score such as DAS28 which may provide an objective indication of activity. Severe disease is defined as DAS28 >5.1, an adequate response as improvement in DAS28 ≥1.2 points, low disease activity as DAS28 <3.2 and remission as DAS28<2.6[9,17].

Recommended first-line treatment for people diagnosed with active RA is a combination of DMARDs including methotrexate (MTX) and at least one other DMARD, ideally within 3 months of onset of persistent symptoms in patients where combination therapy is not appropriate (e.g. co-morbidities, pregnancy or contraindication) NICE recommends starting DMARD monotherapy with emphasis on dose escalation for clinical efficacy[4].

Treatment escalation may be required to rapidly control disease, lower disease activity, and therefore reduce the impact of the disease in terms of joint function and everyday living. The importance of disease control is highlighted by NICE Quality Standards for RA which recommend that patients with active RA are offered treatment escalation until the disease is controlled to an agreed “low disease activity target” for each patient[10].

Following cDMARDs, bDMARDs are recommended. Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab, abatacept, and biosimilars to originator where available, all in combination with MTX, are recommended as options for treating RA, if the disease is severe, i.e. a disease activity score DAS28 >5.1 and the disease is not responding to treatment with a combination of cDMARDs[4,17]. Adalimumab, etanercept, certolizumab pegol and tocilizumab are approved for use in combination with MTX or as monotherapy for patients intolerant to MTX or because it is contraindicated. Infliximab, golimumab and abatacept are approved for use only in combination with MTX.

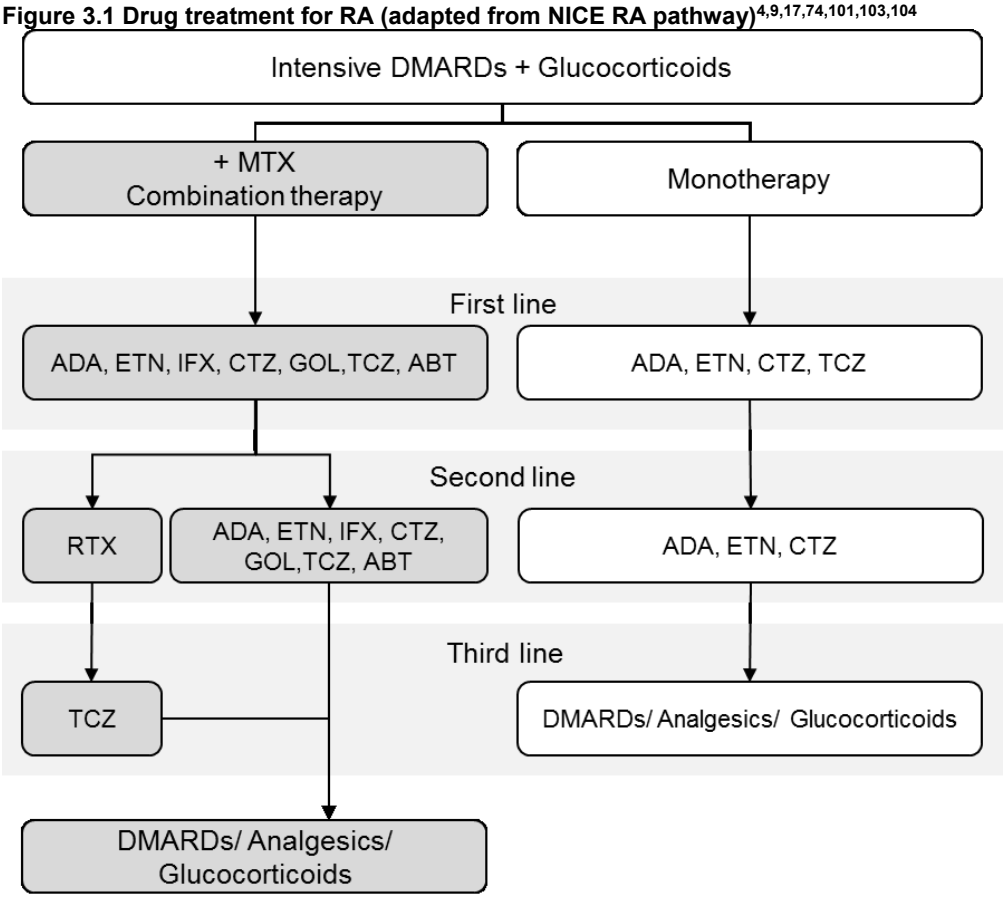
In patients with severe RA who have had an inadequate response to, or are intolerant to, other bDMARDs including at least one TNFi, rituximab in combination with MTX is

recommended. If patients are unable to have rituximab (MabThera®) (contraindication to rituximab, or when rituximab is withdrawn because of an adverse event), then adalimumab, etanercept, infliximab, golimumab, certolizumab pegol, abatacept, and tocilizumab each in combination with MTX, are recommended as treatment options[9,17]. Adalimumab, etanercept and certolizumab pegol may also be used as monotherapy in this patient population[9,17].

A graphical representation of the NICE treatment pathway 2016 is shown in Figure 3.1 Further details on the guidelines and relevant technology appraisals can be found in Appendix 4. A short summary of international RA guidelines is also provided in Appendix 4.

NICE guideline CG79 does not recommend bDMARDs for moderate RA, an area of unmet clinical need highlighted by UK clinical experts consulted during the development of CG79[4]. This is discussed further in Section 3.5.8.

Figure 3.1 Drug treatment for RA (adapted from NICE RA pathway)[4,9,17,74,101,103,104]



ABT=abatacept; ADA=adalimumab; CTZ=certolizumab pegol; DMARD=disease-modifying anti-rheumatic drug; ETN=etanercept; GOL=golimumab; IFX=infliximab; MTS=methotrexate; TRX=rituximab; TCZ=tocilizumab.

3.5 Need for new treatment options — Limitation associated with current treatments

3.5.1.1 Lack of sustained remission with disease-modifying anti-rheumatic drugs

Despite the availability of multiple DMARDs, lack of disease control remains a significant clinical issue with only a minority of RA patients achieving clinical remission, sustained remission or low disease activity[41-47]. Inadequate disease control is also associated with treatment discontinuation with 27% of RA patients discontinuing a TNFi within the first year primarily due to failure to respond, loss of efficacy or intolerance[105,106].

Patients who do not achieve an adequate response with treatments, or who discontinue treatment, increase the likelihood disease progression and functional deterioration.

In the UK, a study of 704 recently diagnosed RA patients showed that only 11% of patients with recent onset RA achieved sustained remission at all three measured time points (sustained remission defined as DAS28- erythrocyte sedimentation rate [ESR]/ C-reactive protein [CRP] <1.6 at all 3-, 4- and 5-year follow-ups) despite treatment with DMARDs (monotherapy or combination therapy). Twenty-five percent of patients achieved remission after 3 years (defined as DAS28-ESR/CRP <1.6), 26% at 4 years and 22% at 5 years [41]. This study reflects similar findings from other countries where, despite treatment, the number of patients achieving complete remission remains low[41-47].

NICE recommends that patients should be managed to an agreed low disease activity[4]. Patients in remission have a higher HRQoL, better physical function and greater work capacity compared to patients with inadequate disease control.

Further treatment options are required to prevent progression of joint damage, avoid persistent pain/fatigue, reduce psychosocial impairment and reduce mortality for those patients in whom current treatments do not provide adequate disease control[7,41,48-52].

3.5.2 Methotrexate adherence is suboptimal due to inefficacy and tolerability

MTX, the most commonly used cDMARD, has the potential to decrease disease activity, delay radiographic progression and improve HRQoL and as a result, many clinicians initiate therapy with MTX as a first-line monotherapy. However, less than 50% of patients demonstrate a good clinical response as per EULAR/ACR criteria and of those, only 30% achieve low disease activity; furthermore, 66% of patients discontinue MTX due to insufficient response or toxicity[16,107-110].

MTX could be associated with suboptimal treatment adherence and persistence in some patients with RA, as a result, there is a cohort of patients who are unable to receive MTX due to intolerance and require biologic monotherapy[14]. Patients who do not achieve an adequate response with MTX treatments, or who discontinue treatment, increase the likelihood of disease progression and functional deterioration.

3.5.3 Tumour necrosis factor inhibitor failure remains a serious clinical challenge

Available since 2002, TNFis were the first bDMARDs approved for the treatment of RA and are the most commonly used bDMARD either in combination with MTX or as monotherapy for patients unable to take MTX due to intolerance (6–21%)[15,111] . TNFis can facilitate clinical response or remission at an early stage of the disease process and multiple studies confirm their robust efficacy[105,112]. However, failure to respond remains a serious concern for patients with RA treated with TNFis.

Estimates of TNFi efficacy depend on several factors — including disease duration and number of previously failed DMARDs — but clinical trials suggest that 40–50% of RA patients treated for at least 6 months with one of the first-generation TNFis (etanercept, adalimumab, and infliximab) fail to achieve the ACR 50% improvement (ACR50) criteria and over 70% of these patients fail to achieve DAS28 remission (DAS28 <2.6)[113].

Approximately one-third of patients do not respond or fail to respond from the outset and do not achieve an ACR20 response[112,114,115]. A proportion of patients experience a primary lack of efficacy, fail to respond from the outset and do not achieve an ACR20 response[115]. Other patients experience a secondary loss of efficacy, whereby patients fail to maintain an initial response because of acquired drug resistance, which may be linked to an antibody response to the drug[116,117]. As many as 50% of patients receiving infliximab may develop secondary non-response during the first year of treatment with a TNF inhibitor[118].

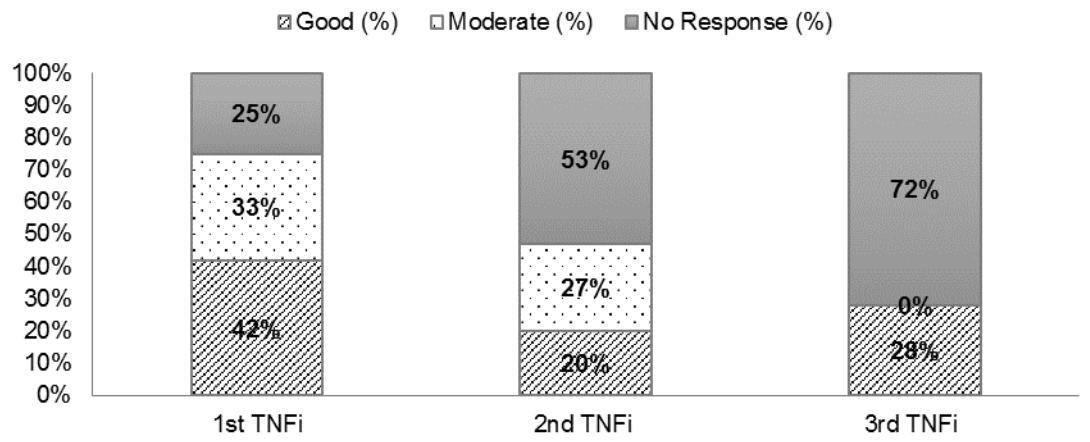
A substantial proportion of patients discontinue TNFi therapy due to an inadequate response, loss of response, or intolerance, with around 15% switching to an alternative TNFi within 12 months of initiating the original TNFi treatment[105,106,119].

Patients with an inadequate response to a TNFi, or who are intolerant to TNFi treatment, are likely to remain uncontrolled and outside of their low disease activity target.

3.5.4 TNF cycling is associated with suboptimal outcomes

After TNFi failure, patients can be treated with an alternative TNFi (TNFi cycling) or switch to a bDMARD with an alternative mode of action — a non-TNFi[27,28]. TNFi cycling is associated with suboptimal outcomes and the likelihood of response to a subsequent TNFi decreases with increasing number of previous TNFi treatments; less than half of RA patients cycling to a second TNFi have a clinically significant response (Figure 3.2)[27,28,80,120]. Despite this, after discontinuing a prior TNFi, moving to another TNFi rather than switching to a non-TNFi remains common clinical practice[119,121,122].

Figure 3.2 DAS28/EULAR response rates in RA patients undergoing TNFi cycling[80]



DAS28=Disease Activity Score 28; EULAR= European League Against Rheumatism; RA=rheumatoid arthritis; TNFi=tumour necrosis factor inhibitor

Patients who switch to a non-TNFi bDMARD including the IL-6 inhibitor tocilizumab, B-cell inhibitor rituximab, T-cell inhibitor abatacept or the Janus kinase inhibitor tofacitinib— have better outcomes and are significantly more likely to continue therapy than patients that cycle TNFis (Table 3.2)[25,27,28,81].

The “Rotation of anti-TNF Or Change of class of biologic” (ROC) trial demonstrated superior and sustained efficacy with an alternative mode of action versus TNFi cycling in RA patients who have failed their first TNFi (Table 3.2)[81].

Table 3.2 TNFi versus a non-TNFi for TNFi irresponsive RA patients[81]

	TNFi	Non-TNFi	p
EULAR good/moderate response at Week 12	48%	64%	0.003
EULAR good/moderate response at Week 52	43%	60%	0.006
LDA at Week 52	23%	41%	0.003
DAS28-ESR remission at Week 52	14%	26.9%	0.008

DAS28=Disease Activity Score 28; ESR=erythrocyte sedimentation rate; EULAR=European League Against Rheumatism; LDA=low disease activity; Ra=rheumatoid arthritis; TNFi=tumour necrosis factor inhibitor

Real-world data from the SWITCH RA trial indicate that switching to rituximab — an anti-CD20 B-cell-depleting therapy — is associated with significantly improved clinical effectiveness compared with switching to a second TNFi in RA patients with an inadequate response to one previous TNFi[25].

Data from a large database analysis of treatment patterns and efficacy in TNFi cyclers (n=5,020) and patients who switch to a non-TNFi (n=1,925) confirms that patients who switch to a non-TNFi have better clinical outcomes, are significantly less likely to switch again within 6 months ($p<0.001$) and are significantly more likely to persist with therapy through to 12 months ($p<0.001$)[27].

A retrospective cohort study of a United States claims database showed that patients who switch to a non-TNFi rather than cycle to another TNFi are 43% more likely to be treated effectively ($p=0.006$), 39% more likely to continue medication after switch ($p=0.003$), and 36% less likely to switch again ($p<0.001$)[28]. The mean cost for the first switch was $US1,976 (£1,587) for alternative mode of action switchers and $US2,969 (£2,384) for TNFi cyclers. Mean RA treatment costs in the 12-month post-switch period and the total cost of RA-related medical care were significantly lower for alternative mode of actions switchers compared with TNFi cyclers ($US29,001 vs. $US34,917 [£23,285 vs. £28,035], $p<0.001$; and $US37,804 vs. $US42,116 [£30,349 vs. £33,811], $p<0.001$)[28].

These data — supporting switching to an alternative mode of action following TNFi failure — are reflected in national and international clinical guidelines[9,17,37,38,101].

The IL-6 receptor inhibitors offer an alternate mode of action to TNFis as they target both the innate and adaptive immune systems implicated in RA (Section 2.5.1). Treatment with IL-6 monotherapy has been shown to provide greater efficacy compared with TNFi monotherapy in a head-to-head trial[33,34].

This IL-6 class benefit is confirmed by the data available for sarilumab in the MONARCH trial which demonstrated superiority in a head-to-head comparison with adalimumab monotherapy (see Section 4.7.5 for further details). The efficacy of IL-6 inhibition as an alternative mode of action in active RA patients with inadequate response or intolerance to TNFi was demonstrated in the TARGET trial (see Section 4.7.3 for further details)[57].

3.5.5 Tumour necrosis factor inhibitor plus methotrexate is associated with safety concerns

TNFi monotherapy is less effective than TNFi combination therapy i.e. plus MTX[19]. Therefore, national and international guidelines recommend that TNFis are used in combination with a cDMARD, preferably MTX[9,17,37,38,74,123].

However, MTX is contraindicated in some RA patients and the use of concomitant MTX is an important safety concern when prescribing a TNFi as HRQoL can be significantly affected by MTX intolerances. Up to 45% of patients experience MTX associated adverse events (AEs), up to 4% of patients experience serious AEs and toxicity leads to discontinuation in up to a 25% of patients[16]. Thus, a significant proportion of patients may be treated suboptimally despite being prescribed MTX. In addition to the limitations of TNFi monotherapy, the only non-TNFi licensed as monotherapy is tocilizumab[35]. There is therefore an unmet need for additional licensed, efficacious therapies in monotherapy.

In contrast to TNFi monotherapy, studies suggest that IL-6 monotherapy is as effective as IL-6 combination therapy[34].

The clinical efficacy and safety of subcutaneous sarilumab in moderate-to-severe RA has been demonstrated in a comprehensive clinical trial programme that included patients with an inadequate response to one or more DMARDs or TNFis, or in whom DMARDs are contraindicated[1,55-58,64]. More specific discussions on the sarilumab clinical trial programme are presented in Section 4.7.

3.5.6 Tumour necrosis factor inhibitor dose escalation is associated with increased costs

Within clinical practice, dose escalation with the aim of controlling disease is common[105,124], despite scant evidence to support efficacy benefits. A European study — which included UK patients — found that up to 35% of patients had their TNFi dose increased due to lack of, or loss of, adequate response. The study concluded that dose escalations had no additional impact on clinical efficacy or disease activity, but did translate into significant increases in the total cost of care — up to €2,266 per patient per year (approximately £1,900 [£0.86/€])[124]. Thus, the earlier implementation of alternative treatment options would appear to be a sensible strategy from an economic perspective.

3.5.7 Rituximab is associated with uncertainties regarding dosing, slower onset of action than other biological disease-modifying anti-rheumatic drugs, serious adverse events, and retreatment is allowed only every six months

Rituximab is a chimeric monoclonal antibody that targets the CD20 molecule expressed on the surface of B cells. It was first used in the treatment of non-Hodgkin's lymphoma and later approved for the treatment of RA that does not respond adequately to bDMARDs including TNFis[32].

Incomplete data on the dosing at the time of rituximab approval led to uncertainties regarding the optimal administration dose and interval of rituximab and the optimal interval for retreatment, therefore the optimal treatment paradigm for rituximab has not yet been fully definitively determined[29-31]. In TA375, rituximab retreatment was modelled at nine months therefore this assumption is also used in the economic consideration of this appraisal.[17]

Although rituximab is the least expensive bDMARD currently available, the onset of action of rituximab is slower than that of the other bDMARDs with clinical responses typically taking 3–4 months after initial infusion, and, because duration of response is quite variable, optimal timing for retreatment is difficult to predict[29-31].

Randomised controlled trials (RCTs) and post-marketing surveillance suggest rituximab use is associated with serious adverse events (SAEs). Patients older than 65, are at a significantly higher risk of AEs and SAEs compared to younger patients[30,32,125]. Rituximab can cause severe—including fatal —infusion reaction. Infusion reactions, are one of the most common SAEs associated with rituximab, occurring in around 25% of patients, with many reactions developing within 30−120 minutes of the first infusion and in some cases, may lead to intensive care unit admission [30,32]. Cardiac monitoring is required during and after rituximab infusions in all patients with a history of arrhythmias or angina, and although rare, cases of fatal heart failure have been reported in rituximab treated patients independent of pre-existing heart disease [30,32]. Repeated treatment with rituximab is associated with hypogammaglobinaemia, which may increase the risk of serious infections and reactivation of hepatitis B infection has been reported in RA patients receiving rituximab[32]. Finally, the rare but fatal progressive multifocal leukoencephalopathy associated with rituximab should be noted[32].

Additionally, because repopulation of B cells following rituximab treatment can take 6–9 months, treatment with rituximab should be given no more frequently than every 6 months[17,32].

NICE recommend the use of rituximab in combination with MTX only in adults with severe active RA who have had an inadequate response to, or are intolerant of, other DMARDs including at least one TNFi[9,17]. This is in contrast to European guidelines that advocate the use of rituximab as a first-line agent in cDMARD naïve patients in whom other agents are contraindicated[37].

3.5.8 Moderate rheumatoid arthritis — an area of unmet clinical need

Patients with moderate RA are an important and often poorly studied subgroup. Despite recommendations for clinical remission or low disease activity as key targets in RA, many patients with moderate RA disease activity (DAS28 >4 – ≤5.1) remain on cDMARDs rather than switching to more aggressive treatment strategies and thus are at risk of radiographic progression particularly when objective signs of inflammation (CRP or rheumatoid factor [RF]) are present[53,54].

Results from the UK Early RA Study (ERAS) demonstrate that patients with moderate disease activity, radiographically progress despite cDMARDs and this progression is similar to that observed for severe disease[54,126]. These results highlight that targeting this subgroup and aiming for clinical remission or low disease activity in moderate RA is as important as in patients with severe RA.

Based on cost-effectiveness acceptability, current NICE guidelines restrict biologic usage to patients with severe disease only, i.e. people with DAS28>5.1[17]. DAS28 is one of the most commonly used measures of disease response but unlike ACR response, which is categorical, DAS is a continuous measurement. UK clinical experts suggest that the cut-off points in the DAS scale to define low, moderate or severe disease activity are arbitrary and clinical distinctions on either side of the boundaries of the cut-off points are not necessarily clinically meaningful[17].

Due to a lack of treatment options, patients with uncontrolled moderate disease activity are continued on high intensity cDMARD therapy —despite no clinical benefit — until their disease reaches the severe state. Moderate RA patients may also be offered short term glucocorticoids to improve symptoms and maintain disease control but NICE recommendation is limited to short term glucocorticoids to improve symptoms in newly diagnosed patients (Section 3.4)[4].

Low dose glucocorticoids are recognised to have beneficial effects in RA, however, prolonged use may increase the risk of AEs including cardiovascular events, osteoporosis, ophthalmological events, diabetes, and infection[127,128]. Therefore, guidelines recommend

tapering glucocorticoids as soon as clinically feasible with steroid-free remission as an increasingly important treatment goal[37]. Despite these safety concerns, UK data suggest that 14% of patients with RA take oral glucocorticoids long term[129].

The availability of bDMARDs would be a welcome addition to treatment options for patients with moderate disease activity uncontrolled by cDMARD therapy. Currently, guidelines do not indicate treatment with bDMARDs in patients with moderate active disease. Clinical experience suggests that, regardless of DAS, disease that responds badly to cDMARD therapy, is likely to respond to other treatments. During development of TA375, the NICE appraisal committee understood that there was clinical interest in the use of bDMARDs in people with moderate active disease (DAS28<5.1) whose disease was not controlled on cDMARDs and supported the concept of identifying people likely to have rapid disease progression in order to target treatment with bDMARDs[17].

DAS28 is currently used to identify people suitable for treatment with bDMARDs, but cannot be utilised to define patients with rapid disease progression. Rapid clinical progression may be identified based on persistent synovitis and failure of the disease to respond to combination therapy with cDMARDs, plus[17,54]:

- Persistent elevation of inflammatory markers (such as CRP) and
- Presence of erosions on X-ray and
- Positive for anti-citrullinated protein antibodies (ACPA)/ RF.

These measures had been validated individually, and all are used in clinical practice within the NHS. Clinical experts commenting on TA375 considered that disease which has not responded to combination therapy, in people who have these criteria, would progress faster than in people who do not have these criteria.

Clinical opinion suggests that restriction of treatment to cDMARDs in patients with moderate RA may be suboptimal. In TA375 the moderate RA patients assessed were those are able to respond adequately to and are tolerant of cDMARDs, conversely, this appraisal considers only those patients who do not respond adequately to, or are intolerant to cDMARDs. Although there is a paucity of randomised controlled clinical trial data in truly moderate RA populations, we demonstrate that the use of sarilumab is cost-effective for moderate RA in patients who do not to respond to or are intolerant of cDMARD therapy; this is discussed further in Section 5.

3.6 Anticipated position of sarilumab in the therapeutic pathway of care

This submission considers sarilumab for the treatment of adults with moderate-to-severe active RA in combination with MTX or as monotherapy for patients with active disease who:

- Are inadequate responders to one or more cDMARDs (including MTX)
- Are intolerant to or inadequately respond to one or more bDMARDs (TNFi or other mode of action)
- Are intolerant to MTX or for whom continued MTX is inappropriate

The potential place of sarilumab in the UK treatment pathway based on the current NICE-recommended treatment options and the NICE scope for this appraisal is shown below (Table 3.3 and Figure 3.2).

The treatment options reflected in the NICE scope are defined by disease severity (moderate and severe RA) and by the comparator.

The only other bDMARD with a similar mode of action to sarilumab i.e., inhibition of IL-6 signalling and recommended by NICE in the UK for the treatment of severe RA, is tocilizumab. According to expert clinical opinion, it is anticipated that in clinical practice, sarilumab would be considered in the same patient populations and at the same point in treatment pathway as tocilizumab. Tocilizumab is therefore regarded as the most relevant comparator for sarilumab (and the product most likely to be displaced by sarilumab) in patients with severe disease. In patients with moderate disease, the most relevant comparators are cDMARDs.

In Section 5 cost-effectiveness of sarilumab is presented for patients with moderate-to-severe RA after failure or intolerance to cDMARDs or after failure of at least one TNFi. Moderate disease is reflected separately in the model by restricting the population to those with a baseline DAS score of 3.2 >5.1 and >5.1 for severe RA patient groups; in line with NICE recommendations. The model considers all recommended DMARDs included in this scope but with particular focus on tocilizumab.

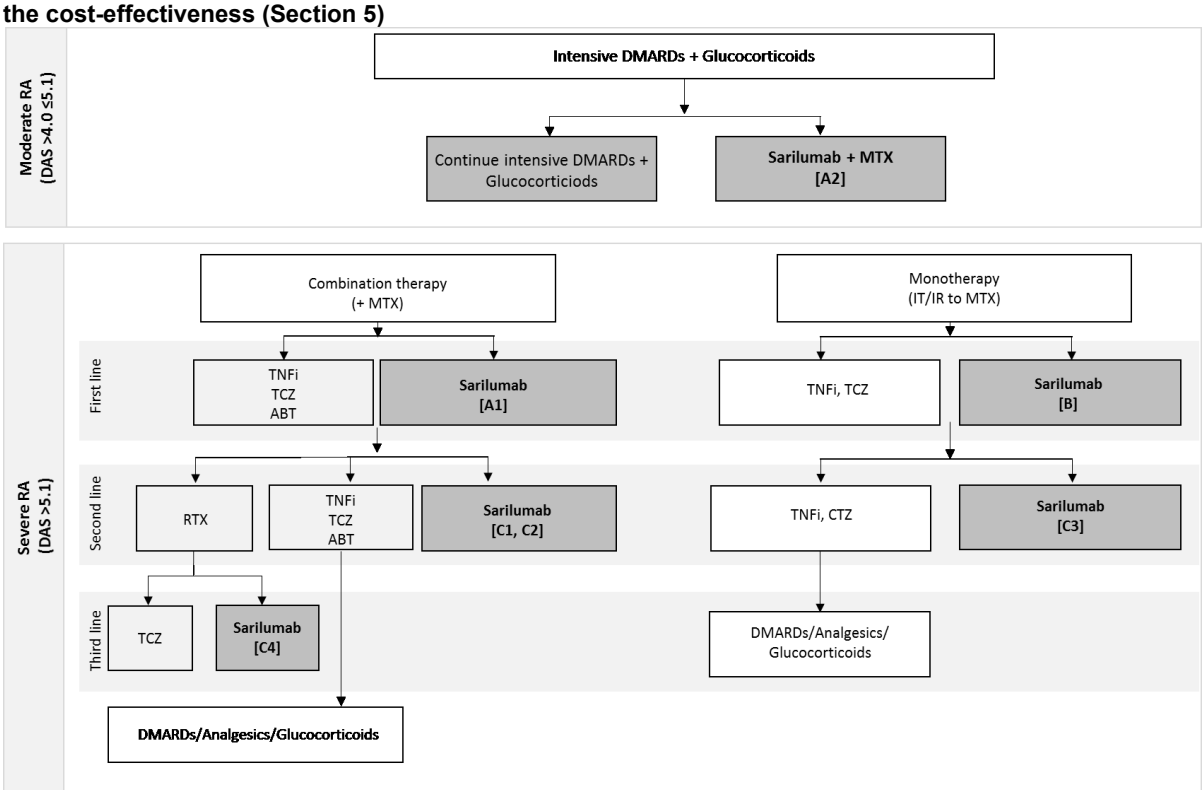
The populations considered as per the scope are described in Table 3.3 and reflected in Figure 3.2.

Table 3.3 Populations assessed in the de novo analysis

Population	Description
A1	Patients with severe active RA that has not responded adequately to, or are intolerant of therapy with cDMARDs (combination with MTX)
A2	Patients with moderate active RA that has not responded adequately to, or are intolerant of therapy with cDMARDs (combination with MTX), at risk of rapid progression
B	Patients with severe active RA that has not responded adequately to, or are intolerant of therapy with cDMARDs (monotherapy)
C1	Patients with severe active RA that have not responded adequately to, or are intolerant of therapy with DMARDs including at least one TNFi (RTX intolerant in combination with MTX)
C2	Patients with severe active RA that have not responded adequately to, or are intolerant of therapy with DMARDs including at least one TNFi (RTX tolerant in combination with MTX)
C3	Patients with severe active RA that has not responded adequately to, or are intolerant of therapy with DMARDs including at least one TNFi (RTX intolerant in monotherapy)
C4	Patients with severe, active disease despite treatment with bDMARDs recommended according to NICE guidance (combination with MTX)

bDMARD=biologic disease-modifying anti-rheumatic drug; cDMARD=conventional disease-modifying anti-rheumatic drug; DMARD=disease-modifying anti-rheumatic drug; MTX=methotrexate; RA=rheumatoid arthritis; RTX=rituximab; TNFi=tumour necrosis factor inhibitor

Figure 3.2 Anticipated place in therapy for sarilumab within the UK showing population assessed within the cost-effectiveness (Section 5)



ABT=abatacept; ADA=adalimumab; cDMARD=conventional disease-modifying anti-rheumatic drug; CTZ=certolizumab; DAS=disease activity scale; ETN=etanercept; GC=glucocorticoids; GOL=golimumab; IR=irresponsive; IT=intolerant; RA=rheumatoid arthritis; RTX=rituximab; TCZ=tocilizumab; TNFi=tumour necrosis factor inhibitor

3.7 Estimated eligible patient population for sarilumab

An estimate of the patient population eligible for sarilumab is given below in Table 3.4. The eligible patient numbers have been estimated using recently published prevalence and incidence data, and the costing template from NICE TA195/TA198, which stated 10% of RA patients, are eligible for treatment with biologic therapies[9,101].

Table 3.4 Rheumatoid arthritis population eligible for sarilumab — UK data[8,9,130]

	Number	Per 100,000
Existing patients		
RA patients	372,791	671
Eligible for biological therapy	37,280	68
New patients per year		
RA patients	21,199	39
Eligible for biological therapy	2,120	4

RA=rheumatoid arthritis

In considering sarilumab in these populations, the NICE final scope for this appraisal is addressed.

3.8 Equality issues

It is not anticipated that the use of this technology is likely to raise any equality issues.

4 Clinical effectiveness

Summary of clinical evidence

- A systematic literature review (SLR) identified five randomised controlled trials (RCTs) comparing sarilumab (Kevzara®) with other therapies that included patient populations and therapies relevant to the decision problem.
- These five RCTs were part of the global, multicentre clinical trial programme to determine the safety and efficacy of sarilumab.
- All five studies included adult patients with moderate-to-severe active, longstanding rheumatoid arthritis (RA). Predominately functional class II and III with mean disease duration of around 7–12 years and, when relevant, a substantial proportion of the patients had previously been treated with biological disease-modifying anti-rheumatic drugs (bDMARDs)[1,56-58,131]:
    - **MOBILITY A:** A Phase II, randomised, double-blind, placebo-controlled, multicentre, two-part, dose-ranging and confirmatory study with an operationally seamless design, evaluating efficacy and safety of sarilumab on top of MTX in patients with active RA who are inadequate responders to MTX therapy (Section 4.3.1.1)[131]
    - **MOBILITY B:** A Phase III, randomised, double-blind, placebo-controlled, multicentre, two-part, dose-ranging and confirmatory study with an operationally seamless design, evaluating efficacy and safety of sarilumab on top of MTX in patients with active RA who are inadequate responders to MTX therapy (Section 4.3.1.2)[56]
    - **TARGET:** A Phase III, randomised double-blind, parallel, placebo-controlled study assessing the efficacy and safety of sarilumab added to cDMARD therapy in patients with RA who are inadequate responders to or intolerant of TNFi (Section 4.3.1.3)[57]
    - **ASCERTAIN:** A Phase III, randomised, double-blind, double-dummy study assessing the safety, tolerability (and efficacy as an exploratory endpoint) of sarilumab and tocilizumab in patients with RA who are inadequate responders to or intolerant of TNFi (Section 4.3.1.4)[58]

- **MONARCH:** A randomised, double-blind, parallel-group study assessing the efficacy and safety of sarilumab monotherapy versus adalimumab monotherapy in patients with active RA who are inadequate responders to MTX therapy (Section 4.3.1.5)[1]

- All studies met their primary efficacy endpoints (Section 4.7), and overall, the clinical trial programme demonstrates that[1,55-59]:
  - Sarilumab provides reliable and significant response against moderate-to-severe disease activity regardless of patient treatment history (inadequate responders to or intolerant of MTX or TNFi)
  - Sarilumab provides rapid and sustained improvement in moderate-to-severe signs and symptoms and an increased probability of achieving and sustaining clinical remission, compared with MTX/cDMARD alone
  - Sarilumab significantly reduces structural joint damage. Reduction of radiographic progression should limit further functional decline
  - Sarilumab has demonstrated significant and clinically meaningful improvements across a broad range of patient-reported outcomes (PROs), including health-related quality of life (HRQoL), physical function, pain, fatigue, sleep, morning stiffness and participation
  - Sarilumab monotherapy was superior to adalimumab monotherapy in improving signs and symptoms and physical function in patients with severe active RA at Week 24, with a similar incidence of adverse events (AE) and infections between the treatments
  - Sarilumab and tocilizumab safety and tolerability was assessed in ASCERTAIN however, exploratory efficacy endpoints were evaluated and suggest that sarilumab efficacy is broadly comparable to that of tocilizumab

4.1 Identification and selection of relevant studies

4.1.1 Search strategy

To identify relevant clinical evidence, a systematic literature review (SLR) was undertaken. This SLR was used as the basis of a network meta-analysis (NMA) to provide comparative effectiveness estimates of sarilumab and relevant comparators. Comprehensive literature searches were undertaken in MEDLINE, Embase, Cochrane databases, and conference proceedings. Studies were selected per the pre-defined populations (P), interventions (I), comparisons (C) and outcomes (O) study (S) (PICOS) described below. Screening of abstracts, full texts, and data extraction was performed by two independent reviewers with resolution of any discrepancies by a third reviewer, per National Institute for Health and Care Excellence (NICE) guidance[132].

The search strategy (Appendix 5.1) was initially implemented on 31st March 2015, and an update was performed on 6th December 2016 (Appendix 5.2). The initial review included all investigational drugs whereas the update restricted investigational drugs to those likely to be relevant future comparators for sarilumab. All investigational products are however beyond the scope of this appraisal therefore this had no impact on identifying the relevant clinical evidence. The updated search was validated against the initial search by searching the same time horizon as the initial search yielding similar results.

4.1.2 Clinical data sources

In the initial search, the following electronic databases were used with the following platforms:

- MEDLINE and MEDLINE In-Process — using Ovid®.
- Embase — using Ovid®.
- The Cochrane Controlled Trials Registry databases — using Ovid®.
- The Cochrane Database of Systematic Reviews.
- Centre for Reviews and Dissemination — using Ovid®.

In the update search, the following electronic databases were used from the following platforms:

- Embase® — Embase.com platform.
- MEDLINE® — Embase.com platform.
- MEDLINE® In-Process — Pubmed.com platform.
- Cochrane (CENTRAL) — Cochrane platform.

- Centre for Reviews and Dissemination — Cochrane platform.

Conference proceedings for the previous 4 years of the two key rheumatology conferences (American College Rheumatology [ACR] and European League Against Rheumatism [EULAR]) were also searched. 2013/2014 proceedings were searched using Ovid® in the initial search and 2015/2016 proceedings were searched through hand searching in the update.

Registries of randomised trials were also searched at ClinicalTrials.gov and apps.who.int/trialsearch.

4.1.3 Study selection

Titles and abstracts were retrieved for all identified records and then screened independently by two researchers against the pre-defined PICOS inclusion and exclusion criteria presented in Table 4.1. Disagreements were resolved by consensus by a third reviewer. For disagreements not resolved by consensus, a fourth reviewer served as the referee. For included studies, a quality assessment was performed using the methods recommended in the current NICE specification for manufacturer and sponsor submission of evidence. Finally, data were extracted from the included studies into project-specific Microsoft Excel® tables by two independent extractors.

The inclusion/exclusion criteria were designed to align with the anticipated licence indication of sarilumab and the decision problem and describe the criteria for study selection (Table 4.1 and Table 4.2). To summarise, the SLR focused on the following populations, and key efficacy and safety endpoints were extracted and analysed including ACR20, 50, and 70 criteria (ACR 20%, 50% 70% improvement), Health Assessment Questionnaire Disability Index (HAQ-DI), 28-joint disease activity score (DAS28) remission (DAS28 <2.6), EULAR response, van der Heijde modified Total Sharp Score (mTSS), serious infections (SI) and serious adverse events (SAE):

1) Adult patients (≥18 years) with moderately to severely active RA who have had inadequate response to one or more conventional disease-modifying anti-rheumatic drugs (cDMARDs)

2) Adult patients (≥18 years) with moderately to severely active RA who have had inadequate response to one or more biological DMARDs (bDMARDs) (tumour necrosis factor inhibitor [TNFi] or other mechanism of action)

3) Adult patients (≥18 years) intolerant to methotrexate (MTX) or for whom continued MTX is inappropriate.

Table 4.1 Eligibility criteria used in the initial search

Criteria		Inclusion	Exclusion
STUDY DESIGN	Abstract selection	RCTs above Phase I	• Case series/reports, letters to editor, commentary, editorials • Observational and registry studies • Non-English publications • Preclinical/Pharmacokinetic/Pharmacogenomic studies • Animal or in vitro studies • Literature review/meta-analysis[a] • Phase I study • Prognostic study • Retrospective study • Open-label extension and extended access studies • Post hoc studies and pooled analyses[a] • Any other type of non-randomised study
	Full-text selection	RCT above Phase I	
POPULATION	Abstract and full-text selection	• Adult patients (≥18 years) with moderately to severely active RA who have had inadequate response to one or more cDMARDs • Adult patients (≥18 years) with moderately to severely active RA who have had inadequate response to one or more bDMARDS (TNFi or another MoA) • Adult patients (≥18 years) intolerant to MTX or for whom continued MTX is inappropriate	• Patients without RA • Patients with diseases other than RA • Patients with rheumatic diseases other than RA • Patients not being treated with an intervention of interest • Patients naïve for cDMARD
TREATMENT / INTERVENTION	Abstract and full-text selection	The following interventions are of interest at any dosage or administration type: • Sarilumab (REGN88, sarilumab153191) • Etanercept (Enbrel) • Tocilizumab (RoActemra/Actemra) • Adalimumab (Humira) • Abatacept (Orencia) • Infliximab (Remicade) • Rituximab (MabThera/Rituxan) • Tofacitinib (Xeljanz) • Anakinra (Kineret) • Certolizumab (Cimzia) • Golimumab (Simponi) • Biosimilar DMARDs (see Appendix 5.3)	Other treatments

Criteria		Inclusion	Exclusion
		• Investigational drugs (see Appendix 5.4)	
COMPARATOR	Abstract and full-text selection)	Placebo or any of the above listed treatments as monotherapy or in combination with a cDMARD(s) (i.e. MTX, leflunomide, hydroxychloroquine, minocycline, sulfasalazine, azathioprine, sodium aurothiomalate, and auranofin) or cDMARD as monotherapy or in combination with other cDMARD(s)	Other treatments not in the above listed treatments
OUTCOMES	Abstract and full-text selection	No selection was made on outcomes. *After the screening phase top-line data extraction was performed to detect which outcomes were selected for data extraction*	None[b]
Timepoint		No start limit – 31st March 2015	
Language		English language	Non-English language

[a]Systematic literature reviews and meta-analyses (2010 – present) will be noted in a separate "study design" exclusion column; using this list of reviews, we will select the most recent and relevant systematic literature reviews/meta-analyses and check the reference lists of the reviews for relevant studies. For post hoc and pooled analyses, the reference list was also checked for relevant studies.

[b]Studies were not excluded based on the outcomes at the screening phase. Outcomes were selected during the top-line data extraction phase.

PICOS-T = population, intervention, comparison, outcomes, study, and time horizon.

bDMARD= biological disease-modifying anti-rheumatic drug; cDMARD=conventional disease-modifying anti-rheumatic drug; MoA=mode of action; MTX=methotrexate; RA=rheumatoid arthritis; RCT=randomised controlled trial

Note: These exclusion criteria, along with the PICOS-T criteria noted in Table 4.1 were applied during the abstract and full-text screening process to select appropriate studies.

Table 4.2 Eligibility criteria used in the update search

Criteria		Inclusion	Exclusion
STUDY DESIGN	Abstract selection	RCTs above Phase I	• Case series/reports, letters to editor, commentary, editorials; • Observational and registry studies; • Non-English publications; • Preclinical/Pharmacokinetic/Pharmacogenomic studies; • Animal or in vitro studies; • Literature review/meta-analysis[a]; • Phase 1 study; • Prognostic study; • Retrospective study; • Open-label extension and extended access studies; • Post hoc studies and pooled analyses; • Any other type of non-randomised study.
	Full-text selection	RCTs above Phase I	
POPULATION	Abstract and full-text selection	• Adult patients (≥18 years) with moderately to severely active RA who have had inadequate response to one or more cDMARDs • Adult patients (≥18 years) with moderately to severely active RA who have had inadequate response to one or more biologic DMARDS (TNFi or another MoA) • Adult patients (18 years or older) intolerant to MTX or for whom continued MTX is inappropriate	• Patients without RA • Patients with diseases other than RA • Patients with rheumatic diseases other than RA • Patients not being treated with an intervention of interest • Patients naïve for cDMARD

TREATMENT / INTERVENTION	Abstract and full-text selection	• Interventions of interest include only licensed and late phase 3 molecules:
		• Sarilumab (REGN88, sarilumab153191)
		• Licensed:
		  • Etanercept (Enbrel)
		  • Tocilizumab (RoActemra/Actemra)
		  • Adalimumab (Humira)
		  • Abatacept (Orencia)
		  • Infliximab (Remicade)
		  • Rituximab (MabThera/Rituxan)
			Other investigational treatments

Criteria		Inclusion	Exclusion
		• Tofacitinib (Xeljanz) • Anakinra (Kineret) • Certolizumab (Cimzia) • Golimumab (Simponi) • Biosimilar DMARDs (Appendix 5.3) • Late Phase III: • Baricitinib (FDA submission in January 2016) • Sirukumab (FDA and EMA submissions in September 2016)	
COMPARATOR	**Abstract and full-text selection)**	Placebo or any of the above listed treatments as monotherapy or in combination with a cDMARD(s) (i.e.,MTX, leflunomide, hydroxychloroquine, minocycline, sulfasalazine, azathioprine, sodium aurothiomalate, and auranofin) or cDMARD as monotherapy or in combination with other cDMARD(s)	Other treatments not in the above listed treatments
OUTCOMES	**Abstract and full-text selection**	All outcomes extracted in the original review including ACR (20/50/70), DAS28 remission, EULAR response, and mTSS at 24 weeks, HAQ-DI CFB, SIs and SAEs were extracted in the update review	None[b]
Timepoint		March 2015 to 6th December 2016	
Language		English language	Non-English language

PICOS-T = population, intervention, comparison, outcomes, study, and time horizon.

ACR20/50/70=American College of Rheumatology 20%, 50% and 70% improvement; bDMARD= biological disease-modifying anti-rheumatic drug; cDMARD=conventional disease-modifying anti-rheumatic drug; CFB=change from baseline; DAS28=28-joint disease activity score; EMA= European Medicines Agency; EULAR, European League Against Rheumatism; FDA, Food and Drug Administration; HAQ-DI=Health Assessment Questionnaire Disability Index; MoA=mode of action; mTSS= modified Total Sharp Score; MTX=methotrexate; RA=rheumatoid arthritis; RCT=randomised controlled trial; SAE=serious adverse events; SI=serious infections; TNFi=tumour necrosis factor inhibitor

Note: These exclusion criteria, along with the PICOS-T criteria noted in Table 4.2 were applied during the abstract and full-text screening process to select appropriate studies.

[b]Studies were not excluded based on the outcomes at the screening phase

4.1.4 Documenting the search and screening process

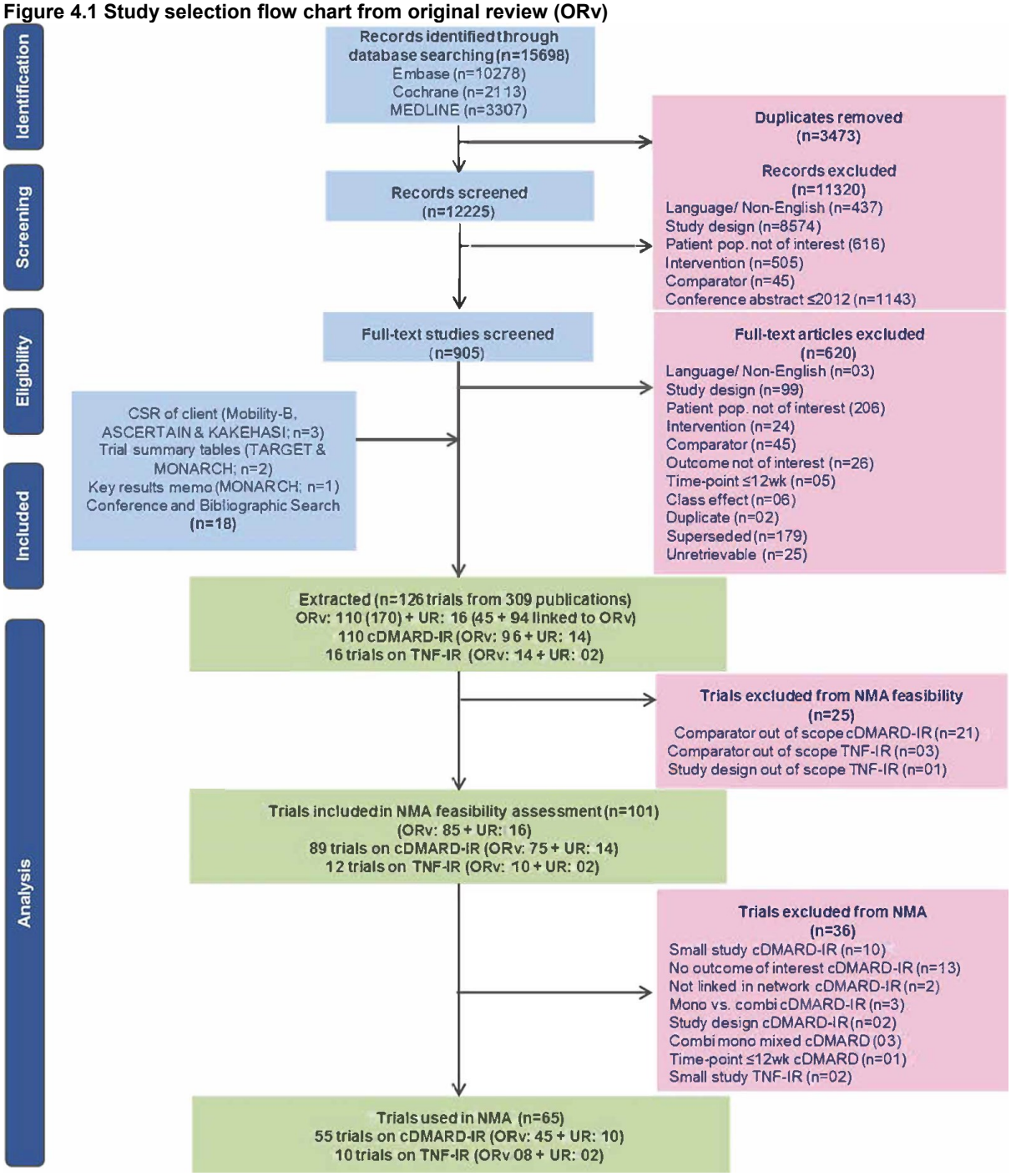
The literature search identified a total of 15,698 citations. The abstract review excluded 14,793 citations that did not meet the selection criteria. Specifically, 8,574 citations were excluded due to study design, 3,473 were found to be duplicates, 1,143 due to conference held before 2013, 437 were excluded due to language, 505 due to intervention, 616 due to patient population, 45 due to comparator, leaving 905 citations for full-text screening.

The review of these remaining citations excluded 406 that did not meet the selection criteria. Of these, 179 citations were superseded (i.e. all the data provided in the abstract were reported in a subsequent full-text publication), 206 were excluded on the basis of population out of scope, 99 were excluded due to study design, 25 were not retrievable (i.e. pooled or post hoc analysis of which the original studies cannot be identified), 25 did not include an intervention of interest, 26 did not include outcomes of interest, 45 did not include a comparator of interest, two were duplicates, six publications provided class effect (e.g. TNF class) data only and five were excluded on time point ≤12 weeks. Further, conference searching and bibliographic validation using relevant SLRs yielded 18 additional citations. In parallel, six documents (five studies) provided by Sanofi Genzyme were added to the evidence base but only four studies were used in the analysis:

- Clinical study report (CSR) of MOBILITY B study
- Trial summary tables for TARGET study
- Trial summary tables for MONARCH study
- CSR of ASCERTAIN study
- CSR of KAKEHASI study

A final set of 309 citations that met the criteria was retrieved by the SLR, reporting results of 126 RCTs (Figure 4.1).

Figure 4.1 Study selection flow chart from original review (ORv)



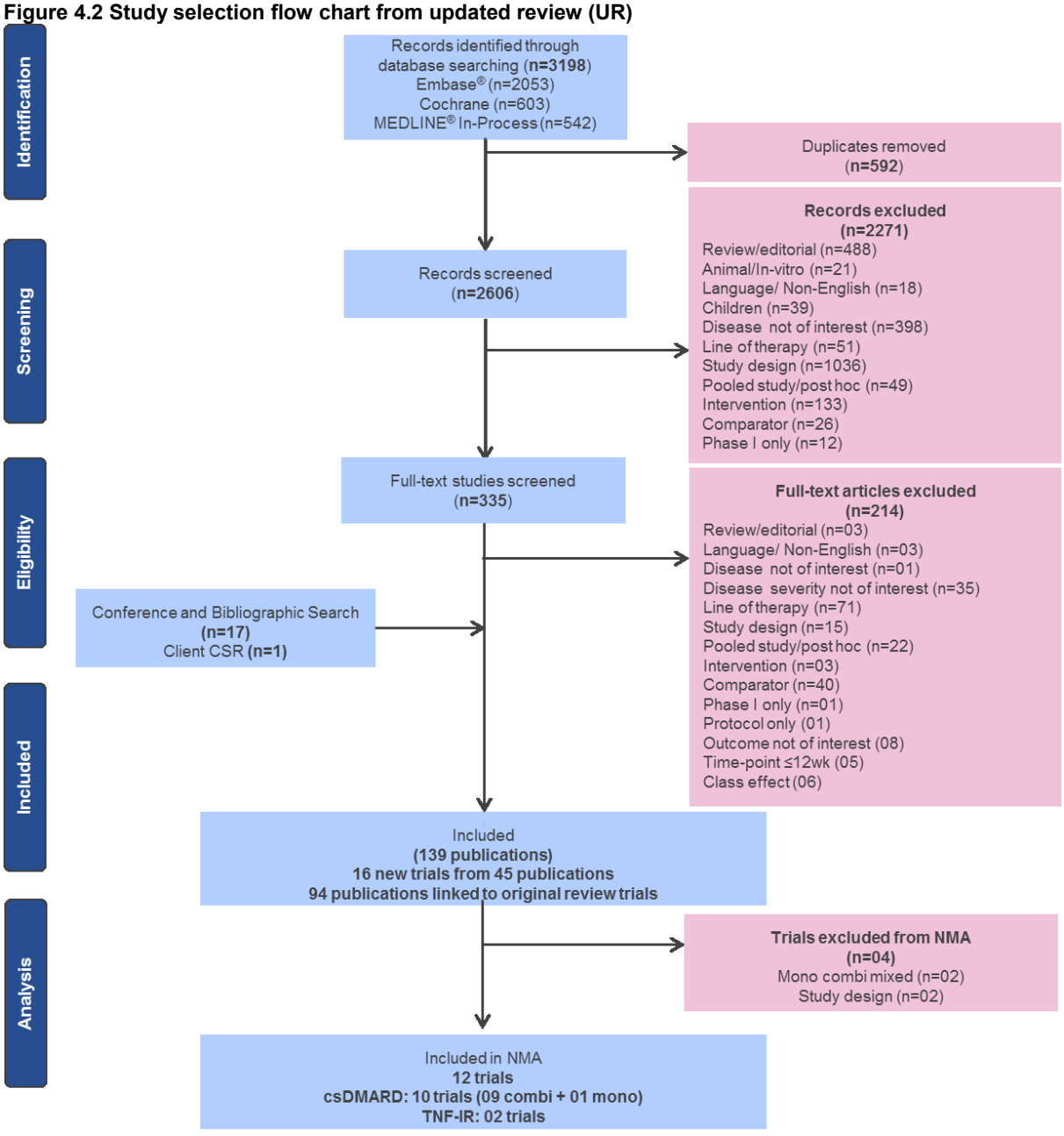
cDMARD-IR=conventional disease-modifying anti-rheumatic drug irresponsive; CSR=clinical study report; MTX=methotrexate; NMA=network meta-analysis; ORv=original review; SLR=systematic literature review; TNF-IR=tumour necrosis factor irresponsive; UR=updated review

The following changes were made to the evidence base in the update review:

- Additions to the original review: Update review identified total 139 publications consisting of 16 new studies from 45 publications and 94 publications linked to the original review studies.

- Reductions to the original review: Total number of included studies in original review was decreased by one because Bingham 2013[133] was linked to GO-FURTHER trial[134-136]. Further, consideration of two investigational agents in late phase 3 (sirukumab and baricitinib) resulted in addition of one study (JADA[137]) excluded during the original review to the final NMA studies (Figure 4.2).

Figure 4.2 Study selection flow chart from updated review (UR)



csDMARD-IR/cDMARD-IR=conventional disease-modifying anti-rheumatic drug irresponsive; CSR=clinical study report; MTX=methotrexate; NMA=network meta-analysis; SLR=systematic literature review; TNF-IR=tumour necrosis factor irresponsive; UR=updated review

4.2 List of relevant randomised controlled trials

4.2.1 List of relevant randomised controlled trials comparing sarilumab with other therapies

Together, Table 4.3 and Table 4.4 lists the randomised controlled trials (RCTs) identified in the SLR that compare sarilumab with other therapies. The RCTs in Table 4.3 include all key RCTs in the sarilumab Phase II/III clinical trial programme and include comparisons with relevant lines of therapy and in patient populations in the decision problem.

Five studies in the sarilumab clinical trial programme are relevant to the decision problem and include (Table 4.3):

- **MOBILITY A (**NCT01061736)**,** a 306-patient, dose-ranging, multi-national, randomised, multi-arm, double-blind, placebo-controlled Phase II dose-ranging study, that compared five different dose regimens of sarilumab in combination with MTX with placebo plus methotrexate (MTX). The primary endpoint of the study was the proportion of patients achieving at least an ACR20 after 12 weeks[55,138].

- **MOBILITY B (**NCT01061736)**,** a 1,197-patient, confirmatory, multi-national, randomised, multi-arm, double-blind, placebo-controlled study evaluating the safety and efficacy of sarilumab in combination with MTX versus placebo in combination with MTX in patients with active RA who were inadequate responders to MTX therapy. The primary endpoints of the study were the proportion of patients achieving an ACR20 at Week 24, change in physical function (HAQ-DI) at Week 16, and change in mTSS at Week 52[56,138].

- **TARGET (**NCT01709578), a 546-patient, multi-national, randomised, multi-arm, double-blind, placebo-controlled study evaluating the safety and efficacy of sarilumab in patients with inadequate response or intolerance to TNFis. The primary endpoints are proportion of patients achieving an ACR20 at Week 24 and the change in physical function (HAQ-DI) at Week 12 [57,139].

- **ASCERTAIN (**NCT01768572)**,** a 202-patient, multi-national, randomised, double-blind, double-dummy trial that evaluated the safety and tolerability (and efficacy as an exploratory endpoint) of sarilumab versus tocilizumab in patients with RA who are inadequate responders to or intolerant of TNFis[58,140].

- **MONARCH (**NCT02332590), a 369-patient, head-to-head trial comparing sarilumab monotherapy and adalimumab monotherapy in patients with active RA who are

intolerant of, or considered inappropriate candidates for, continued treatment with MTX therapy. The primary objective of this study was to demonstrate that sarilumab monotherapy is superior to adalimumab monotherapy with respect to signs and symptoms (DAS28- erythrocyte sedimentation rate [ESR]) at Week 24 in patients with active RA who are either intolerant of, or considered inappropriate candidates for continued treatment with MTX, or after at least 12 weeks of continuous treatment with MTX, are determined to be inadequate responders. Adalimumab was selected as a representative comparator for sarilumab because of its status as an approved and widely used bDMARD with an established safety record in RA, both in combination with MTX and as a monotherapy. The primary efficacy endpoint is change from baseline in DAS28-ESR at 24 weeks[1,141].

- **EXTEND** (NCT01146652) is an ongoing, multi-national, open-label extension study to assess long-term efficacy and long-term safety associated with long-term use of sarilumab with or without concomitant DMARDs, including MTX (Section 4.11 and Section 4.14)[59,142]. At the time of the EXTEND data cut, MONARCH had not yet reached completion and patients had not entered the OLE phase.

Other Phase III studies in the sarilumab clinical trial programme include:

- The **ONE** study, which is an interventional, open-label, randomised, parallel-group study assessing the immunogenicity of sarilumab administered as monotherapy in patients ≥18 years with severe active RA[143]

- The **EASY** study, which assessed the utility of the sarilumab pre-filled pen (auto-injector device) and a pre-filled syringe in patients with moderate-to-severe active RA[144]

- The **KAKEHASI** study, which assessed the safety and efficacy of sarilumab plus MTX in Japanese patients with moderate-to-severe active RA (Section 4.14)[145]

Although these three trials are complete, these studies do not form part of the decision problem.

Table 4.3 List of Phase II/III trials relevant for technology appraisal

STUDY NCT number	MOBILITY A NCT01061736	MOBILITY B NCT01061736	TARGET NCT01709578	ASCERTAIN NCT01768572	MONARCH NCT02332590	EXTEND NCT01146652
Interventions	Sarilumab + MTX	Sarilumab + MTX	Sarilumab + cDMARD	Sarilumab + cDMARD	Sarilumab	Sarilumab + cDMARD Sarilumab monotherapy
Comparator	Placebo + MTX	Placebo + MTX	Placebo + cDMARD	Tocilizumab + cDMARD	Adalimumab	NA Experimental extension study
N	306	1,197	546	202	369	2,023
Population	Adults MTX-IR	Adults MTX-IR	Adults TNFi-IR/IT	Adults TNFi-IR/IT	Adults MTX-IR/IT	Adults cDMARD/TNFi-IR/IT
Aim/objective of the study	Phase II dose-ranging study, comparing five dose regimens of sarilumab in combination with MTX to demonstrate the safety and efficacy of sarilumab in patients with active RA who are IR to MTX therapy	Demonstrate the safety and efficacy of sarilumab in combination with MTX in patients with active RA who are inadequate responders to MTX therapy	Demonstrate the safety and efficacy of sarilumab in patients who are inadequate responders to or intolerant of TNFi	Evaluate the safety and tolerability of sarilumab and tocilizumab in patients with RA who are inadequate responders to or intolerant of TNFi	Demonstrate that sarilumab monotherapy is superior to adalimumab monotherapy in patients with active RA who are either IT of, or considered inappropriate candidates for continued treatment with MTX	To assess the long-term safety of sarilumab in patients with RA
Length	12 weeks	52 weeks	24 weeks	24 weeks	24 weeks	Ongoing—at least 264 weeks
Phase	II	III	III	III	III	III
Primary study reference	Huizinga 2014[55]	Genovese 2015[56]	Fleischmann 2017[57]	ClinicalTrials.gov[140] Sanofi Genzyme Data on File (CSR)[58]	Burmester 2016[1]	ClinicalTrials.gov[142] Sanofi Genzyme Data on File (CSR)[59]
Study included in the NMA	Yes	Yes	Yes	Yes	Yes	No

cDMARDs=conventional disease-modifying anti-rheumatic drug; CSR=clinical study report; IR=irresponsive; IT=intolerant; MTX=methotrexate; NCT number= National Clinical Trial Identifier RA=rheumatoid arthritis;

Table 4.4 List of Phase III trials not relevant for technology appraisal

Study NCT number	ONE NCT02121210	EASY NCT02057250	KAKEHASI NCT02293902
Interventions	Sarilumab monotherapy	Sarilumab + MTX Pre-filled pen	Sarilumab + MTX
Comparator	Nil/NA	Placebo	Placebo
N	132	217	243
Population	Adults cDMARD-IR/IT	Adults cDMARD-IR/IT	Japanese adults MTX-IR
Aim/objective of the study	To assess immunogenicity and efficacy of sarilumab monotherapy	To assess the robustness and usability of sarilumab pre-filled pen when used by RA patients in unsupervised settings	To demonstrate that sarilumab plus MTX reduces signs and symptoms of RA in Japanese patients with moderate-to-severe active RA with an inadequate response to MTX
Length	24 weeks	12 weeks	52 weeks
Phase	III	III	III
Primary study reference	Sanofi Genzyme Data on File[146] ClinicalTrials.gov[143]	Sanofi Genzyne Data on File[78] ClinicalTrials.gov[144]	Sanofi Genzyme Data on File[147] ClinicalTrials.gov[145]
Study included in the NMA	No	No	No

cDMARDs=conventional disease-modifying anti-rheumatic drug; CSR=clinical study report; IR=irresponsive; IT=intolerant; MTX=methotrexate; NCT number= National Clinical Trial Identifier RA=rheumatoid arthritis;

4.3 Summary of methodology of the relevant randomised controlled trials

4.3.1 Study design summary

The primary objectives of the five key sarilumab trials were to evaluate the safety and efficacy in terms of clinical signs and symptoms, radiological progression, and physical function of subcutaneously (SC) administered sarilumab for the treatment of patients with moderate-to-severe, active RA[1,55-59]:

- In combination with MTX (MOBILITY A and MOBILITY B).
- In combination with a cDMARD (TARGET and ASCERTAIN).
- Or as a monotherapy (MONARCH).

The primary objective of ASCERTAIN was to evaluate the safety and tolerability (efficacy as an exploratory endpoint) of sarilumab and tocilizumab in combination with cDMARDs in patients with RA who are inadequate responders to or intolerant of TNFi. MONARCH also aimed to demonstrate the clinical superiority of sarilumab monotherapy versus adalimumab monotherapy.

All protocols were approved by the appropriate ethics committees/institutional review boards, and each patient gave written informed consent. RCTs were conducted in compliance with institutional review board regulations, the International Conference on Harmonisation Guidelines for Good Clinical Practice, and the Declaration of Helsinki.

4.3.1.1 MOBILITY A study design[55]

MOBILITY A is a randomised, multicentre, 12-week, placebo-controlled, dose-ranging RCT. MOBILITY A utilised an operationally seamless design that comprised a 12-week, six arm, Phase II, dose-ranging study to determine the optimal dose regimens (Figure 4.3). All patients were ≥18 years, with moderate-to-severe, active RA with disease duration ≥3 months and were irresponsive to MTX. In MOBILITY A, 306 patients were randomised (1:1:1:1:1:1) to receive placebo once a week (QW) + MTX (n=52), sarilumab 100 mg QW + MTX (n=50), sarilumab 150 mg QW + MTX (n=50), sarilumab100 mg Q2W + MTX (n=51), sarilumab 150 mg Q2W + MTX (n=51), or sarilumab 200 mg Q2W + MTX (n=52) (Figure 4.3).

Rescue with open-label sarilumab 200 mg Q2W was allowed on or after Week 16 for patients without improvement in tender joint count (TJC) or swollen joint count (SJC) (defined as <20% improvement compared with baseline) at two consecutive assessments,

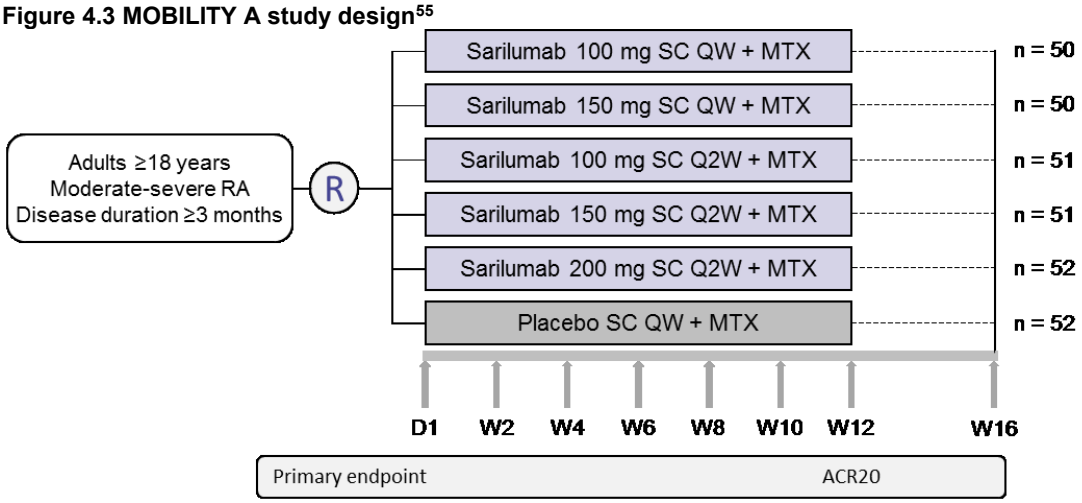
or at the discretion of the investigator. All patients who completed the double-blind treatment period were eligible for inclusion in the long-term OLE safety study EXTEND.

The primary endpoint, the ACR20 response rate at Week 12, was assessed in the intention-to-treat (ITT) population (Table 4.7). Secondary endpoints included ACR50 and ACR70 responses, change from baseline in individual disease activity measures (SJC, TJC, physician and patient global assessment of disease activity, patient's pain score, C-reactive protein [CRP], HAQ-DI, DAS28-CRP), and proportion of patients achieving disease remission defined as DAS28-CRP <2.6 (Table 4.7).

Safety variables included AEs and clinical laboratory parameters and the treatment-emergent adverse event (TEAE) observation period was defined as the time from the first dose up to the end of the follow-up period. Laboratory tests included:

- Haematology: haemoglobin, haematocrit, red blood cell count and morphology (if red blood cell count is abnormal), white blood cell count, white blood cell differential, and platelet count
- Liver function tests: prothrombin time, albumin, aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin, conjugated bilirubin, and unconjugated bilirubin
- Lipid profiles: triglycerides, total cholesterol, high density lipoprotein (HDL) cholesterol, and low density lipoprotein (LDL) cholesterol
- Clinical chemistry: fasting glucose, total protein, calcium, sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), lactate dehydrogenase (LDH), creatinine, and uric acid.

Figure 4.3 MOBILITY A study design[55]



ACR20=American College of Rheumatology 20% improvement; D=day; MTX=methotrexate; QW=once a week; Q2W=once every 2 weeks; SC=subcutaneous; R=randomisation; RA=rheumatoid arthritis; W=week

4.3.1.2 MOBILITY B study design[56]

MOBILITY B is a Phase III, randomised, double-blind, multicentre, 52-week, placebo-controlled RCT to confirm the efficacy and safety of two dose regimens (150 mg Q2W and 200 mg Q2W). All patients were ≥18 years with moderate-to-severe, active RA with disease duration ≥3 months and irresponsive to MTX (Figure 4.4). In MOBILITY B, 1,197 patients were randomised (1:1:1) to receive placebo Q2W + MTX (n=398), sarilumab 150 mg Q2W + MTX (n=400), or sarilumab 200 mg Q2W + MTX (n=399) (Figure 4.4).

Rescue with open-label sarilumab 200 mg Q2W was allowed on or after week 16 for patients without improvement in TJC or SJC (defined as <20% improvement compared with baseline) at two consecutive assessments, or at the discretion of the investigator. All patients who completed the double-blind treatment period were eligible for inclusion in the long-term OLE safety study EXTEND.

MOBILITY B had three co-primary endpoints: 1) proportion of patients achieving an ACR20 at Week 24; 2) change from baseline in physical function assessed using the HAQ-DI at Week 16; and 3) change from baseline in the mTSS score of radiographic progression of structural damage, assessed at Week 52 (Table 4.7). The key secondary endpoint was the proportion of patients achieving a major clinical response, defined as an ACR70 maintained for ≥6 consecutive months. Additional secondary endpoints included all components of the ACR core set of disease activity measures, DAS28-CRP and the Clinical Disease Activity Index (CDAI) (Table 4.7).

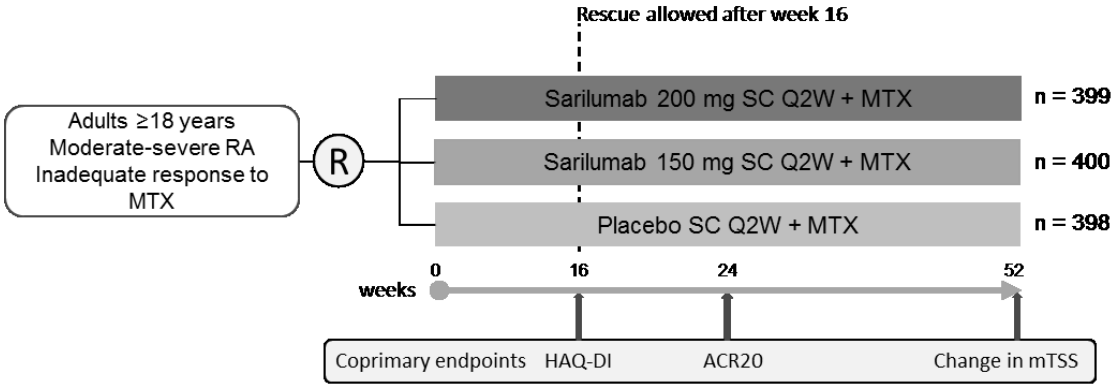
Safety variables included AEs and clinical laboratory parameters. TEAE observation period for patients who completed the double-blind treatment or discontinued the double-blind treatment early was defined as the time from the first dose of treatment up to the end of the study. The TEAE observation period for patients who discontinued the double-blind treatment because of inadequate response (i.e., rescued patients), the TEAE observational period was defined as the time from first dose of double-blind treatment to the date on which the patient was rescued (including the rescue day).

Adverse events of special interest (AESIs) included opportunistic infections, Infections requiring prolonged (>14 days) medication, tuberculosis (TB), increased ALT, neutropenia, thrombocytopenia, demyelinating events, gastrointestinal (GI) perforation/ulceration, and specific cardiovascular events (myocardial infarction, stroke, heart failure etc.).

Laboratory tests included:

- Haematology: haemoglobin, haematocrit, red blood cell count and morphology (if red blood cell count is abnormal), white blood cell count, white blood cell differential, and platelet count
- Liver function tests: PT, albumin, ALT, AST, ALP, total bilirubin, conjugated bilirubin, and unconjugated bilirubin
- Lipid profiles: triglycerides, total cholesterol, HDL cholesterol, and LDL cholesterol
- Clinical chemistry: fasting glucose, total protein, calcium, sodium, potassium, chloride, bicarbonate, BUN, LDH, creatinine, and uric acid.

Figure 4.4 MOBILITY B study design[56]



ACR20=American College of Rheumatology 20% improvement; HAQ-DI=Health Assessment Questionnaire Disability Index; MTX=methotrexate; Q2W=once every 2 weeks; mTSS=modified Total Sharp Score; SC=subcutaneous

4.3.1.3 TARGET study design[57]

TARGET is a Phase III, randomised, double-blind, multicentre, 24-week, placebo-controlled RCT. All patients were ≥18 years with moderate-to-severe, active RA with disease duration ≥6 months and were inadequate responders to or intolerant of TNFi. In TARGET, 546 patients were randomised (1:1:1) to receive placebo + cDMARDs Q2W (n=181), sarilumab 150 mg Q2W + cDMARDs (n=181), or sarilumab 200 mg Q2W + cDMARDs (n=184) (Figure 4.5).

Patients with <20% improvement from baseline in either SJC or TJC for two consecutive assessments were eligible for rescue at Week 12 with open-label sarilumab 200 mg Q2W. All patients who completed the double-blind treatment period were eligible for inclusion in the long-term OLE safety study EXTEND.

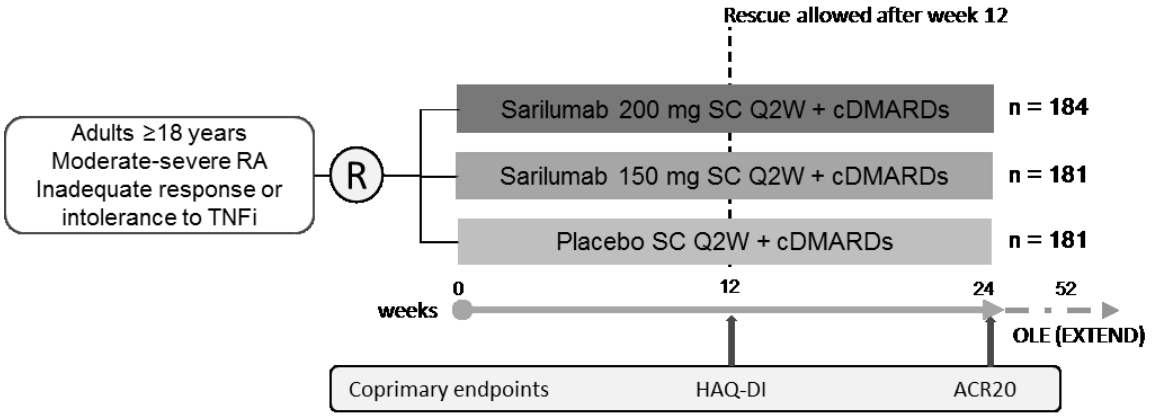
TARGET had two co-primary endpoints: 1) proportion of patients achieving an ACR20 at Week 24; and 2) change from baseline in physical function assessed using the HAQ-DI at Week 12 (Table 4.7). Secondary endpoints included change from baseline in DAS28-CRP at

Week 24, ACR50/70 response rates at Week 24, and proportion of patients achieving disease remission defined as DAS28-CRP <2.6 at Week 24 (Table 4.7).

The observation period used for the safety population was the TEAE period, which included the treatment and follow-up periods (TARGET CSR). Safety assessments included AEs, SAEs and AESIs. Laboratory tests included:

- Haematology: haemoglobin, haematocrit, red blood cell count and morphology (if red blood cell count is abnormal), white blood cell count, white blood cell differential, platelet count, and ANC
- Clinical chemistry: calcium, sodium, potassium, chloride, bicarbonate, BUN, LDH, creatinine, and uric acid
- Liver function tests: albumin, ALT, AST, ALP, total bilirubin, conjugated bilirubin, and unconjugated bilirubin
- Lipid profiles: triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol
- Fasting glucose and glycated haemoglobin (HbA1c)
- Rheumatoid factor (RF), anti-nuclear antibodies (ANA)/dsDNA antibody, and anti-citrullinated peptide antibody (anti-CCP)
- Anti-drug antibody to sarilumab.

Figure 4.5 TARGET study design[57]



ACR20=American College of Rheumatology 20% improvement; cDMARD=conventional disease-modifying anti-rheumatic drug; HAQ-DI=Health Assessment Questionnaire Disability Index; IV=intravenous; OLE=open-label extension; Q2W=once every 2 weeks; R=randomisation; RA=rheumatoid arthritis; SC=subcutaneous; TNFi=tumour necrosis factor inhibitor

4.3.1.4 ASCERTAIN study design[58,140]

ASCERTAIN was a Phase III, randomised, double-blind, double-dummy, multicentre, 24-week, active-comparator RCT assessing the safety, tolerability (and efficacy as an exploratory endpoint) of sarilumab and tocilizumab (at the time the only approved IL-6R blocking agent with the same MoA as sarilumab) in patients with RA who were inadequate responders to or intolerant of TNFi.

The double-blind double-dummy design of ASCERTAIN prevented recall and reporting bias of the safety events. All patients were ≥18 years with moderate-to-severe, active RA with disease duration ≥3 months and were inadequate responders to or intolerant of TNFi.

In ASCERTAIN, 202 patients were randomised (2:1:1) to receive intravenous (IV) tocilizumab 4 mg/kg once every 4 weeks (Q4W) + cDMARD (n=102), sarilumab 150 mg Q2W + cDMARD (n=49), or sarilumab 200 mg Q2W + cDMARD (n=51) (Figure 4.6)

The primary endpoints of ASCERTAIN were: description and number of non-treatment emergent adverse events, treatment emergent adverse events (TEAEs) (from first IMP administration until 6 weeks after the end of treatment visit), serious adverse events (SAEs), and AESIs including but not limited to neutropenia, thrombocytopenia, elevations in hepatic enzymes, lipid levels, cardiovascular events (CV), tuberculosis (TB) and other opportunistic infections, description of laboratory values, vitals signs, and electrocardiogram (ECG) parameters, and occurrence and titer of anti-sarilumab anti-bodies. Exploratory efficacy measurements included ACR20/50/70 response rates at Week 24 and the proportion of patients achieving disease remission defined as DAS28-CRP <2.6 at Week 24 (Table 4.7).

The same safety assessments were applied across the study and treatment arms. The occurrence of AEs including SAEs and AESIs (neutropenia, thrombocytopenia, and changes in hepatic enzymes, lipid levels, CV events, TB, and other opportunistic infections), were collected at every visit.

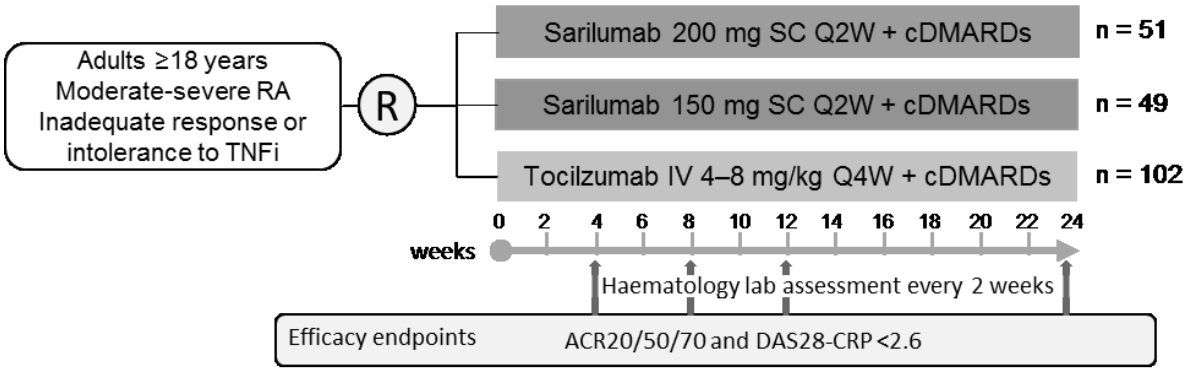
The clinical laboratory data consisted of blood analyses (including haematology and clinical chemistry) and urinalysis. Laboratory tests included:

- Haematology: haemoglobin, haematocrit, red blood cell count and morphology (if red blood cell count is abnormal), white blood cell count, white blood cell differential, platelet count, and absolute neutrophil count (ANC)

- Full chemistry profiles including sodium, potassium, chloride, BUN, creatinine and creatinine clearance, calcium, phosphate, total protein, lactate dehydrogenase, and uric acid
- Liver function tests: albumin, PT, ALT, AST, ALP, total bilirubin, conjugated bilirubin, and unconjugated bilirubin
- Lipid profiles: triglycerides, total cholesterol, HDL cholesterol, and LDL cholesterol
- Fasting glucose and HbA1c
- RF, ANA/dsDNA antibody, anti-CCP, hs-CRP
- ADA to sarilumab.

It is important to note that the recommended posology of tocilizumab is different in Europe and the US[77,148]. Although in the EU the recommended posology of tocilizumab in RA is 8 mg/kg body weight Q4W IV, in ASCERTAIN, tocilizumab was utilised according to the US label, i.e., IV infusion of tocilizumab Q4W were initiated at 4 mg/kg and increased to 8 mg/kg, if needed, based on clinical response (as assessed by the investigator).

Figure 4.6 ASCERTAIN study design[58]



ACR20/50/70=American College of Rheumatology 20%/50%/70% improvement; cDMARD=conventional disease-modifying anti-rheumatic drug; DAS28-CRP=28 joint disease activity score with C-reactive protein; IV=intravenous; MTX=methotrexate; Q2W=once every 2 weeks; Q4W=once every 4weeks; SC=subcutaneous; TNFi=tumour necrosis factor inhibitor

4.3.1.5 MONARCH study design[1]

MONARCH was a Phase III, randomised, multicentre, double-blind, double-dummy, 24-week, active-comparator RCT to assess the superiority of sarilumab compared with adalimumab. Adalimumab was selected as a representative comparator for sarilumab because of its status as an approved and widely used bDMARD with an established safety record as a treatment for patients with RA, both in combination with DMARDs and as

monotherapy. All patients were ≥18 years with severe, active RA with disease duration ≥3 months and were inadequate responders to or intolerant of MTX.

In MONARCH, 369 patients were randomised (1:1) to receive sarilumab 200 mg + placebo Q2W (n=184), or adalimumab 40 mg + placebo Q2W (n=185) (Figure 4.7).

After Week 16, dose escalation to weekly adalimumab or matching placebo in the sarilumab group was permitted for patients who did not achieve ≥20% improvement in TJC or SJC. All patients who completed the double-blind treatment period were eligible for inclusion in the long-term OLE safety study EXTEND.

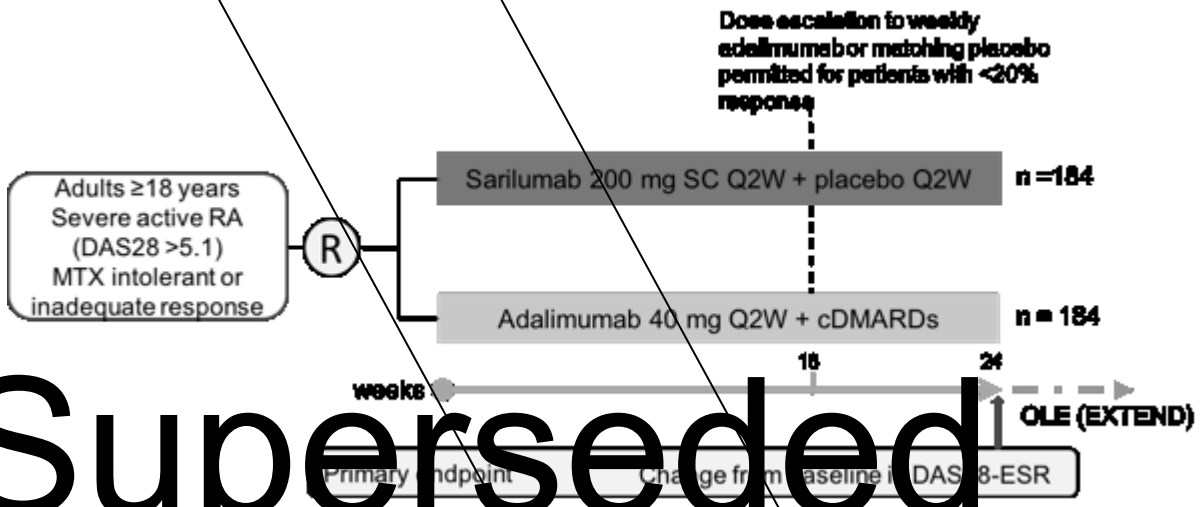
The primary endpoint of MONARCH was the change from baseline in DAS28-ESR at Week 24 (Table 4.7). Secondary endpoints included proportion of patients achieving disease remission defined as DAS28-ESR <2.6 at Week 24, HAQ-DI at Week 24, ACR20/50/70 response rates at Week 24, Medical Outcomes Short Form 36 Health Survey (SF-36) (physical component summary score and mental component summary) at Week 24, and Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) at Week 24 (Table 4.7).

The TEAE period was defined for the 24 week randomised treatment period as the time from first dose of randomised study treatment up to the day of the first dose of the open-label treatment for patients who completed the randomised treatment and enrolled in the extension. For patients who did not enrol in the extension, the TEAE period was defined as the time from the first dose of randomised study treatment to the last dose date of investigational medicinal product (IMP) + 60 days. The occurrence of AEs, including SAEs and AEs of special interest (neutropenia, thrombocytopenia, and changes in hepatic enzymes, lipid levels, CV events, TB and other opportunistic infections) were reported. Laboratory analysis included:

- Haematology: haemoglobin, haematocrit, red blood cell count and morphology (if red blood cell count is abnormal), white blood cell count, white blood cell differential, platelet count, and ANC
- Full chemistry profiles including sodium, potassium, chloride, bicarbonate, BUN, creatinine and creatinine clearance, calcium, phosphate, total protein, albumin, ALT, AST, alkaline phosphatase, total bilirubin, conjugated bilirubin, unconjugated bilirubin, lactate dehydrogenase, uric acid, prothrombin time, and hs-CRP
- Fasting lipids: Triglycerides, total cholesterol, HDL, LDL and triglycerides

- Fasting glucose and HbA1c
- RF, ANA/dsDNA antibody, and anti-CCP
- ADAs to sarilumab

Figure 4.7 MONARCH study design[1]



cDMARD=conventional disease-modifying anti-rheumatic drug; DAS28-ESR=28-joint count disease activity score-erythrocyte sedimentation rate; MTX=methotrexate; OLE=open-label extension; Q2W=once every 2 weeks; R=randomisation; RA=rheumatoid arthritis; SC=subcutaneous

4.3.1.6 Eligibility criteria

Only subjects who fulfilled all the inclusion criteria and did not meet any of the exclusion criteria were included in the clinical trials. The full inclusion and exclusion criteria for the studies are provided in Table 4.5.

4.3.1.7 Endpoints

Table 4.6 Outcome measures provides full details of primary outcomes measures and definitions. Table 4.7 provides details of the primary and secondary efficacy endpoints for each trial.

Safety endpoints included incidence of TEAEs, serious AEs (SAEs), laboratory safety assessments and presence of sarilumab anti-drug antibodies (ADAs) .

Table 4.5 Inclusion and exclusion criteria[1,55-58]

Study	Inclusion criteria	Exclusion criteria
MOBILITY A and B	Patients aged 18–75 years Diagnosis of RA as defined by the 1987 revised ACR criteria Patients were included if they had active RA (defined as a SJC ≥6 [of 66 joints assessed], TJC ≥8 [of 68 joints assessed], and hs-CRP level ≥6 mg/L [upper limit of normal <6 mg/L]), with a disease duration of ≥3 months despite treatment with MTX for a minimum of 12 weeks at a stable dosage (10–25 mg/week), at the time point of ≥6 weeks prior to screening In addition, patients were required to have at least one documented bone erosion (on radiograph) or be positive for anti-CCP antibodies or seropositive for RF on screening laboratory tests at baseline Stable MTX dose requirement: 6–25mg[a]	Patients were excluded if they had: Uncontrolled concomitant diseases Significant extra-articular manifestations of RA Functional class IV RA Other inflammatory joint disease Current/recurrent infections Prior non-response (in the opinion of the investigator) to a bDMARD Treatment with oral prednisone or equivalent >10 mg per day within 4 weeks prior to the randomisation visit or use of parenteral or intra-articular glucocorticosteroids within 4 weeks prior to the screening visit Started treatment or changed dose of current treatment with NSAIDs/COX2 inhibitors or oral corticosteroids for 4 weeks prior to baseline Prior therapy in last 3 months with TNFi current treatment with non-MTX cDMARDs
TARGET	Diagnosis of RA ≥6 months' duration, according to the ACR/EULAR 2010 RA classification criteria ACR class I–III functional status, based on 1991 revised criteria Prior TNFi therapy failure and/or intolerance to at least one TNFi drug hs-CRP ≥8 mg/L at screening Moderate to severely active RA, defined as: At least 8 of 68 tender joints and 6 of 66 swollen joints at screening and baseline visits and hs-CRP ≥8 mg/L at screening Continuous treatment with one or a combination of non-bDMARDs (except for simultaneous combination use of leflunomide and MTX) for at least 12 consecutive weeks prior to randomisation and on stable dose(s) for at least 6 consecutive weeks prior to screening: MTX: 10–25 mg/week PO or intra-muscular (or per local labelling requirements for the treatment of RA if the dose range differs) Leflunomide: 10–20 mg PO daily Sulfasalazine: 1,000–3,000 mg PO daily Hydroxychloroquine: 200–400 mg PO daily	Patients <18 years of age or legal adult age Past history of, or current, autoimmune or inflammatory systemic or localised joint disease(s) other than RA Treatment with any DMARD other than those allowed per protocol and limited to the maximum specified dosage within 12 weeks prior to baseline Prior treatment with TNFi agent within ≈5 half-lives Prior treatment with any cell-depleting agents including, but not limited to, rituximab without a normal lymphocyte and CD19 + lymphocyte count Prior treatment with anti-IL-6 or anti-IL-6R antagonist therapies including, but not limited to, tocilizumab or sarilumab Use of oral prednisone >10 mg/dL or equivalent per day, or a change in dosage within 4 weeks prior to randomisation Any parenteral or intra-articular glucocorticoid injection within 4 weeks prior to baseline
MONARCH	Diagnosis of RA, according to the ACR/EULAR 2010 RA classification criteria with ≥3 months' disease duration ACR class I–III functional status, based on the 1991 revised criteria Active RA, defined as: at least eight of 68 tender joints and six of 66 swollen joints, and hs-CRP ≥8 mg/L or ESR ≥28 mm/h assessed between screening and	Age <18 years or the legal age of consent in the country of the study site, whichever is higher Current treatment with DMARDs/ immunosuppressive agents including MTX, cyclosporine, mycophenolate, tacrolimus, gold, penicillamine, sulfasalazine, or hydroxychloroquine within 2 weeks prior to the baseline (randomisation visit), azathioprine or cyclophosphamide within 12 weeks

	randomisation, and DAS28-ESR >5.1 using an ESR assessed between screening and randomisation Patients who per investigator judgement were either intolerant of, or considered inappropriate candidates for, continued treatment with MTX, or inadequate responders if treated with an adequate MTX dose (10–25 mg/week, or 6–25 mg/week for patients within Asia-Pacific region) for at least 12 weeks Signed written informed consent prior to performance of any study-related procedures	prior to baseline (randomisation visit), or leflunomide within 8 weeks prior to the randomisation visit or 4 weeks after cholestyramine washout Treatment with any prior biological agent, including anti-IL-6, IL-6R antagonists, and prior treatment with a JAK inhibitor Use of parenteral corticosteroids or intra-articular corticosteroids within 4 weeks prior to screening Use of oral corticosteroids in a dose higher than prednisone 10 mg or equivalent per day, or a change in dosage within 4 weeks prior to randomisation Exclusion related to tuberculosis
ASCERTAIN	Diagnosis of RA, according to the ACR/EULAR 2010 RA classification criteria with ≥3 months' disease duration ACR class I–III functional status, based on the 1991 revised criteria. Moderate to severely active RA TNFi therapy failures, defined as patients with an inadequate clinical response defined by the investigator, after being treated for at least 3 consecutive months and/or intolerance to at least one TNF antagonist, resulting in or requiring their discontinuation Continuous treatment with one or a combination of cDMARDs for at least 12 consecutive weeks prior to screening and on stable dose(s) for at least 6 consecutive weeks prior to screening	Patients <18 years of age Use of parenteral corticosteroids or intra-articular corticosteroids within 4 weeks prior to screening Use of oral corticosteroids in a dose higher than prednisone 10 mg or equivalent per day, or a change in dosage within 4 weeks prior to screening Past history of, or current, autoimmune or inflammatory systemic or localised joint disease(s) other than RA Patients with active tuberculosis or latent tuberculosis infection. Prior or current history of interstitial lung disease. Prior treatment with anti-IL-6 or anti-IL-6R therapies, including, but not limited to, tocilizumab or sarilumab Treatment with TNFi agents, including etanercept within 28 days prior to randomisation; or infliximab, adalimumab, golimumab, or certolizumab pegol within 42 days prior to randomisation Treatment with RA-directed biological agents with non-TNFα antagonist mechanisms without adequate washout Prior treatment with a JAK inhibitor (e.g. tofacitinib)

[a]Amendment not reported in the clinical study report

ACR= American College of Rheumatology; anti-CCP=anti-cyclic citrullinated peptide; bDMARD=biological disease-modifying anti-rheumatic drug; cDMARD=conventional disease-modifying anti-rheumatic drug; COX2=cyclooxygenase-2; DAS28=28-joint disease activity score; DMARD=disease-modifying anti-rheumatic drug; ESR=erythrocyte sedimentation rate; EULAR=European League Against Rheumatism; hs-CRP=high-sensitivity C-reactive protein; IL-6=interleukin 6; IL-6R=interleukin 6 receptor; IV=intravenous; JAK=Janus kinase; MTX=methotrexate; RA=rheumatoid arthritis; RF=rheumatoid factor; NSAID=non-steroidal anti-inflammatory drug; PO=by mouth; RA=rheumatoid arthritis, SJC=swollen joint count; TJC=tender joint count; TNF=tumour necrosis factor; TNFi=tumour necrosis factor inhibitor

Table 4.6 Outcome measures

<table>
<tr><th>Endpoint</th><th>Description</th></tr>
<tr><td>ACR</td><td>

ACR responses are assessed with a composite rating scale of the ACR that includes seven variables:

TJC — based on 28 joints
SJC — based on 28 joints
Levels of an acute-phase reactant (either the CRP level or the ESR)
Patient’s assessment of pain
Patient’s global assessment of disease activity
Physician’s global assessment of disease activity
Patient’s assessment of physical function (HAQ-DI)

ACR20/50/70 is defined as the proportion of patients achieving at least 20%/50%/70% improvement in both TJC and SJC, and at least 20%/50%/70% improvement in at least three of the five other assessments

</td></tr>
<tr><td>DAS28</td><td>

DAS28 is a composite score that includes four variables:

TJC —based on 28 joints
SJC — based on 28 joints
GH assessment by the patient assessed from the ACR RA core set questionnaire (patient global assessment) in 100 mm VAS

Marker of inflammation assessed by the CRP in mg/L or ESR in mm/hr
It is a continuous measure allowing for measurement of absolute change in disease activity and percentage improvement. It has been extensively validated for use in clinical trials and accepted by health authorities.
The DAS28 score provides a number indicating the current disease activity of the RA. A DAS28-ESR score >5.1 means high disease activity, whereas a DAS28-ESR score <3.2 indicates low disease activity and a DAS28-ESR score <2.6 means disease remission. CRP is used with ESR validation of disease activity.
The EULAR response criteria combine the DAS28 score between two time points. The EULAR response criteria are defined as good, moderate, and non-response.

Table A: EULAR DAS28 response criteria based on improvement
<table>
<tr><td>•</td><td colspan="3">• DAS28 improvement</td></tr>
<tr><td>• Present DAS28↓</td><td>• >1.2</td><td>• >0.6 and ≤1.2</td><td>• ≤0.6</td></tr>
<tr><td>• ≤3.2</td><td>• Good response</td><td>• Moderate response</td><td>• No response</td></tr>
<tr><td>• >3.2 and ≤5.1</td><td>• Moderate response</td><td>Moderate response</td><td>• No response</td></tr>
<tr><td>• >5.1</td><td>• Moderate response</td><td>• No response</td><td>• No response</td></tr>
</table>
Source: http://www.das-score.nl/das28/en/difference-between-the-das-and-das28/importance-of-das28-and-tight-control/eular-response-criteria.html
</td></tr>
<tr><td>HAQ-DI</td><td>

The HAQ is one of the first instruments designed deliberately to capture prospectively and by protocol the long-term influence of multiple chronic illnesses and to allow supplementation by additional measures for particular studies
The disability assessment component of the HAQ, the HAQ-DI, assesses a patient’s level of functional ability and includes questions on fine movements of the upper extremity, locomotor activities of the lower extremity, and activities that involve both upper and lower extremities. There

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

Endpoint	Description
	are 20 questions in eight categories of functioning, which represent a comprehensive set of functional activities — dressing, rising, eating, walking, hygiene, reach, grip, and usual activities. The stem of each item asks over the past week "Are you able to …" perform a particular task. The patient's responses are made on a scale from zero (no disability) to three (completely disabled). Each category contains at least two specific component questions.

SDAI	• The SDAI includes five components assessed in the ACR questionnaire as follows:
	  • TJC — based on 28 joints
	  • SJC — based on 28 joints
	  • Patient's global disease activity (based on a scale from 0 to 100 mm)
	  • Physician's global disease activity (based on a scale from 0 to 100 mm)
	  • CRP (mg/dL)
	• The SDAI is a simple numerical summation of these five individual components, and ranges from 0.1 to 86
	• The SDAI remission is defined as a SDAI score ≤3.3

CDAI	• The CDAI is a composite index constructed to measure clinical remission in RA that does not include a laboratory test, and is a numerical summation of four components:
	  • SJC — 28 joints
	  • TJC — 28 joints
	  • Patient's global disease activity (in cm)
	  • Physician's global assessment (in cm)
	• Scores range from 0 to 76
	• CDAI remission is defined as a CDAI score ≤2.8

Radiographic progression of mTSS	• Radiographic progression of mTSS is defined as a CFB in the mTSS >0. A CFB in the mTSS of ≤0 is considered no progression
Radiographic progression of the ES	• Radiographic progression of the ES is defined as a CFB in the ES >0. A CFB in the ES of ≤0 is considered no progression. In the sarilumab trials, the event of missing a baseline value or missing a CFB value in the ES is considered progression
Radiographic progression of the JSN score	• Radiographic progression of the JSN score is defined as the CFB in the JSN score >0. A CFB in the JSN score of ≤0 is considered no progression. In the sarilumab trials, the event of missing a baseline value or missing a CFB value in the JSN score is considered progression
Boolean-based ACR/EULAR remission	• Boolean-based ACR/EULAR remission is achieved when a patient satisfies all of the following four criteria at a given time point: TJC and SJC (based on the assessment of 28 joints) ≤1, CRP ≤10 mg/L, and patient global VAS ≤10 (mm)

ACR=American College of Rheumatology; CDAI=Clinical Disease Activity Index; CFB=change from baseline; CRP=C-reactive protein; DAS28=28-joint disease activity score; ESR=erythrocyte sedimentation rate; ES=erosion score; EULAR=European League Against Rheumatism; GH=general health; HAQ=Health Assessment Questionnaire; HAQ-DI=Health Assessment Questionnaire Disability Index; JSN=joint space narrowing; mTSS=modified Total Sharp Score; RA=rheumatoid arthritis; SDAI=Simplified Disease Activity Index; SJC=swollen joint count; TJC=tender joint count; VAS=visual analogue scale

Table 4.7 Endpoints[1,55-58]

	MOBILITY A	MOBILITY B	TARGET	ASCERTAIN[a]	MONARCH
Efficacy					
Primary	ACR20 Week 12	ACR20 at Week 24 Change in HAQ-DI from BL to Week 16 Change in mTSS from BL to Week 52	ACR20 response at Week 24 Change in HAQ-DI from BL to Week 12	No primary efficacy endpoints	Change in DAS28-ESR from BL to Week 24
Secondary	ACR50, ACR70 at Week 12 Change in each of the seven ACR components from BL to Week 12 Change in DAS28 from BL to Week 12 DAS28 remission Week 12 EULAR response (non-responders vs. responders) at Week 12 ACRn at Week 12	ACR 70 maintained for ≥6 consecutive months Change in each of the seven ACR components to Week 24 and 52 mTSS at Week 24 ACR50, ACR70, EULAR response at Weeks 24 and 52 Proportion with DAS28-CRP ≤3.2, DAS28-CRP ≤2.6, CDAI remission (≤2.8) and SDAI remission (≤3.3) at Weeks 24 and 52	Change in DAS28-CRP, CDAI and HAQ-DI from BL to Week 24 ACR50/70 Week 24 DAS28-CRP <2.6 at Week 24	No secondary efficacy endpoints	ACR20/50/70, DAS28-ESR remission, DAS28-ESR LDA, DAS28-CRP remission, DAS28-CRP LDA, HAQ-DI at Week 24
Patient-reported outcomes	PtGA, pain, FACIT-F at Week 12	PtGA, pain, FACIT-F, SF-36 (component scores [PCS, MCS] and domain scores [physical functioning, role physical, body pain, general health, vitality, social; functioning, role emotional and mental health]) at Week 24 and 52	PtGA, pain, FACIT-F, SF-36 (component scores [PCS, MCS] and domain scores [physical functioning, role physical, body pain, general health, vitality, social; functioning, role emotional and mental health]) at Week 12 and 24	Exploratory analysis only	SF-36 PCS and MCS, FACIT-F at Week 24
Exploratory				ACR20/50/70 at Week 12 Change in DAS28-CRP and DAS28-CRP remission rate from BL to Week 12	
Safety					
AEs, SAEs and AEs of special interest including neutropenia, thrombocytopenia, and changes in hepatic enzymes, lipid levels, CV events, TB and other opportunistic infections.					

aThis study was not powered for efficacy comparisons – efficacy variables are summarised descriptively
ACR20/50/70=American College of Rheumatology 20%/50%/70% improvement; BL=baseline; CDAI=Clinical Disease Activity Index; cDMARD=conventional synthetic biologic disease-modifying anti-rheumatic drug; DAS28-CRP=28-joint count disease activity score–C-reactive protein; DAS28-ESR=28-joint disease activity score - erythrocyte sedimentation rate; DMARD=non-biologic disease-modifying anti-rheumatic drug; FACIT-F=Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI=Health Assessment Questionnaire Disability Index; JSN=joint space narrowing; LDA=low disease activity; MCS=mental component score; mTSS=modified Total Sharp Score; MTX=methotrexate; PCS=physical component score; PtGA=patient global assessment; RAID=rheumatoid arthritis impact of disease; SDAI=Simplified Disease Activity Index SF-36=Short Form 36 health questionnaire; TSS=Total Sharp Score; WPS-RA=Work Productivity Survey Rheumatoid Arthritis

4.3.2 Comparative summary of trial methodology

A summary of the trial methodologies are presented in Table 4.8.

Table 4.8 Comparative summary of trial methodologies[1,55-58]

	MOBILITY A	MOBILITY B	TARGET	ASCERTAIN	MONARCH
Setting	Secondary care (outpatient) Self-administered or administered by a caregiver	Secondary care (outpatient) Self-administered or administered by a caregiver	Secondary care (outpatient) Self-administered or administered by a caregiver	Secondary care (outpatient) Self-administered (whenever possible)	Secondary care (outpatient) Self-administered (whenever possible)
Trial design	12-week, multicentre, randomised, double-blind, placebo-controlled Phase II study	52-week, multicentre, randomised, double-blind, placebo-controlled Phase III study	24-week, multicentre, randomised, double-blind, placebo-controlled Phase III study	24-week, multicentre, randomised, double-blind, double-dummy, placebo-controlled Phase III study	24-week, multicentre, randomised, double-blind, double-dummy, Phase III superiority study
Patient population	N=306 MTX irresponsive adults (18–75 years) with moderate to severely active RA (SJC ≥6, TJC ≥8, hs-CRP ≥0.[illegible] mg/dL) with disease duration ≥3 months despite treatment with MTX for a minimum of 12 weeks at a stable dosage (10–25 mg/week)	N=1,197 MTX irresponsive adults (18–75 years) with moderate to severely active RA (SJC ≥6, TJC ≥8, hs-CRP ≥0.[illegible] mg/dL) with disease duration ≥3 months despite treatment with MTX for a minimum of 12 weeks at a stable dosage (10–25 mg/week)	N=546 TNFi irresponsive/intolerant adults (≥18 years) with moderate to severely active RA (SJC ≥6, TJC ≥8, hs-CRP ≥0.[illegible] mg/dL) with disease duration ≥3 months and an inadequate response or intolerance to ≥1 TNFi therapy as defined by the investigator	N=202 TNFi irresponsive/intolerant adults (≥18 years) with moderate to severely active RA (SJC ≥4, TJC ≥4, hs-CRP ≥[illegible] mg/L, with disease duration ≥3 months and an inadequate response or intolerance to ≥1 TNFi after being treated ≥3 consecutive months	N=369 MTX irresponsive/intolerant adults (≥18 years) with severely active RA (SJC ≥6, TJC ≥8, hs-CRP ≥8 mg/L/ESR ≥22 mm/hours, DAS28-ESR >5.1) with disease duration ≥3 months and an inadequate response or intolerance to MTX for a minimum of 12 weeks at a stable dosage (10–25 mg/week or 6–26 mg/week in the Asia-Pacific region)
Location of data collection	262 study locations in the US, Argentina, Australia, Austria, Belarus, Belgium, Brazil, Canada, Chile, Colombia, Czech Republic, Egypt, Estonia, Finland, Germany, Greece, Hungary, India, South Korea, Lithuania, Malaysia, Mexico, Netherlands, New Zealand, Norway, Philippines, Poland,	262 study locations in US, Argentina, Australia, Austria, Belarus, Belgium, Brazil, Canada, Chile, Colombia, Czech Republic, Egypt, Estonia, Finland, Germany, Greece, Hungary, India, South Korea, Lithuania, Malaysia, Mexico, Netherlands, New Zealand, Norway, Philippines, Poland,	196 study locations in US, Argentina, Australia, Austria, Brazil, Canada, Chile, Colombia, Czech Republic, Ecuador, Germany, Greece, Guatemala, Hungary, Israel, Italy, South Korea, Lithuania, Mexico, Netherlands, New Zealand, Peru, Poland, Portugal, Romania, Russia, Slovakia,	78 study locations in US, Argentina, Belgium, Brazil, Czech Republic, Estonia, Finland, Hungary, Israel, Italy, Mexico, Netherlands, New Zealand, Norway, Poland, Romania, Russia, Spain, Sweden, UK	86 study locations in US, Chile, Czech Republic, Egypt, Estonia, Finland, Germany, Hungary, Israel, South Korea, Peru, Poland, Romania, Russia, South Africa, Spain, Ukraine, UK

	MOBILITY A	MOBILITY B	TARGET	ASCERTAIN	MONARCH
	Portugal, Romania, Russia, South Africa, Spain, Taiwan, Thailand, Turkey, Ukraine	Portugal, Romania, Russia, South Africa, Spain, Taiwan, Thailand, Turkey, Ukraine	Spain, Taiwan, , Turkey, Ukraine		
Interventions	Placebo QW + MTX (n=52) Sarilumab 100 mg QW + MTX (n=50) Sarilumab 150 mg QW + MTX (n=50) Sarilumab100 mg Q2W + MTX (n=51) Sarilumab 150 mg Q2W + MTX (n=51) Sarilumab 200 mg Q2W + MTX (n=52) Rescue with open-label sarilumab 200 mg Q2W allowed on or after Week 16 for patients without >20% improvement from BL in TJC or SJC at two consecutive assessments, or at the discretion of the investigator	Placebo Q2W + MTX (n=398) Sarilumab150 mg Q2W + MTX (n=400) Sarilumab 200 mg Q2W + MTX (n=399) Rescue with open-label sarilumab 200 mg Q2W allowed on or after Week 16 for patients without >20% improvement from BL in TJC or SJC at two consecutive assessments, or at the discretion of the investigator	Placebo Q2W + cDMARDs (n=181) Sarilumab 150 mg Q2W + cDMARDs (n=181) Sarilumab 200 mg Q2W + cDMARDs (n=184). Patients with <20% improvement from baseline in either SJC or TJC for two consecutive assessments were eligible for rescue at Week 12 with open-label sarilumab 200 mg Q2W	IV tocilizumab 4 mg/kg Q4W + cDMARD (n=102) Sarilumab 150 mg Q2W + cDMARD (n=52) Sarilumab 200 mg Q2W + cDMARD (n=51)	Sarilumab 200 mg + placebo Q2W (n=184) Adalimumab 40 mg + placebo Q2W (n=185)
Data from pre-specified outcomes	Yes	Yes	Yes	Yes	Yes
Assessments	Components of ACR core set and associated measures determined at randomisation and Weeks 2, 4, 8 and 12	Components of ACR core set and associated measures determined at randomisation and then Q2W to Week 12, Q4W Week 12 to 28 and Q8W thereafter. Radiographs of hands/wrists and feet at baseline, Week 24 and Week 52	Components of ACR core set and associated measures determined at randomisation, Week 2, Week 4 and Q4W thereafter	ADA immunoassay and PK at randomisation, Week 12 and Week 24 Components of ACR core set and associated measures determined at randomisation, Week 4, 8, 12 and 24	Components of ACR core set and associated measures determined at randomisation, Week 12 and Week 24
Pre-planned	Subgroup analysis of ACR20 by gender, race,	Subgroup analysis of ACR20, HAQ-DI and mTSS	Subgroup analysis of HAQ-DI by gender, race, region,	No subgroup analysis for	Subgroup analysis of DAS28-ESR by gender,

	MOBILITY A	MOBILITY B	TARGET	ASCERTAIN	MONARCH
subgroups	region, age, baseline weight, BMI, prior bDMARD use, RF, anti-CCP antibody, baseline CRP, duration of RA, number of prior DMARDs, smoking history	by gender, race, region, age, baseline weight, BMI, prior bDMARD use, RF, anti-CCP antibody, baseline CRP, duration of RA, number of prior DMARDs, smoking history	age, baseline weight, BMI, number prior TNFi, RF, anti-CCP, baseline CRP, duration RA, number of prior DMARDs, smoking history	efficacy endpoints	race, region, age, baseline weight, BMI, number prior TNFi, RF, anti-CCP, baseline CRP, baseline ESR, duration RA, number of prior DMARDs, MTX history, smoking history

ACR20/50/70=American College of Rheumatology 20%/50%/70% improvement; ADA=anti-drug antibodies; BMI=body mass index; cDMARD=conventional synthetic biologic disease-modifying anti-rheumatic drug; DAS28-ESR= 28-joint count disease activity score- erythrocyte sedimentation rate; DMARD=non-biologic disease-modifying anti-rheumatic drug; HAQ-DI=Health Assessment Questionnaire Disability Index; IV=intravenous; mTSS=modified Total Sharp Score; MTX=methotrexate; PFS=pre-filled syringe; Q2W=every two weeks; Q4W=every 4 weeks; SC=subcutaneous; TNFi=tumour necrosis factor inhibitor

4.4 Statistical analysis and definition of study groups in the relevant randomised controlled trials

4.4.1 Analysis populations

The three-different population analysis for sarilumab are:

1. *Placebo-controlled (cDMARD/MTX) population*

   The 52-week placebo-controlled population included patients from one Phase II study of 12-week duration (MOBILITY A) and two Phase III efficacy studies (one of 24-week duration [TARGET] and the other of 52-week duration [MOBILITY B]). In this population, 661 patients, 660 patients, and 661 patients received sarilumab 200 mg, sarilumab 150 mg, or placebo once every 2 weeks, respectively, in combination with conventional DMARDs.

2. *Sarilumab + DMARD long-term safety population*

   The safety of sarilumab in combination with DMARDs was evaluated based on data from seven studies (ONE was excluded), of which two were placebo-controlled, consisting of 2887 patients (long-term safety population). Of these, 2170 patients received sarilumab for at least 24 weeks, 1546 for at least 48 weeks, 1020 for at least 96 weeks, and 624 for at least 144 weeks.

3. *Sarilumab monotherapy population*

   The use of sarilumab as monotherapy was assessed in 132 patients, of which 67 received sarilumab 200 mg and 65 patients received sarilumab 150 mg without concomitant DMARDs

4.4.2 Sample size determination

For MOBILITY A, MOBILITY B, TARGET and MONARCH, the sample size per treatment group was calculated to provide a power of at least 90% to detect a statistically significant difference in the primary efficacy endpoint(s) (Table 4.9). The sample size in ASCERTAIN was based on empirical/practical considerations and clinical judgement. No formal sample size calculations were performed.

Table 4.9 Sample size determinations and corresponding powers[1,55-58]

	MOBILITY A	MOBILITY B	TARGET	ASCERTAIN	MONARCH
	Sample size calculations were performed using nQuery Advisor 6.01 software				
Minimum sample size required	50 patients per group	372 patients per group	174 patients per group	202 in total	170 patients per group
Methodology used for sample size determination	Based on change in mTSS at Week 52. Assuming alpha=0.01, 80% power, 40% RR in placebo and 75% RR in active treatment[a]	Based on change in mTSS at Week 52. Assuming alpha=0.025, 90% power and Week 52 mean change of 1.10 sarilumab and 0.35 placebo, with associated SD of 2.6[a]	Based on change in HAQ-DI at Week 24. Assuming alpha=0.025, 90% power and Week 24 mean change of 0.35 sarilumab and 0.05 placebo, with associated SD of 0.79[a]	Sample size of this study based on practical considerations and clinical judgement. No formal sample size calculations were performed	Based on change in DAS-28 at Week 24. Assuming alpha=0.025, 90% power and Week 24 mean difference of 0.6 between active treatments, with associated SD of 1.7[a]
Power	ACR20 power 80%	mTSS power 90% ACR20 power >99% HAQ-DI power 98%	ACR20 power 99% HAQ-DI power >90%	NR	DAS28 >90%

[a]Assumed mean changes and SD are based on results from the tocilizumab clinical trial programme (Hoffmann-La Roche 2008, Emery 2008).
ACR20=American College of Rheumatology 20% improvement; DAS28=28-joint disease activity score; HAQ-DI=Health Assessment Questionnaire Disability Index; mTSS=modified Total Sharp Score; NR=not relevant; RR=response rate; SD=standard deviations

4.4.3 Interim analyses and stopping guidelines

Interim analyses were neither planned in the protocol nor performed for MOBILITY A, MOBILITY B, TARGET, ASCERTAIN, or MONARCH.

4.4.4 Demographics and baseline characteristics

Patient characteristics, including demographics, medical history, and subject accountability were summarised by treatment and overall for the ITT population. The summaries were performed using descriptive statistics — e.g. mean, standard deviation (SD), median, minimum, and maximum for quantitative values and counts and percent for qualitative variables. The safety and pharmacokinetic populations were based on the treatment received; the ITT population was based on the randomised treatment group.

4.4.5 Statistical methods used to compare groups for primary and secondary endpoints

Efficacy analyses were conducted in ITT populations, which consisted of all randomised patients who received at least one dose of sarilumab and the statistical methodologies utilised in the five key studies are described in Table 4.10[1,55-58].

Table 4.10 Statistical methodology[1,55-58]

	MOBILITY A	MOBILITY B	TARGET	MONARCH	ASCERTAIN
Primary efficacy endpoints (ITT population)					
Primary analysis	ACR20 improvement analysed using 2-sided CMH test stratified by prior biologic use/region. Separate pairwise comparisons of RR active dose vs. placebo. MH estimate of OR and corresponding 95% CI derived by testing each active dose regimen versus placebo separately at each visit. Correction for the multiplicity that arose from testing multiple doses of sarilumab against placebo was addressed using the Hommel procedure with the Hommel adjusted p<0.05 considered statistically significant. Patients who discontinued treatment due to lack of efficacy or used rescue medication were considered as non-responders for all time points beyond the time they discontinued or started rescue medication. For patients who discontinued due to reasons other than lack of efficacy, LOCF procedure was applied to missing data for all 7 ACR components from the point of treatment discontinuation or rescue.	ACR20 improvement analysed responses by non-responder imputation analyses and evaluated using 2-sided CMH test stratified by prior biologic use/region. Change in HAQ-DI Week 16 analysed using MMRM adjusted for region, prior biologic use and BL HAQ-DI as covariates, For change in mTSS score BL to Week 52, missing or post-rescue therapy data were imputed by linear extrapolation approach for any patient having at least 1 BL and ≥1 post-BL radiograph during double-blind period. Data analysed by a rank analysis of covariance model. Radiographic data before rescue therapy period included as observed. Post-rescue therapy data were imputed using linear extrapolation. Changes from baseline in continuous variables (except mTSS), presented as LS mean (p). Bonferroni correction and hierarchical testing procedure for each dose of sarilumab used to control the Type I error rate at a	ACR20 improvement analysed using 2-sided CMH test stratified by prior biologic use/region. Change in HAQ-DI Week 12 analysed using MMRM adjusted for region, prior biologic use, visit, treatment-by-visit interaction and BL HAQ-DI as covariates - data collected after treatment discontinuation or rescue were classified as missing. Bonferroni correction and hierarchical testing procedure for each dose of sarilumab used to control the Type I error rate at a significance level of 0.05.	Change in DAS28-ESR Week 24 analysed using MMRM adjusted for treatment, visit, treatment-by-visit interaction and region as fixed effects and BL DAS28-ESR as a continuous covariate.	Descriptive statistics only Efficacy variables summarised using counts, proportions, mean, SE, and corresponding 95% CI.

	MOBILITY A	MOBILITY B	TARGET	MONARCH	ASCERTAIN
		significance level of 0.05.			
Sensitivity analysis	LOCF approach to impute missing TJC and SJC, and considered all patients 'non-responders' for all subsequent analysis time points after treatment discontinuation (for any reason) or rescue medication use.	LOCF approach for ACR20 to impute missing or post-rescue ACR components. LOCF approach for HAQ-DI to impute missing or post-rescue HAQ-DI values. Change in HAQ-DI by ANCOVA model with the baseline covariate adjusted for prior biologic use and region. Mean rank imputation, LOCF, no imputation (observed data in double-blind period only or data collected post-rescue period/after treatment discontinuation) or linear extrapolation used to impute missing mTSS.	LOCF approach (from point of treatment discontinuation) for ACR20 to impute missing data. LOCF and multiple imputation approach for HAQ-DI to impute missing data after rescue or treatment discontinuation.	Two sensitivity analyses: Included all data (including assessments made after permanent treatment discontinuation) Included all data after treatment discontinuation or adalimumab (or matching placebo) dose increase was set to missing and a multiple imputation approach was used.	None
Secondary efficacy endpoints					
	Descriptive statistics including number of subjects, mean, SE, LS means, difference in LS means (95% CI, p) for comparisons of each sarilumab dose against placebo Multiplicity in ACR50 and ACR70 corrected post hoc using simple Bonferroni adjustment with the unadjusted p<0.01 considered statistically significant ANCOVA model, including terms for baseline,	Categorical endpoints analysed using CMH test stratified by prior biologic use and region, after missing or post-rescue responses imputed using non-responders or progression imputation Continuous endpoints analysed using MMRM adjusted for prior biologic use, region, and the baseline covariate, with no imputation performed for missing or post-rescue measurements.	Categorical endpoints analysed using CMH 2-sided test stratified by prior biologic use and region Continuous endpoints analysed using MMRM adjusted for region, prior biologic use, visit, treatment-by-visit interaction and BL HAQ-DI as a covariate - data collected after treatment discontinuation or rescue were classified as missing.	Categorical endpoints analysed using CMH 2-sided test stratified by region. Patients who discontinued treatment before Week 24 classified as non-responders Continuous endpoints analysed using MMRM adjusted for treatment, visit, treatment-by-visit interaction and region as fixed effects and BL DAS28-ESR as a continuous covariate p <0.05 considered statistically significant when all preceding endpoints in	As above

	MOBILITY A	MOBILITY B	TARGET	MONARCH	ASCERTAIN
	treatment, prior biological use and region, was used to assess treatment differences in the change from BL for each of the seven ACR components and for DAS28-CRP.			the pre-defined hierarchy were statistically significant.	

ACR= American College of Rheumatology; ACR20=American College of Rheumatology 20% improvement; ANCOVA=analysis of covariance; BL=baseline; CI=confidence interval; CMH=Cochran-Mantel-Haenszel; DAS28-CRP=Disease Activity Score 28- C-reactive protein; DAS28-ESR=Disease Activity Score 28- eosinophil sedimentation rate; HAQ-DI=Health Assessment Questionnaire Disability Index; LOCF=last observation carried forward; LS=least square; MH=Mantel-Haenszel; MMRM=Mixed model for repeated measures; mTSS=modified Total Sharp Score; OR=odds ratio; SJC=swollen joint count; TJC=tender joint count

4.4.6 Subgroup analyses

Descriptive statistics including number (n) and incidence of response by subgroup were provided for each treatment group. The Mantel-Haenszel estimate of the odds ratio and the corresponding 95% confidence interval (CI) were derived by testing each active treatment group versus placebo separately by subgroup. A logistic regression model with terms of treatment, region, region-by-treatment interaction, and prior biological use was conducted to explore the relationship between region and treatment. A logistic regression model with terms of treatment, prior biological use, prior biological use-by-treatment interaction, and region was conducted to test the interaction between treatment and prior biological use. For any other subgroup, a logistic regression model with terms of treatment, subgroup, subgroup-by-treatment interaction, prior biological use, and region was conducted to test the subgroup-by-treatment interaction.

4.5 Participant flow and baseline characteristics

Phase II/III studies were international multicentre studies with patients enrolled from North America, Central America, South America, Europe, South Africa, Asia and Australia.

ASCERTAIN included six study locations in the UK (Doncaster, Edinburgh, Leeds, London, Southampton and Wigan) and MONARCH included a single UK study location (Leytonstone)[140,141]

A total of 2,620 patients were randomised in the five Phase III studies and included in the ITT population. Of these patients, 1,862 completed the study treatment period.

A summary of reasons for not completing study treatment periods across Phase III studies can be found in Table 4.11. These were mainly due to lack of efficacy or AEs that were low in frequency and not different between treatment groups or studies (Table 4.11). CONSORT flow diagrams can be found below (Figure 4.8 to Figure 4.10).

An overview of the baseline characteristics for each trial is described in Table 4.12. Baseline demographic and disease characteristics of the patients were similar across the seven Phase III RCTs. The patients included in these trial populations were adults with moderate-to-severe RA; patients had a mean age of 52.5 years (range 19–88), were predominately Caucasian/white females, mean RA duration was 10.0 years, and the majority of patients were categorised as being in RA functional class II. The patient characteristics are thought to be similar to those of the UK RA population; this is further explored in Section 5.

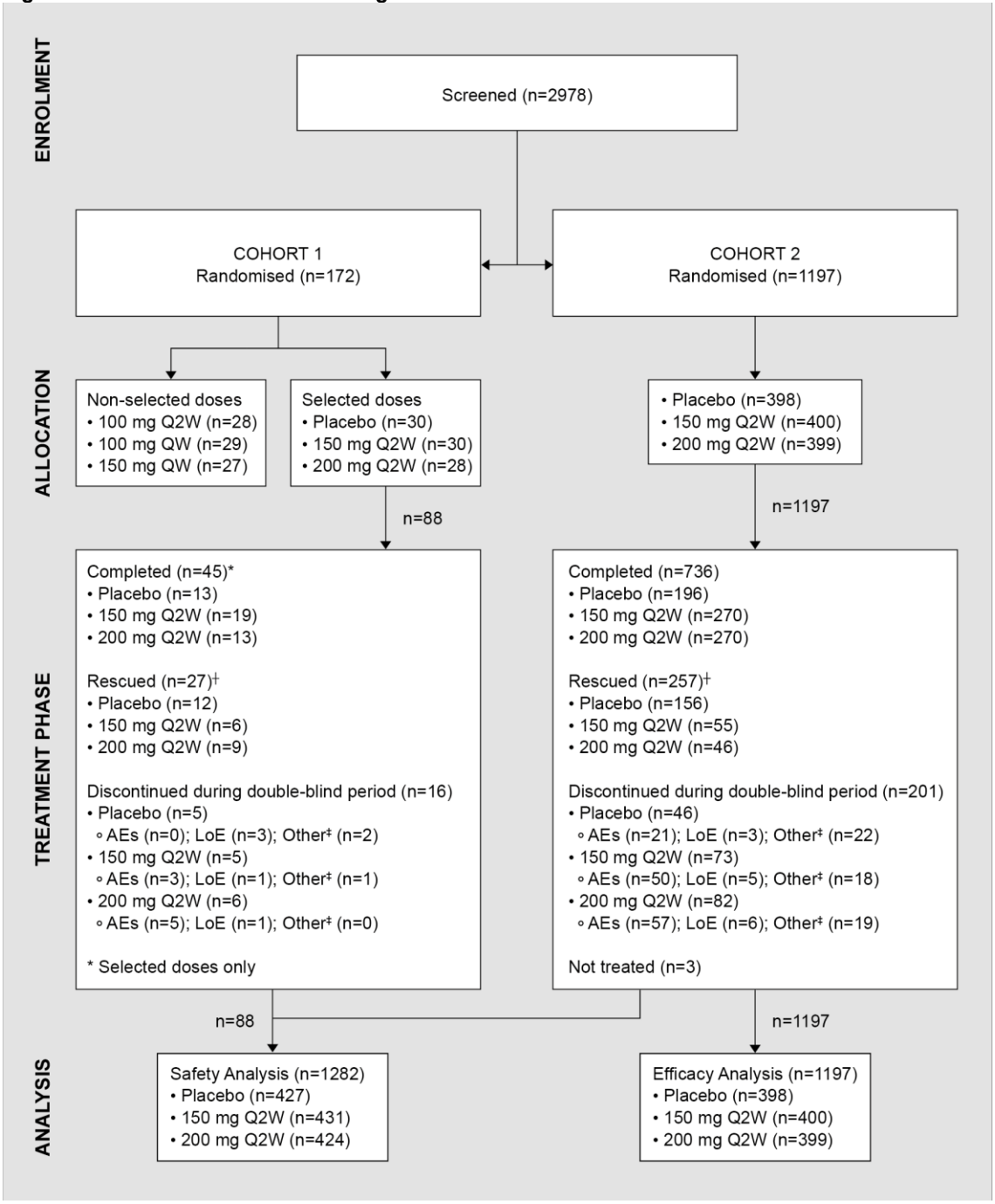
Prior/concomitant use of a cDMARD for RA was reported in 100% of patients and MTX — either alone or in combination with other cDMARDs — was the most common background therapy. When not an exclusion criterion (MONARCH), substantial proportions of patients reported prior use of one bDMARD treatment for RA and, when reported (TARGET), more patients discontinued TNFis due to inadequate response compared with intolerance (92.3% vs. 7.0%); as such TARGET is primarily composed of a population with inadequate response to TNFi.

Table 4.11 Study population and reasons for discontinuation[1,55-58]

	MOBILITY A	MOBILITY B	TARGET	ASCERTAIN	MONARCH
N	306	1,197	546	[redacted]	369
Discontinuations, n (%)	35 (17.4)	201 (16.8)	73 (13.3)	[redacted]	47 (12.7)
AEs, n (%)	24 (7.8)	128 (10.6)	44 (8.0)	[redacted]	26 (7.0)
Lack of efficacy, n (%)	7 (2.2)	14 (1.2)	11 (2.0)	[redacted]	6 (1.6)
Poor compliance, n (%)	0	0	4 (0.7)	[redacted]	4 (1.1)
Other, n (%)	4 (1.3)	59 (4.9)	14 (2.5)	[redacted]	11 (3.0)

AE=adverse event; N=number

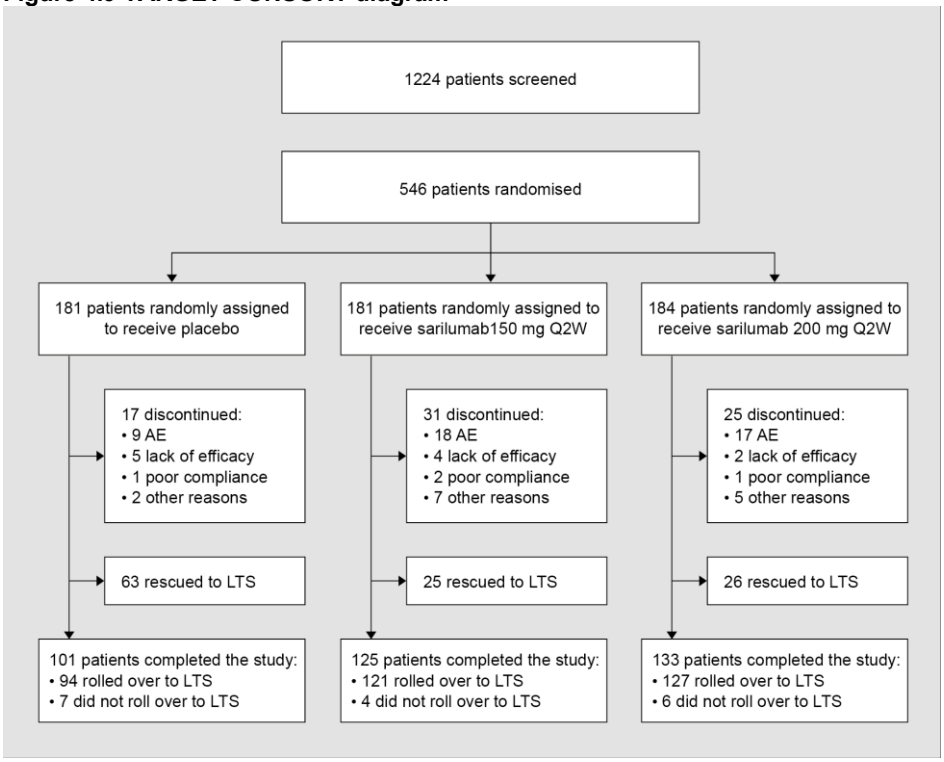
Figure 4.8 MOBILITY B CONSORT diagram[56]



*Selected doses only; †From week 16 onward, patients who did not achieve a ≥20% improvement from baseline in the swollen joint count or tender joint count at two consecutive assessments were offered rescue therapy with open-label sarilumab 200 mg Q2W. ‡Other discontinuations included poor compliance with protocol, patient choice/preference, use of any biologic agents, or any treatment unblinding.

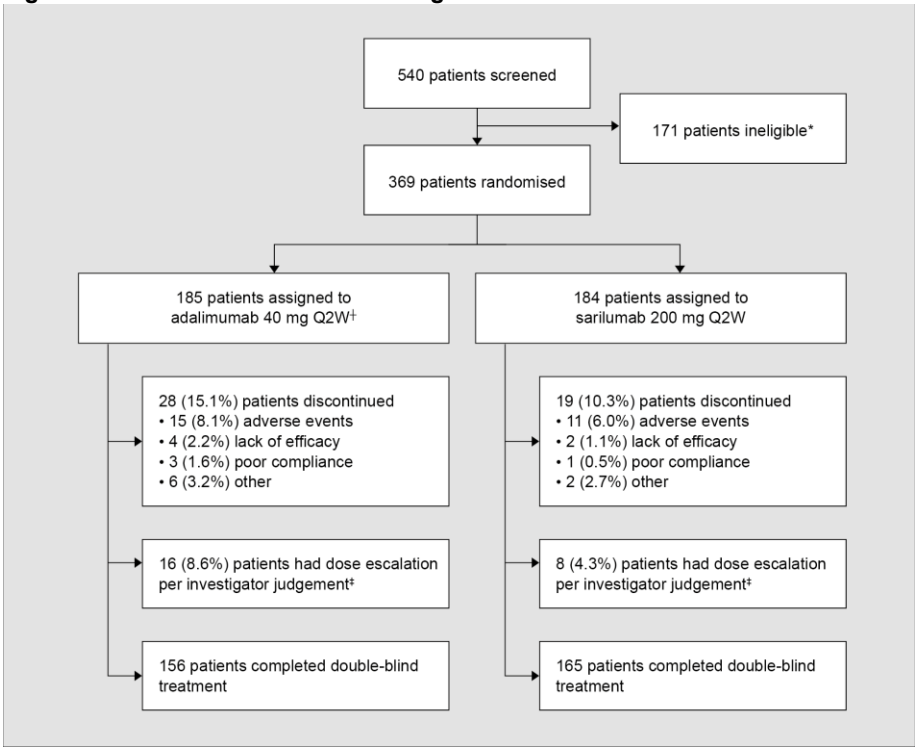
AEs: adverse events; LoE: lack of efficacy; Q2W=once every 2 weeks

Figure 4.9 TARGET CONSORT diagram[57]



AEs: adverse events; LoE: lack of efficacy; LTS=long-term study; Q2W=once every 2 weeks

Figure 4.10 MONARCH CONSORT diagram[1]



*Primary reasons for patient ineligibility were meeting the exclusion criteria related to tuberculosis (12.0%) or failure to meet the inclusion criterion for severity of disease (8.1%); † One patient was randomised but not treated in the adalimumab group; ‡The actual number of patients who received a dose-escalation kit on the basis of meeting protocol criteria were 6 (3.2%) in the adalimumab group and 5 (2.7%) in the sarilumab group.

AEs: adverse events; Q2W=once every 2 weeks

Table 4.12 Baseline characteristics[1,55-58]

	MOBILITY A	MOBILITY B	TARGET	ASCERTAIN	MONARCH
Age, mean (SD)	52.2 (12.5)	50.8 (11.7)	52.9 (12.4)	[redacted]	52.2 (12.3)
Males, %	20.6	18.3	18.1	[redacted]	16.8
Race, %					
Caucasian/White	93.8	86.4	71.1	[redacted]	90.8
Black	2.6	2.4	3.7	[redacted]	1.1
Asian/Oriental	2.0	8.0	0.9	[redacted]	3.0
Other	1.6	3.2	24.4	[redacted]	5.1
Weight kg, mean (SD)	74.86 (15.27)	74.39 (18.52)	78.22 (21.52)	[redacted]	72.05 (17.15)
BMI kg/m^2, mean (SD)	28.28 (5.64)	28.26 (6.34)	29.53 (7.17)	[redacted]	27.18 (6.05)
Duration of RA since diagnosis in years, mean (SD)	7.81 (8.08)	9.03 (7.85)	12.09 (9.40)	[redacted]	7.33 (7.99)
RA functional class, %					
I	6.2	11.7	9.5	[redacted]	17.9
II	70.3	67.2	57.7	[redacted]	65.0
III	23.5	21.2	32.8	[redacted]	17.1
IV	0	0	0	[redacted]	0
RF +ve, %	79.7	84.9	75.5	[redacted]	65.8
Anti-CCP +ve, %	82.0	86.9	78.1	[redacted]	76.0
TJC (0–68), mean (SD)	27.39 (14.93)	26.85 (14.07)	28.88 (15.22)	[redacted]	27.32 (13.41)
SJC (0–66), mean (SD)	17.38 (9.73)	16.82 (9.49)	19.93 (11.49)	[redacted]	18.04 (10.50)
CRP in mg/L, mean (SD)	2.78 (2.96)	22.23 (23.69)	26.82 (25.89)	[redacted]	20.71 (26.78)

	MOBILITY A	MOBILITY B	TARGET	ASCERTAIN	MONARCH
HAQ-DI (0–3), mean (SD)	1.59 (0.62)	1.64 (0.64)	1.78 (0.63)	[redacted]	1.64 (0.60)
DAS28-CRP, mean (SD)	6.11 (0.84)	5.96 (0.90)	6.20 (0.91)	[redacted]	6.01 (0.89)
Prior cDMARD use, %	100	100	100	[redacted]	100
Number of cDMARDs, %					
0	0	0	0	[redacted]	0
1	92.8	NR	53.5	[redacted]	46.3
2	4.9	NR	27.5	[redacted]	31.2
≥3	2.3	NR	19.0	[redacted]	22.5
Prior bDMARD use, %	24.5	27.9	100	[redacted]	0
Prior TNFi use, %	NR	NR	100%	[redacted]	0
Number of TNFi, %					
1	NR	NR	76.8	[redacted]	0
≥1	NR	NR	23.2	[redacted]	0

bDMARD= biological disease-modifying anti-rheumatic drug; BMI=body mass index; CDAI=Clinical Disease Activity Index; cDMARDs=conventional synthetic disease-modifying anti-rheumatic drug; DAS28-CRP=28-joint count disease activity score-C-reactive protein; DAS28-ESR= 28 joint count disease activity score - erythrocyte sedimentation rate; HAQ-DI=Health Assessment Questionnaire Disability Index; HCQ=hydroxychloroquine; hs-CRP=high-sensitivity C-reactive protein; LEF=leflunomide; mTSS=modified Total Sharp Score; MTX=methotrexate; NR=not reported; OLE=open-label extension; RA=rheumatoid arthritis; SJC=swollen joint count; TJC=tender joint count; TNFi=tumour necrosis factor inhibitor; SSZ=sulfasalazine

4.6 Quality assessment of the relevant randomised controlled trials

4.6.1 Criteria for assessing studies and assessing risk of bias and generalisability of individual randomised controlled trials

Regular site monitoring ensured the quality of trial conduct and quality data assurance. Management of clinical trial data was performed according to the following rules and procedures. Data entry and validation were carried out using standard validated remote data capture computer software (Oracle Clinical/RDC version 4.5.3). Data were stored in an Oracle database on a UNIX server. Data entry was performed directly from the investigator site from the data source documents and signed electronically by the authorised site personnel. Moreover, any modification in the database was traced using an audit trail. Patient questionnaires were completed in paper booklets and were shipped to the sponsor for double data entry.

The sponsor conducted investigator meetings and training sessions for clinical research associates as well as individual site initiation meetings to develop a common understanding of the clinical study protocol, electronic case report form (e-CRF), and study procedures, in compliance with Good Clinical Practice.

4.6.2 Summary of quality assessment criteria in the Phase III studies

Table 4.13 Summary of quality assessment[1,55-58]

Trial name	MOBILITY A	MOBILITY B	TARGET	ASCERTAIN	MONARCH
Was randomisation carried out appropriately?	YES	YES	YES	YES	YES
Was the concealment of treatment allocation adequate?	YES	YES	YES	*	YES
Were the groups similar at the outset of the study in terms of prognostic factors?	YES	YES	YES	YES	YES
Were the care providers, participants and outcome assessors blind to treatment allocation?	YES	YES	YES	YES	YES
Were there any unexpected imbalances in drop-outs between groups?	NO	NO	NO	NO	NO
Is there any evidence to suggest that the authors measured more outcomes than they reported?	NO	NO	NO	NO	NO
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	YES	YES	YES	YES	YES

* A double-dummy system was used to mask sarilumab versus tocilizumab.
Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination)

A summary of the quality assessment of the trials is shown in Table 4.13. The complete quality assessments for each RCT are included in Appendix 6.

4.7 Clinical effectiveness results of the relevant randomised controlled trials

4.7.1 MOBILITY A – sarilumab plus methotrexate in methotrexate-irresponsive patients with moderate-to-severe rheumatoid arthritis (dose-defining study)

MOBILITY A demonstrated that four sarilumab doses (150 mg Q2W, 100 mg QW, 200 mg Q2W, and 150 mg QW) administered in combination with MTX over 12 weeks were effective in reducing the signs and symptoms of moderate-to-severe RA in patients with an inadequate response to MTX (Figure 4.11 and Table 4.14)[55].

Although 150 mg and 200 mg Q2W were similar in efficacy, suppression of neutrophil counts and some safety parameters were less marked in the 150 mg Q2W group. Neutropenia (Grade 1, absolute neutrophil count (ANC)≥1500–<2000) was reported in one patient in the placebo group and there was a general dose-related reduction in neutrophil count during treatment with sarilumab; In the 100 mg QW, 200 mg Q2W and 150 mg QW groups, ANC≥500–<1000 was reported in three, six and four patients respectively, and in the 200 mg Q2W and 150 mg QW groups an ANC<500 was reported in four and one patient(s) respectively[55]. The 150 mg Q2W dose group yielded a relatively small average decrease from baseline in neutrophil count at Week 12[55]. For further discussions on safety, please refer to Section 4.12.1.1.

These data, taken together with the more convenient dosing interval, supported Q2W dosing as optimal for sarilumab when dosed at 150 mg and 200 mg[55].

4.7.1.1 Improvements in signs and symptoms

The proportion of patients achieving an ACR20 response was significantly higher for sarilumab 150 mg QW plus MTX versus placebo at Week 12 (72.0% vs. 46.2%, multiplicity adjusted p=0.0203). Higher ACR20 responses were also attained with 150 mg Q2W plus MTX (67%; unadjusted [nominal] p=0.0363) and 200 mg Q2W plus MTX (65%; unadjusted p=0.0426) versus placebo plus MTX (Figure 4.11) [55].

4.7.1.2 Improvements in secondary endpoints

Sarilumab 150 mg and 200 mg Q2W plus MTX resulted in improved ACR50/ACR70 response rates and DAS28-CRP improvement from baseline vs. placebo, most with

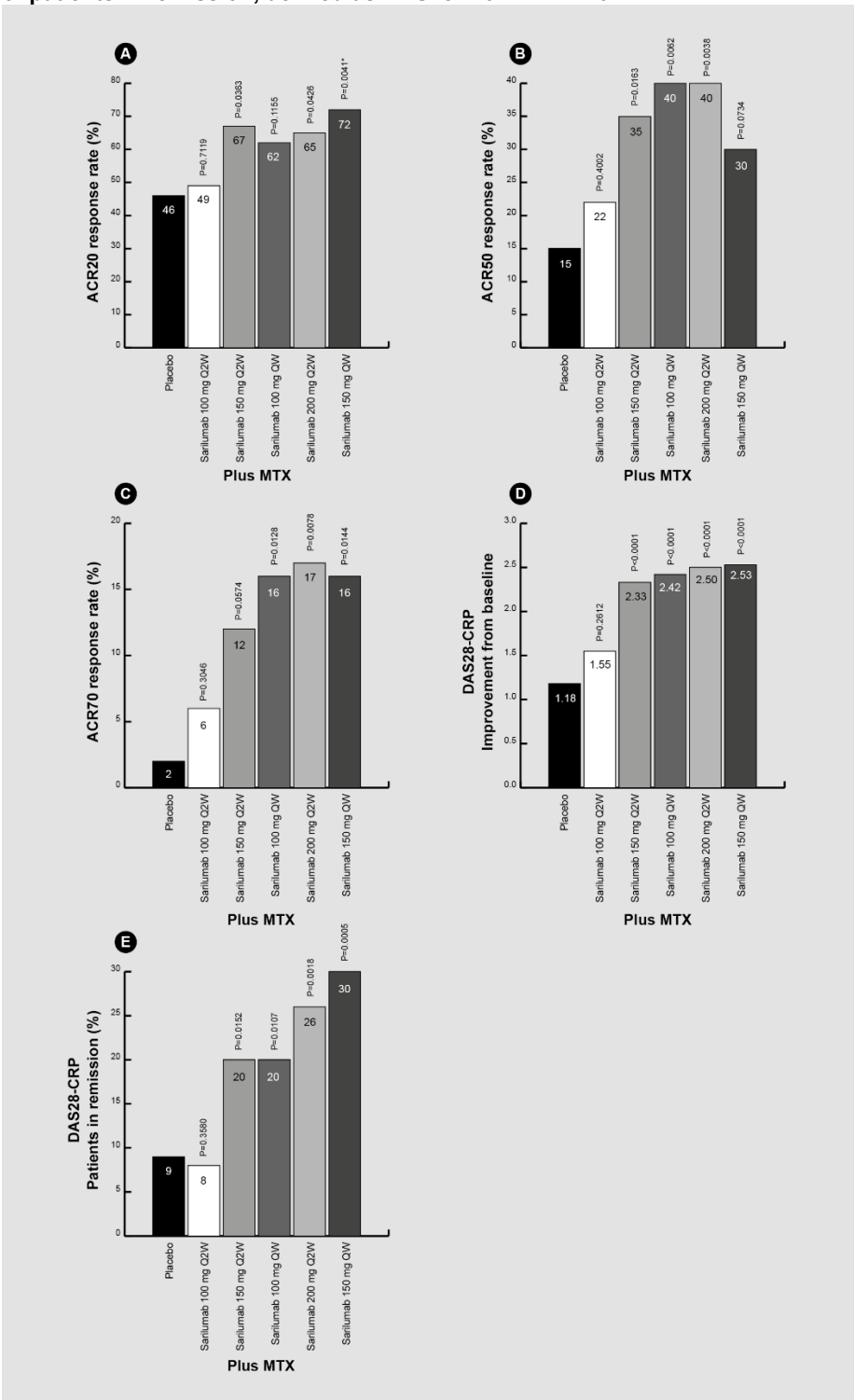
unadjusted p<0.05 (Figure 4.11B–D); these doses also led to improvement in the clinical components of the ACR assessment (Table 4.14). Evaluation of DAS28-CRP suggested a dose-response with highest incidence DAS28-CRP <2.6 in the 150 mg QW group (Figure 4.11)[55].

Sarilumab also demonstrated efficacy in terms of reduced CDAI a measure of clinical response independent of acute-phase reactants that may favour IL-6 inhibition. Change in CDAI scores baseline to Week 12 confirms decreased clinical activity associated with sarilumab 150 mg and 200 mg Q2W plus MTX versus placebo and this difference was statistically significant for the 200mg Q2W dose (p=0.0025) (Table 4.15) [55].

4.7.1.3 Overall summary of results

Sarilumab improved signs and symptoms of RA over 12 weeks in patients with moderate-to-severe RA. Sarilumab 150 mg and 200 mg Q2W had the most favourable efficacy, safety and dosing convenience

Figure 4.11 ACR and DAS28 with CRP response at Week 12: (A) ACR 20% improvement, (B) ACR 50% improvement, and (C) ACR 70% improvement at week 12 (D) improvement from baseline, and (E) number of patients in remission, defined as DAS28 with CRP <2.6[55]



* Adjusting for multiplicity resulted in significance

American College of Rheumatology; ACR20/50/70= American College of Rheumatology 20%/50%/70% improvement; CRP=C-reactive protein; DAS28=28-joint count disease activity score; MTX=methotrexate; Q2W=every 2 weeks; QW=every week

.

Table 4.14 Change from baseline in American College of Rheumatology components at Week 12[55]

	Placebo (n=52) LS Mean (SE)	Sarilumab 100 mg Q2W (n=51) LS Mean (SE)	Sarilumab 150 mg Q2W (n=51) LS Mean (SE)	Sarilumab 100 mg QW (n=50) LS Mean (SE)	Sarilumab 200 mg Q2W (n=52) LS Mean (SE)	Sarilumab 150 mg QW (n=50) LS Mean (SE)
TJC (0–68)	−8.72 (1.69)	−11.87 (1.70)	−15.64 (1.70)	−14.43 (1.73)	−14.57 (1.69)	−12.84 (1.72)
p-value vs. placebo		0.1740	0.0029	0.0151	0.0118	0.0772
SJC (0–68)	−6.74 (1.13)	−5.97 (1.13)	−9.36 (1.14)	−9.93 (1.16)	−10.16 (1.12)	−8.87 (1.15)
p-value vs. placebo		0.6184	0.0894	0.0410	0.0268	0.1698
Pain (VAS)	−22.28 (3.46)	−21.02 (3.47)	−29.05 (3.49)	−29.19 (3.55)	−32.46 (3.48)	−25.26 (3.51)
p-value vs. placebo		0.7899	0.1531	0.1499	0.0332	0.5312
Physician global (VAS)	−26.79 (2.88)	−28.85 (2.89)	−34.32 (2.90)	−35.20 (2.95)	−39.66 (2.89)	−34.91 (2.92)
p-value vs. placebo		0.6021	0.0559	0.0347	0.0012	0.0410
Patient global (VAS)	−21.10 (3.39)	−20.12 (3.40)	−27.57 (3.42)	−30.22 (3.47)	−31.66 (3.41)	−27.80 (3.44)
p-value vs. placebo		0.8312	0.1636	0.0522	0.0241	0.1515
HAQ-DI	−0.26 (0.07)	−0.35 (0.07)	−0.62 (0.07)	−0.42 (0.07)	−0.57 (0.07)	−0.45 (0.07)
p-value vs. placebo		0.3527	0.0003	0.0997	0.0019	0.0545
CRP (mg/L)	−3.1 (2.8)	−10.2 (2.8)	−21.9 (2.8)	−25.0 (2.9)	−21.9 (2.8)	−20.7 (2.9)
p-value vs. placebo		0.0661	<0.0001	<0.0001	<0.0001	<0.0001

CRP=C-reactive protein HAQ-DI=Health Assessment Questionnaire Disability Index; LS=least square; QW=every week; Q2W=every 2 weeks; SE=standard error; SJC=swollen joint count; TJC=tender joint count; VAS=visual analogue scale.

Table 4.15 CDAI scores from score baseline to Week 12[55]

	Placebo (n=52)	Sarilumab 100 mg Q2W (n=51)	Sarilumab 150 mg Q2W (n=51)	Sarilumab 100 mg QW (n=50)	Sarilumab 200 mg Q2W (n=52)	Sarilumab 150 mg QW (n=50)
Baseline, mean (SD)	40.63 (12.85)	44.74 (13.53)	41.41 (13.31)	40.32 (10.82)	40.37 (12.32)	40.48 (10.22)
Week 12, mean (SD)	25.99 (16.09)	26.94 (17.03)	18.79 (13.17)	18.38 (11.82)	16.90 (11.78)	19.85 (15.34)
p-value for change from baseline[a]		0.2494	0.0056	0.0122	0.0025	0.0361

[a]Using ANOVA (type 3)

ANOVA=analysis of variance; CDAI Clinical Disease Activity Index; Q2W=once every 2 weeks; QW=every week; SD=standard deviation

4.7.2 MOBILITY B — sarilumab plus methotrexate in methotrexate-irresponsive patients with moderate-to-severe rheumatoid arthritis

Sarilumab when added to a background of MTX was associated with significant improvements versus placebo plus MTX in all three co-primary endpoints: ACR20 response at Week 24, HAQ-DI at Week 16 and change in mTSS at Week 52 ($p<0.0001$ for all co-primary endpoints) (Table 4.16). These were confirmed by all planned sensitivity analyses[56].

4.7.2.1 Improvements in signs and symptoms

A significantly greater percentage of patients receiving sarilumab 150 mg plus MTX and sarilumab 200 mg plus MTX had an ACR20 response versus placebo at Week 24 (58.0% and 66.4% vs. 33.4%; $p<0.0001$ vs. placebo for both comparisons) (Table 4.16 and Figure 4.12)[56].

The ACR20 response was maintained throughout the duration of the study (to Week 52), and a similar benefit with both sarilumab doses was observed when the ACR50 and ACR70 improvement response rates were assessed (Figure 4.12). In the pre-specified sensitivity analyses (last observation carried forward [LOCF]), which included patients who received rescue therapy and patients who discontinued treatment, ACR20 responses at Week 24 were significantly greater in patients receiving sarilumab 150 mg plus MTX and sarilumab 200 mg plus MTX versus placebo (64.0% and 71.4% vs. 35.7%; $p<0.0001$ vs. placebo for both comparisons)[56,61].

4.7.2.2 Improvements in physical function

Sarilumab 150 mg and sarilumab 200 mg plus MTX resulted in statistically significant improvements versus placebo plus MTX in change from baseline in HAQ-DI at Week 16 (−0.53 and −0.55 vs. −0.29; $p<0.0001$), and a significantly greater proportion of patients achieved a clinically meaningful HAQ-DI response (change from baseline ≥0.3, 53.8% and 57.4% vs. 42.5; $p=0.0012$ for 150 mg and $p<0.0001$ for 200 mg) (Table 4.16)[56].

4.7.2.3 Inhibition of structural damage

Significantly reduced radiographic progression of structural damage was observed with sarilumab 150 mg and sarilumab 200 mg plus MTX versus placebo at Week 52 (mean change from baseline in the mTSS, 0.9 and 0.25 vs. 2.78; $p< 0.0001$ vs. placebo for both comparison) (Table 4.16)[56].

A significantly greater percentage of patients receiving sarilumab 150 mg and sarilumab 200 mg plus MTX had no radiographic progression (defined as mean change from baseline in

the mTSS of ≤0) versus placebo at Week 52 (47.8% and 55.6% vs. 38.7%; p<0.01 sarilumab 150 mg vs. placebo, and p<0.0001 sarilumab 200 mg vs. placebo) (Table 4.16)[56].

Both components of the mTSS score (ES and JSN score) were significantly reduced with sarilumab 150 mg and sarilumab 200 mg plus MTX versus placebo at Week 52 (ES p<0.0001 vs. placebo both comparisons; JSN score p<0.0001 sarilumab 150 mg vs. placebo and p<0.0001 sarilumab 200 mg vs. placebo) and the reduction in radiographic structural damage was significantly different versus placebo at the first post-baseline measurement at Week 24 (p<0.01 vs. placebo for both comparisons) (Figure 4.13)[56].

4.7.2.4 Higher rates of clinical remission

Sarilumab 150 mg and sarilumab 200 mg plus MTX were associated with a significantly higher rate of clinical response (defined as achieving ACR70 for at least 24 consecutive weeks during the 52 week period) and remission (defined by DAS28-CRP, SDAI, CDAI or ACR/EULAR Boolean-based remission) versus placebo at Week 24, with benefits sustained at Week 52 (Table 4.16 and Table 4.17)[56,61]:

- Major clinical response: a significantly greater proportion of patients treated with sarilumab 150 mg and 200 mg plus MTX achieved a major clinical response versus placebo (12.8% and 14.8% vs. 3.0%; p<0.0001) (Table 4.16)
- DAS28-CRP (<2.6): a significantly greater proportion of patients treated with sarilumab 150 mg and 200 mg plus MTX achieved remission versus placebo at Week 24 (27.8% and 34.1% vs. 10.1%; p<0.0001) (Table 4.17)
- CDAI (≤2.8): a greater proportion of patients treated with sarilumab 150 mg and 200 mg plus MTX achieved CDAI response versus placebo at Weeks 24 (10.3% and 13.8% vs. 5.0%; p<0.0001 for both comparisons [Table 4.17]) with benefits enhanced by Week 52 (14.8% and 18.0% vs. 4.8%; p<0.0001 for both comparisons)
- [redacted]: a greater proportion of patients treated with sarilumab 150 mg and 200 mg plus MTX achieved remission versus placebo at Weeks 24 [redacted]
- ACR/EULAR Boolean-based remission (TJC and SJC [28 joints] ≤1, CRP ≤10 mg/L, and patient global VAS ≤10 mm): A greater proportion of patients treated sarilumab 150 mg and 200 mg plus MTX achieved remission versus placebo at Weeks 24 [redacted]

[redacted] with benefits enhanced by Week 52 [redacted]

4.7.2.5 Improvements in patient-reported outcomes and health-related quality of life

At baseline, the 36-item Short Form survey (SF-36) mean domain scores were approximately 20–50 points lower than an in the age- and gender-matched normative population, indicating substantial impairment of general health status in these patients[64].

Least mean square improvements from baseline at Week 24 in patient global assessment (PtGA), pain, and HAQ-DI scores were significantly greater with sarilumab 150 mg and 200mg plus MTX than placebo ($p<0.0001$ for both doses) and were maintained at Week 52 (Table 4.18 and Figure 4.14)[64]. The Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) demonstrated significantly greater improvement at Week 24 with sarilumab 150 mg and 200 mg that placebo and was maintained through Week 52 ($p < 0.0001$ for both doses at both time points) (Table 4.18 and Figure 4.14)[64].

Significant improvements were reported in the SF-36 physical component summary and mental component summary scores at Week 24 with 150 mg and 200mg plus MTX than placebo ($p<0.05$) (Table 4.18)[64]. Greater improvements were also observed with sarilumab in all eight domains of the SF-36 (physical functioning, role physical, body pain, general health, vitality, social functioning, role emotional, and mental health), at Week 24 and at Week 52 ($p < 0.05$) with the exception of the MCS and role emotional scores with sarilumab 150 mg at Week 52 (Table 4.18)[64]. Improvements in PtGA, pain, HAQ-DI, and FACIT-Fatigue scores were evident 2 weeks after the start of treatment (Figure 4.14)[64].

Responder analyses

In post hoc, responder analyses, the percentages of patients reporting improvement equal to or greater than the minimal clinically important difference were higher with both doses of sarilumab than placebo across all PROs ($p < 0.05$), resulting in a number need to treat (NNT) ranging from 4.0 (physical component summary score for sarilumab 200 mg Q2W) to 8.6 (mental component summary score for sarilumab 150 mg Q2W) (Figure 4.15)[64].

The percentage of patients who reported improvement equal to or greater than the MCID in individual SF-36 domains was consistently higher with both doses of sarilumab versus placebo for all domains ($p < 0.05$) (Figure 4.16); the NNT ranged from 3.8 (BP with the sarilumab 200 mg dose) to 9.7 (MH with the sarilumab 150 mg dose). The majority (59.4–89.8 %) of ACR20 responders reported clinically meaningful improvement across PROs[64].

4.7.2.6 Overall summary of results

Sarilumab 150 mg and 200 mg Q2W plus MTX provided statistically significant improvements in the signs and symptoms of RA compared with placebo in patients with moderate-to-severe RA and inadequate response or intolerance to MTX ($p<0.0001$)[56].

Sarilumab 150 and 200 mg Q2W plus MTX provided sustained clinical efficacy (to Week 52), as shown by significant improvements in symptomatic, functional, and radiographic outcomes ($p<0.0001$)[56].

Treatment with sarilumab (150 mg or 200 mg) also resulted in statistically significant and clinically relevant improvements in PROs and HRQoL at 24 and 52 weeks ($p<0.0001$)[56,64].

Table 4.16 Efficacy results for MOBILITY-B[56]

	Placebo + MTX (N=398)	Sarilumab 150 mg Q2W + MTX (N=400)	p	Sarilumab 200 mg Q2W + MTX (N=399)	p
Signs and symptoms					
ACR20 response at Week 24, n (%)[a]	133 (33.4)	232 (58.0)	< 0.0001	265 (66.4)	< 0.0001
ACR50 response at Week 24, n (%)	66 (16.6)	148 (37.0)	< 0.0001	182 (45.6)	<0.0001
ACR70 response at Week 24, n (%)	29 (7.3)	79 (19.8)	< 0.0001	99 (24.8)	<0.0001
ACR20 response at Week 52, n (%)	126 (31.7)	214 (53.5)	<0.0001	234 (58.6)	<0.0001
ACR core set of disease activity measures, adjusted mean change from baseline at Week 24, using MMRM					
SJC (of 66 joints assessed)	−6.66 ±.045	−10.6 ± 0.42	<0.0001	−11.3 ± 0.42	<0.0001
TJC (of 68 joints assessed)	−10.1 ± 0.69	−16.9 ± 0.66	<0.0001	−17.4 ± 0.66	<0.0001
Patient's global assessment by VAS, mm	−15.7 ± 1.36	−28.3 ± 1.29	<0.0001	−32.9 ± 1.28	<0.0001
Physician's global assessment by VAS, mm	−24.6 ± 1.23	−37.5 ±1.17	<0.0001	−40.3 ± 1.16	<0.0001
Patient's assessment of pain by VAS, mm	−15.4 ± 1.42	−28.5 ± 1.35	<0.0001	−31.8 ± 1.34	<0.0001
HAQ-DI	−0.33 ± 0.03	−0.53 ± 0.03	<0.0001	−0.55 ± 0.03	<0.0001
CRP, mg/dL	−0.0 ± 0.12	−1.3 ± 0.12	<0.0001	−1.7 ± 0.12	<0.0001
Major clinical response (ACR70 response maintained for ≥24 weeks), n (%)[a]	12 (3.0)	51 (12.8)	<0.0001	59 (14.8)	<0.0001
DAS28-CRP, LS mean change from baseline to Week 24 (SE)	−1.17(0.080)	−2.45(0.076)	< 0.0001	−2.82(0.075)	<0.0001
DAS28-CRP response at Week 24, n (%)					
Score <2.6[b]	40 (10.1)	111 (27.8)	<0.0001	136 (34.1)	<0.0001
Score ≤3.2	67(16.8)	159 (39.8)	<0.0001	196 (49.1)	<0.0001
CDAI response (score ≤ 2.8) at Week 24, n (%)	20 (5.0)	41 (10.3)	<0.0001	55 (13.8)	<0.0001
Physical function (HAQ-DI)					
HAQ-DI, adjusted mean change from baseline at Week 16, using MMRM[a]	−0.29 ± 0.03	−0.53 ± 0.03	<0.0001	−0.55 ± 0.03	<0.0001

	Placebo + MTX (N=398)	Sarilumab 150 mg Q2W + MTX (N=400)	p	Sarilumab 200 mg Q2W + MTX (N=399)	p
HAQ-DI response (MCID ≥0.3), n (%)					
At Week 16	169 (42.5)	215 (53.8)	<0.01	229 (57.4)	<0.0001
At Week 24	133 (33.4)	204 (51.0)	<0.0001	205 (51.4)	<0.0001
At Week 52	104 (26.1)	188 (47.0)	<0.0001	190 (47.6)	<0.0001
Radiographic progression (mTSS)					
Mean change from baseline in mTSS at week 52, using rank ANCOVA[b]	2.78 ± 7.73	0.90 ± 4.66	<0.0001	0.25 ± 4.61	<0.0001
No radiographic progression, n (%)					
At Week 24	158 (39.7)	185 (46.3)	<0.0001	226 (56.6)	<0.0001
At Week 52[a]	154 (38.7)	191 (47.8)	<0.01	222 (55.6)	<0.0001

[a]Mean changes from baseline values are presented as the least squares mean ± SEM, with the exception of the change in total modified SHS, presented as the mean ± SD. No radiographic progression was defined as a mean change from baseline in the total SHS of ≤0.
[b]Endpoint in pre-defined hierarchy

ACR20 = American College of Rheumatology 20% improvement; ACR70 = American College of Rheumatology 70% improvement; ANCOVA = analysis of covariance; CDAI = Clinical Disease Activity Index; CRP = C-reactive protein; DAS28-CRP = 28-joint disease activity score using CRP level; HAQ-DI = Health Assessment Questionnaire Disability Index; LS=least squares; MMRM = mixed model for repeated measures; MCID = minimal clinically important difference; mTSS=modified Total Sharp Score; Q2W=once every 2 weeks; SJC=swollen joint count; TJC=tender joint count; VAS = visual analogue scale

.

Table 4.17 Other secondary endpoints[61]

	Placebo + MTX (N= 398)	Sarilumab 150 mg Q2W + MTX (N=400)	p	Sarilumab 200 mg Q2W + MTX (N=399)	p
Week 24					
CDAI, LSM change from baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FACIT – F	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SF-36 Physical	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SF-36 Mental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sleep	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 52					
FACIT- F	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SF-36 Physical	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SF-36 Mental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sleep	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WPAI percent work impairment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

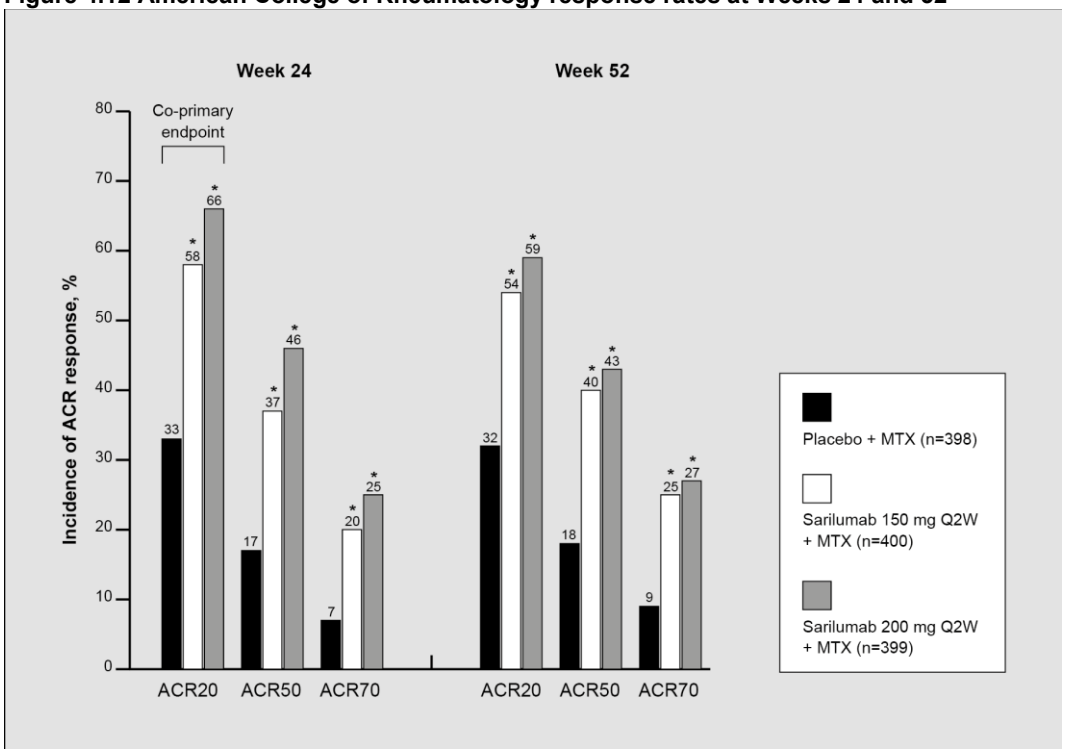
CDAI = Clinical Disease Activity Index; FACIT-F=Functional Assessment of Chronic Illness Therapy-Fatigue; LSM=least squares mean; SE=standard error; SF-36= Short Form 36; WPAI= Work Productivity Activity Impairment

Table 4.18 Patient-reported outcomes (PRO)[64]

PRO, LSM change from baseline (SE)	Week 24					Week 52				
	Placebo + MTX (N=398)	Sarilumab 150 mg Q2W + MTX (N=400)	p	Sarilumab 200 mg Q2W + MTX (N=399)	p	Placebo + MTX (N=398)	Sarilumab 150 mg Q2W + MTX (N=400)	p	Sarilumab 200 mg Q2W + MTX (N=399)	p
PtGA	−15.7 ± 1.4	-28.3 ± 1.3	<0.0001	−32.9 ± 1.3	<0.0001	−20.3 ± 1.5	−31.7 ± 1.4	<0.0001	−32.8 ± 1.4	<0.0001
Pain VAS	−15.4 ± 1.4	-28.5 ± 1.4	<0.0001	−31.8 ± 1.3	<0.0001	−19.3 ± 1.6	−32.7 ± 1.4	<0.0001	−33.1 ± 1.4	<0.0001
HAQ-DI	−0.32 ± 0.03	-0.56 ± 0.03	<0.0001	−0.57 ± 0.03	<0.0001	−0.27 ± 0.04	−0.62 ± 0.03	<0.0001	−0.63 ± 0.03	<0.0001
FACIT-F	5.8 ± 0.5	8.6 ± 0.5	<0.0001	9.2 ± 0.5	<0.0001	6.1 ± 0.5	9.1 ± 0.5	<0.0001	9.2 ± 0.5	<0.0001
SF-36 component scores										
PCS	5.2 ± 0.5	8.0 ± 0.5	<0.0001	8.4 ± 0.5	<0.0001	5.6 ± 0.6	9.2 ± 0.5	<0.0001	9.1 ± 0.5	<0.0001
MCS	3.9 ± 0.6	5.7 ± 0.6	<0.05	8.2 ± 0.6	<0.0001	5.5 ± 0.7	7.1 ± 0.6	-	8.4 ± 0.6	<0.001
SF-36 domain scores										
Physical functioning	11.9 ± 1.5	17.5 ± 1.3	<0.05	18.2 ± 1.3	<0.001	13.9 ± 1.6	21.3 ± 1.4	<0.001	21.3 ± 1.4	<0.001
Role physical	12.8 ± 1.4	18.7 ± 1.3	<0.001	20.4 ± 1.3	<0.0001	15.5 ± 1.5	20.7 ± 1.3	<0.05	22.5 ± 1.3	<0.001
Body pain	15.3 ± 1.3	25.3 ± 1.2	<0.0001	27.6 ± 1.2	<0.0001	16.7 ± 1.5	28.1 ± 1.3	<0.0001	28.0 ± 1.3	<0.0001
General health	7.6 ± 1.1	12.80 ± 1.0	<0.05	15.2 ± 1.0	<0.0001	10.5 ± 1.3	14.5 ± 1.1	<0.05	15.9 ± 1.1	<0.001
Vitality	9.8 ± 1.2	13.9 ± 1.1	<0.05	18.0 ± 1.0	<0.0001	11.4 ± 1.3	17.5 ± 1.1	<0.001	17.7 ± 1.1	<0.001
Social functioning	9.8 ± 1.4	17.3 ± 1.2	<0.0001	20.8 ± 1.2	<0.0001	11.9 ± 1.6	20.4 ± 1.4	<0.0001	20.8 ± 1.4	<0.0001
Role emotional	10.3 ± 1.5	14.6 ± 1.4	<0.05	17.9 ± 1.4	<0.0001	14.8 ± 1.6	17.3 ± 1.4	<0.05	21.4 ± 1.4	<0.01
Mental health	7.4 ± 1.1	10.4 ± 1.0	<0.05	14.0 ± 1.0	<0.0001	9.8 ± 1.2	13.0 ± 1.1	<0.05	14.3 ± 1.1	<0.01

FACIT-F=Functional Assessment of Chronic Illness Therapy-Fatigue scale; HAQ-DI=Health Assessment Questionnaire Disability Index; LSM=least square mean; MCS=mental component summary; MTX=methotrexate; PCS=physical component summary; PRO=patient-reported outcome; PtGA=patient global assessment of disease activity= Q2W =very 2 weeks; SE=standard error; SF-36=36-item Short Form Health Survey-Version 2; VAS=visual analogue scale.

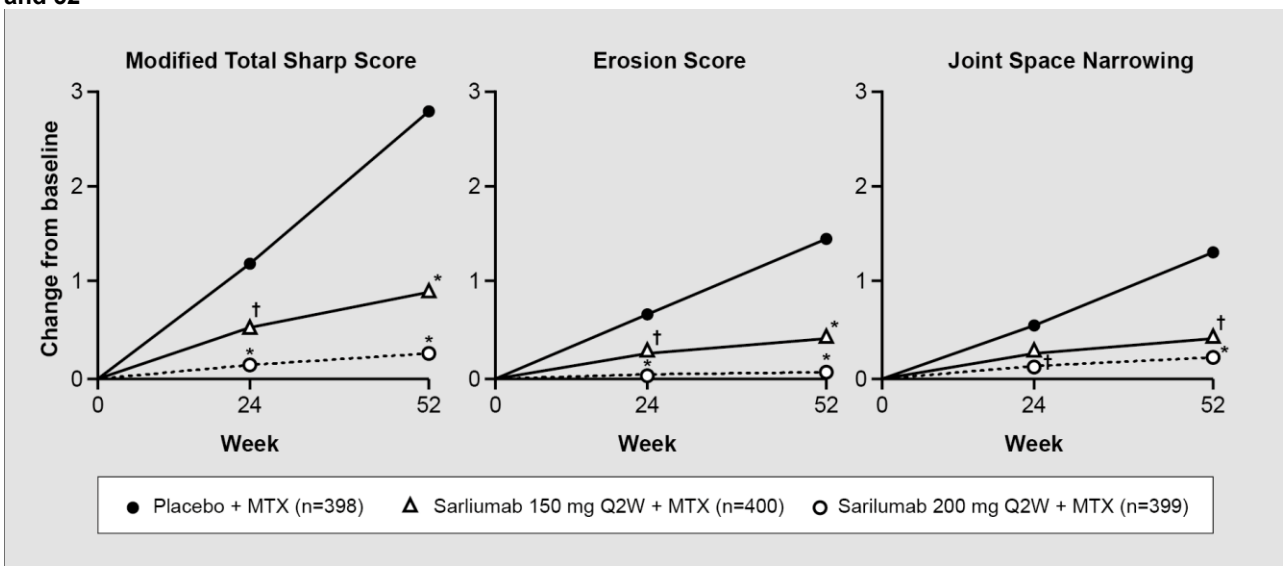
Figure 4.12 American College of Rheumatology response rates at Weeks 24 and 52[56]



*p<0.0001 versus placebo plus MTX (results based on non-responder imputation)

ACR20/50/70=American College of Rheumatology 20%/50%/70% improvement; MTX=methotrexate; Q2W=once every 2 weeks

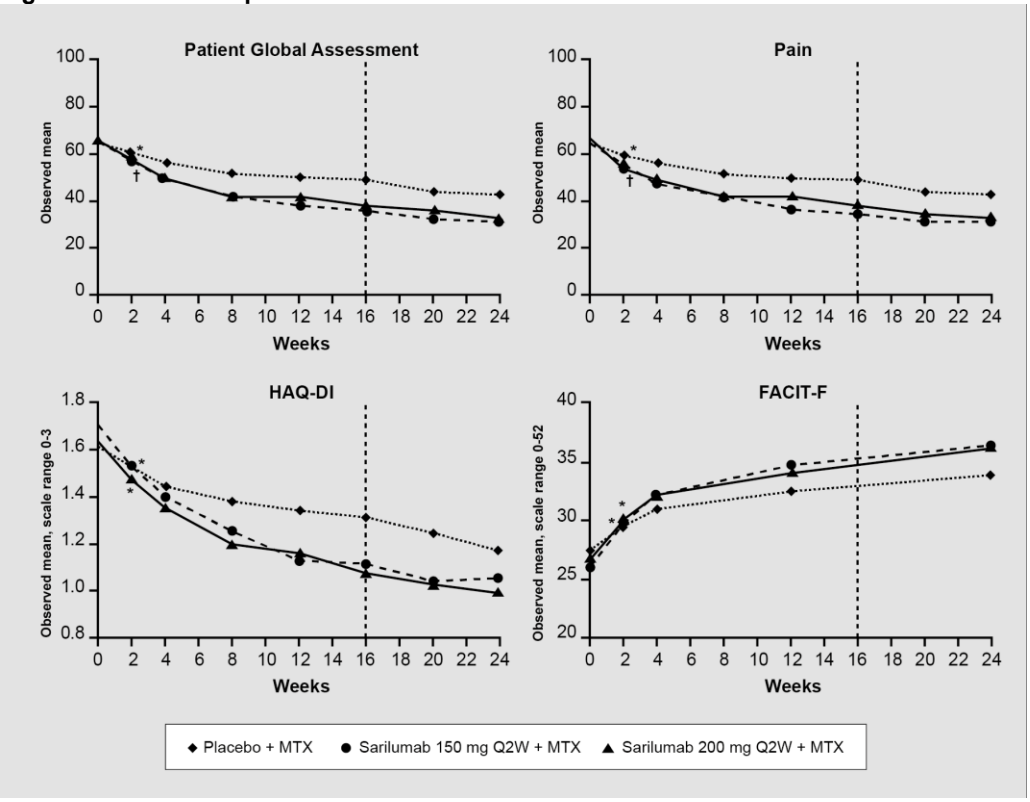
Figure 4.13 Mean change from baseline in radiographic progression of structural damage at Weeks 24 and 52[56]



*p<0.0001 versus placebo plus MTX; †p<0.01 versus placebo plus MTX

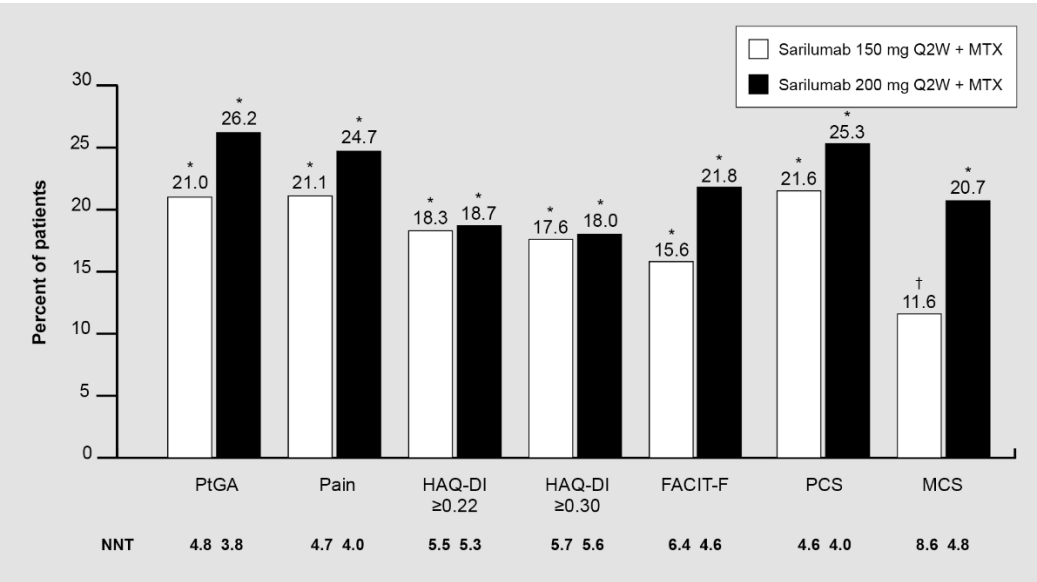
MTX=methotrexate; Q2W=once every 2 weeks

Figure 4.14 Patient-reported outcomes[64]



*p<0.0001 versus placebo plus MTX; †p<0.01 versus placebo plus MTX
FACIT-F= Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI=Health Assessment Questionnaire Disability Index; MTX=methotrexate; Q2W=once every 2 weeks

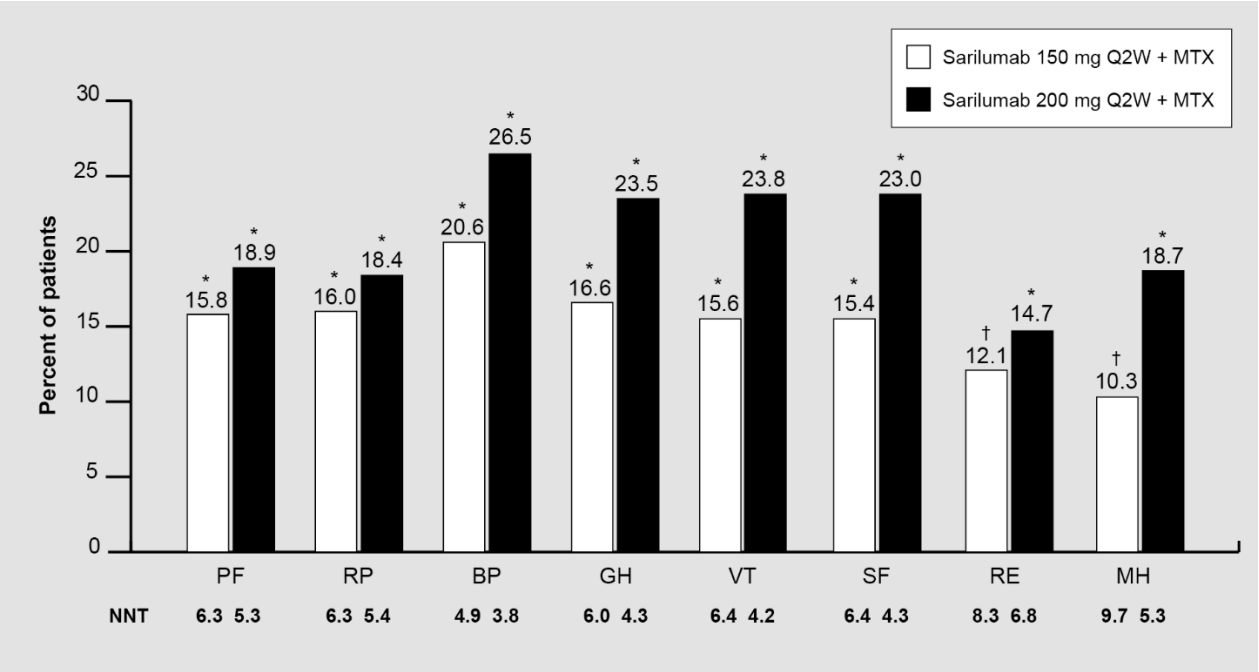
Figure 4.15 Responder analysis: Differences from placebo in the percentage of patients reporting improvement ≥ MCID after 24 weeks of treatment according to PtGA, pain, FACIT-F, HAQ-DI, and the SF-36 physical and mental component scores[64]



*p<0.0001 and †p<0.05 for response rate vs. placebo

BP=body pain; FACIT-F= Functional Assessment of Chronic Illness Therapy-Fatigue; GH=general health; HAQ-DI=Health Assessment Questionnaire Disability Index; MCS=SF-36 mental component scores; MH=mental health; NNT=number needed to treat; PCS=physical component scores; PF=physical functioning; PtGA=patient global assessment; RE=role emotional; RP=role physical; SF=social functioning; VT=vitality.

Figure 4.16 Responder analysis: Differences from placebo in the percentage of patients reporting improvements ≥MCID after 24 weeks of treatment in SF-36 domain score[64]



*p<0.0001 and †p<0.05 for response rate vs. placebo

BP=body pain; FACIT-F= Functional Assessment of Chronic Illness Therapy-Fatigue; GH=general health; HAQ-DI=Health Assessment Questionnaire Disability Index; MCS=SF-36 mental component scores; MH=mental health; NNT=number needed to treat; PCS=physical component scores; PF=physical functioning; PtGA=patient global assessment; RE=role emotional; RP=role physical; SF=social functioning; VT=vitality.

4.7.3 TARGET — sarilumab plus conventional disease-modifying anti-rheumatic drugs in tumour necrosis factor inhibitor irresponsive or intolerant patients with moderate-to-severe rheumatoid arthritis

Sarilumab when added to a background of cDMARDs significantly reduced signs and symptoms, improved physical function, and improved PROs and HRQoL in TNFi-IR/intolerant adults with moderate-to-severe RA (Fleishmann 2017, CSR). Sarilumab 150 mg and 200 mg plus MTX were associated with significant and clinically meaningful improvements versus placebo plus MTX for both co-primary endpoints (ACR20 at Week 24 [p<0.0001 both doses] and change in HAQ-DI at Week 12 [p<0.01 150 mg and p<0.001 200 mg]); these were confirmed by all planned sensitivity analyses (Table 4.19)[57].

4.7.3.1 Improvements in signs and symptoms

A significantly greater percentage of patients receiving sarilumab 150 mg and sarilumab 200 mg plus cDMARDs had an ACR20 response versus placebo at Week 24 (55.8% and 60.9% vs. 33.7%; p<0.0001 vs. placebo for both comparisons) (Table 4.19 and Table 4.20)[57].

Similar results were observed for ACR50 and ACR70 (Table 4.19 and Figure 4.15). Differences versus placebo were apparent as early as Week 4 and response was maintained throughout the duration of the study (Figure 4.18)[57].

Results from the pre- specified sensitivity analysis, in which the LOCF from the point of discontinuation was used to impute missing data, were consistent with those from the primary analyses for ACR20 response[57].

4.7.3.2 Improvements in physical function

Sarilumab 150 mg and sarilumab 200 mg plus cDMARDs resulted in statistically significant improvements versus placebo plus cDMARDs in LSM change from baseline in HAQ-DI at Week 12 (−0.46 and −0.47, vs. −0.26; p<0.001 vs. placebo for both comparisons), and a significantly greater proportion of patients achieved a clinically meaningful HAQ-DI response ≥0.3 (43.1% and 47.3% vs. 31.5%; p<0.05 for 150 mg and p<0.01 for 200 mg) (Table 4.19)[57].

Significant improvements in the HAQ-DI versus placebo were observed by Week 4 (p<0.01 vs. placebo both comparisons) and were sustained throughout the 24-week study period (Figure 4.19)[57].

Results of two sensitivity analyses, in which the LOCF method or multiple imputations were used to impute data collected after rescue or treatment discontinuation, were consistent with those of the primary analyses described above[57].

4.7.3.3 Reduced disease activity and higher rates of clinical response and remission

Sarilumab 150 mg and sarilumab 200 mg plus cDMARDs were associated with [redacted] and a [redacted] (Table 4.19)[62]:

- [redacted] at Week 24, the LSM change in the CDAI from baseline was [redacted]

- [redacted] at Week 24, the LSM change in the SDAI from baseline was [redacted]

- [redacted]: a [redacted] of patients treated with sarilumab 150 mg and 200 mg plus cDMARD [redacted]

- [redacted]: a [redacted] of patients treated sarilumab 150 mg and 200 mg plus cDMARD [redacted]

4.7.3.4 Improvements in patient-reported outcomes and health-related quality of life

Sarilumab 150 mg and sarilumab 200 mg plus cDMARD were associated with statistically significant and/or clinically meaningful improvements in PROs including SF-36 PCS and MCS, FACIT-Fatigue, pain, productivity and participation versus placebo at Week 24 (Table 4.20)[65].

[redacted] from baseline in the EuroQol five dimensions' questionnaire (EQ-5D) measuring generic health status (mobility, self-care, pain, usual activities, and psychological status) were reported at [redacted] for both sarilumab treatment groups compared with placebo [redacted][62].

4.7.3.4.1 Responder analysis

In pre-specified analysis of HAQ-DI and post hoc analyses of other PROs, percentages of patients who reported improvements ≥MCID (i.e., the proportion of responders) were higher with both doses of sarilumab versus placebo across all PROs ($p<0.05$) (Figure 4.20). Additionally, more patients receiving sarilumab reported values ≥MCID in individual SF-36 domains with exception of general for the 150 mg dose and role emotional for both doses (Figure 4.21). These resulted in NNTs ranging from 3.8 (sarilumab 200 mg for pain) to 12.2 (sarilumab 150 mg for role emotional). In the subgroup of ACR20 responders (n=274; 50.2%

of the total population), the majority of patients reported improvements ≥MCID across PROs (range, 52.5–98.2%)[65].

4.7.3.5 Overall summary of results

Sarilumab 150 mg and 200 mg Q2W plus cDMARD(s) provided statistically significant improvements in the signs and symptoms of RA compared with placebo in patients with moderate-to-severe RA and inadequate response or intolerance to TNFis (p<0.0001). In addition to ACR20 responses, a significantly greater proportion of sarilumab-treated patients, achieved ACR50 and ACR70 responses (37.0%, 40.8% vs. 18.2% and 19.9%, 16.3% vs. 7.2% respectively with sarilumab 150 mg and 200 mg 2QW versus placebo [p=0.056 to p<0.001]). Improved ACR20 response rates were observed as early as 8 weeks after treatment initiation and were sustained throughout the 24-week study[57].

Treatment with sarilumab (150 mg or 200 mg) also resulted in statistically significant and clinically relevant improvements in physical function (HAQ-DI improvements of ≥0.22 and ≥0.30 units [nominal p<0.05]) compared with placebo at 12 weeks[57].

Table 4.19 Efficacy results[57,62]

	Placebo + cDMARD (N=181)	Sarilumab 150mg Q2W + cDMARD (N=181)	p	Sarilumab 200mg Q2W + cDMARD (N=184)	p
Signs and symptoms at Week 24					
ACR20, n (%)	61 (33.7)	101 (55.8)	<0.0001	112 (60.9)	<0.0001
ACR50, n (%)	33 (18.2)	67 (37.0)	<0.0001	75 (40.8)	<0.0001
ACR70, n (%)	13 (7.2)	36 (19.9)	0.0002	30 (16.3)	0.0056
Physical function at Week 12					
HAQ-DI, LSM change from baseline (SE)	−0.26 (0.04)	−0.46 (0.04)	<0.001	−0.47 (0.04)	<0.001
Physical function at Week 24					
HAQ-DI, LSM mean change from baseline (SE)	−0.3 (0.05)	−0.5 (0.05)	0.0078	−0.6 (0.05)	0.0004
HAQ-DI change from baseline >3.0, n (%)	57 (31.5)	78 (43.1)	<0.05	87 (47.3)	<0.01
DAS28-CRP, LS mean change from baseline (SE)	−1.38 (0.119)	−2.35 (0.111)	<0.0001	−2.82 (0.108)	<0.0001
Disease activity and remission at Week 24					
DAS28-CRP<2.6, n (%)	13 (7.2)	45 (24.9)	<0.0001	53 (28.8)	<0.0001
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

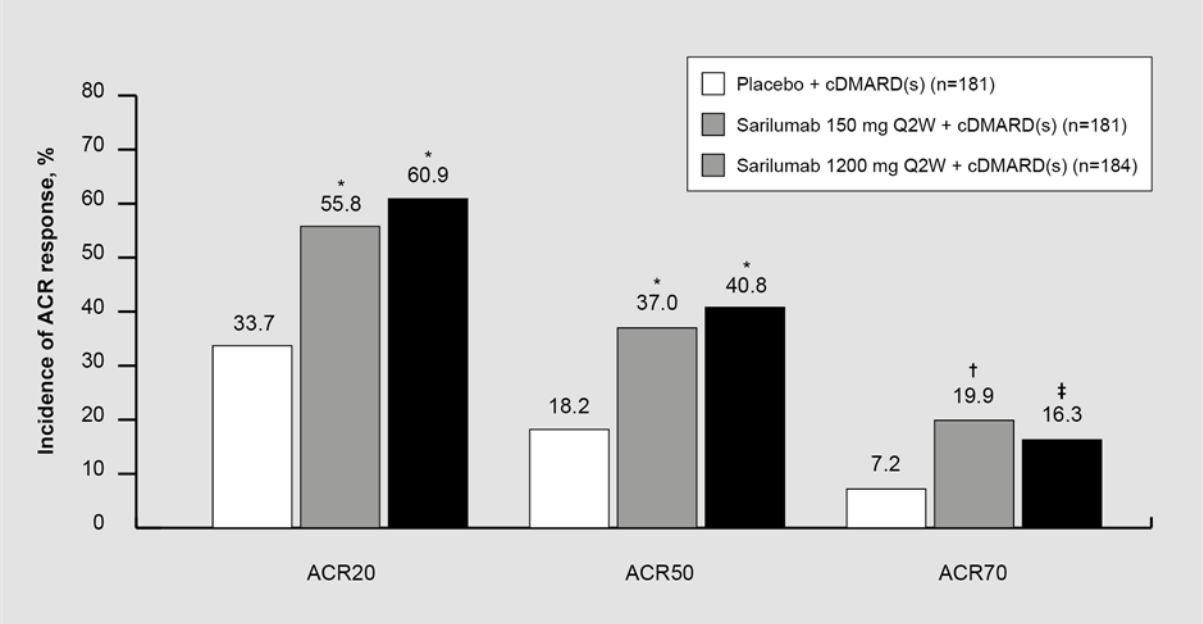
ACR50/70 = American College of Rheumatology 50%/70% improvement; cDMARD=conventional disease-modifying anti-rheumatic drug; EQ-5D-3L= EuroQol - EQ-5 dimension health-related quality of life assessment; FACIT-F= Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI=Health Assessment Questionnaire Disability Index; LS=least square; MTX=methotrexate; Q2W=every 2 weeks; SE=standard error; RAID= Rheumatoid Arthritis Impact of Disease; SF-36= Medical Outcomes Study: 36-Item Short Form Survey; WPS-RA= Work Productivity Survey rheumatoid arthritis

Table 4.20 Patient-reported outcomes (PRO)[65]

PRO, LSM change from baseline (SE)	Week 12					Week 24				
	Placebo + cDMARDs (N =181)	Sarilumab 150 mg Q2W + cDMARDs (N=181)	p	Sarilumab 200mg Q2W + cDMARDs (N=184)	p	Placebo + cDMARDs (N =181)	Sarilumab 150mg Q2W + cDMARDs (N=181)	p	Sarilumab 200mg Q2W + cDMARDs (N=184)	p
PtGA	−13.8±1.8	−25.3±1.8	<0.0001	−27.4±1.8	<0.0001	−19.8±2.2	−29.6±2.1	<0.001	−31.3±2.0	<0.0001
Pain VAS	−15.1±1.9	−26.9±1.9	<0.0001	−30.6±1.9	<0.0001	−21.3±2.3	−31.9±2.1	<0.001	−33.7±2.0	<0.0001
HAQ-DI	−0.26±0.04	−0.46±0.04	<0.001	−0.47±0.04	<0.001	−0.34±0.05	−0.52±0.05	<0.05	−0.58±0.05	
FACIT-F	5.6±0.7	8.0±0.7	<0.05	9.5±0.7	<0.0001	6.8±0.9	9.9±0.8	<0.05	10.1±0.8	
Morning stiffness	−13.4±2.1	−27.3±2.1	<0.0001	−29.4±2.1	<0.0001	−21.7±2.4	−32.3±2.2	<0.001	−33.8±2.1	<0.0001
RAID	−1.3±0.2	−2.3±0.2	<0.0001	−2.5±0.2	<0.0001	−1.8±0.2	−2.6±0.2	<0.05	−2.8±0.2	<0.001
SF-36 component scores										
PCS	3.7±0.6	6.9±0.6	<0.0001	6.8±0.6	<0.0001	4.4±0.7	7.7±0.7	<0.001	8.5±0.6	<0.0001
MCS	3.5±0.7	5.1±0.8		6.5±0.7	<0.05	4.7±0.9	6.3±0.8		6.8±0.8	
SF-36 domain scores										
Physical functioning	6.7±1.7	14.7±1.7	<0.001	4.7±1.7	<0.001	8.5±2.0	16.1±1.9	<0.05	16.8±1.8	<0.05
Role physical	10.3±1.7	16.8±1.7	<0.05	16.3±1.7	<0.05	10.8±2.0	17.9±1.9	<0.05	19.9±1.8	<0.001
Body pain	11.6±1.5	22.0±1.6	<0.0001	24.3±1.5	<0.0001	16.8±1.9	24.3±1.8	<0.05	27.7±1.7	<0.0001
General health	6.4±1.3	8.8±1.3		10.9±1.3	<0.05	8.3±1.5	11.9±1.4		14.8±1.4	<0.05
Vitality	8.5±1.4	13.1±1.5	<0.05	15.1±1.4	<0.001	9.2±1.7	14.5±1.6	<0.05	16.6±1.5	<0.001
Social functioning	9.1±1.7	17.2±1.7	<0.001	16.2±1.7	<0.05	12.9±2.1	19.3±2.0	<0.05	19.6±1.9	<0.05
Role emotional	8.2±1.9	12.6±1.9		13.6±1.9	<0.05	10.5±2.2	14.3±2.0		15.0±2.0	
Mental health	5.3±1.3	7.8±1.3		12.1±1.3	<0.0001	8.0±1.6	10.8±1.5		12.7±1.4	<0.05

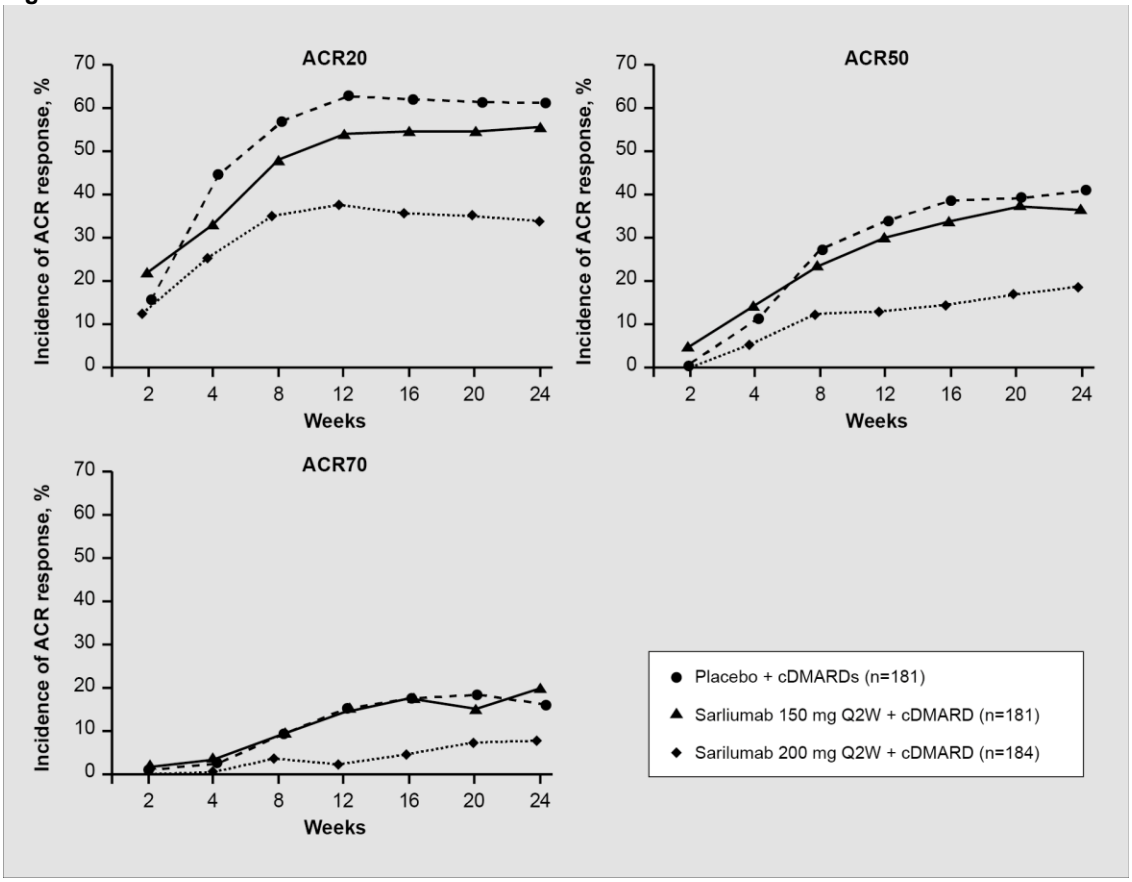
cDMARD= Conventional disease-modifying anti-rheumatic drugs; FACIT-F=Functional Assessment of Chronic Illness Therapy-Fatigue scale; HAQ-DI=Health Assessment Questionnaire Disability Index; LSM=least square mean; MCS=mental component summary; MTX=methotrexate; PCS=physical component summary; PRO=patient-reported outcomes; PtGA=patient global assessment of disease activity; Q2W =once every 2 weeks; SE=standard error; SF-36=36-item Short Form Health Survey-Version 2; VAS=visual analogue scale.

Figure 4.17 ACR 20/50/70 at Week 24[57]



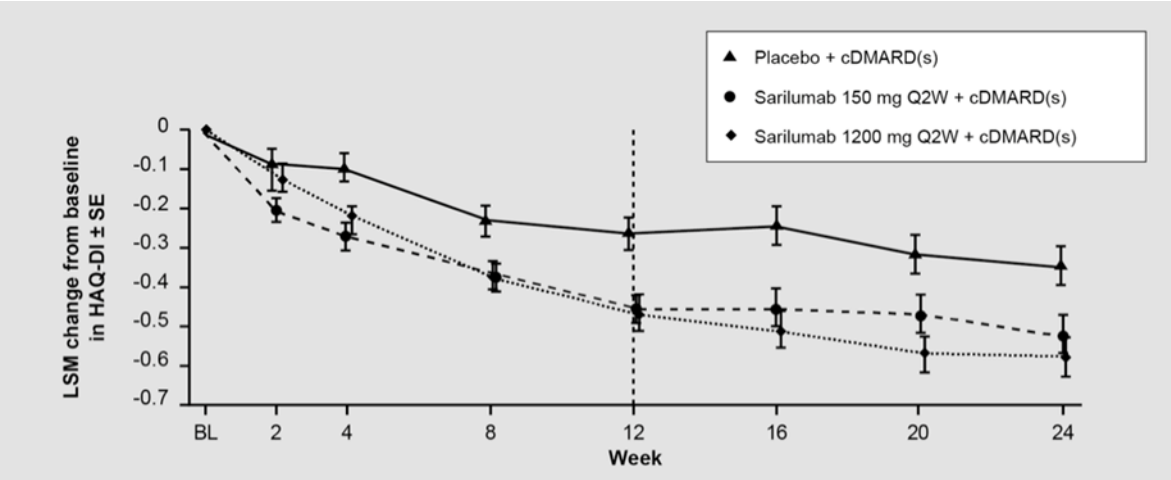
*p<0.0001 vs. placebo + cDMARD, †p=0.0002 vs. placebo + cDMARD, ‡p=0.0056 vs. placebo + cDMARD
ACR20/50/70=American College of Rheumatology 20%/50%/70% improvement; cDMARD=conventional disease-modifying anti-rheumatic drug; sarilumab=sarilumab; Q2W=every 2 weeks

Figure 4.18 ACR 20/50/70 over time[57]



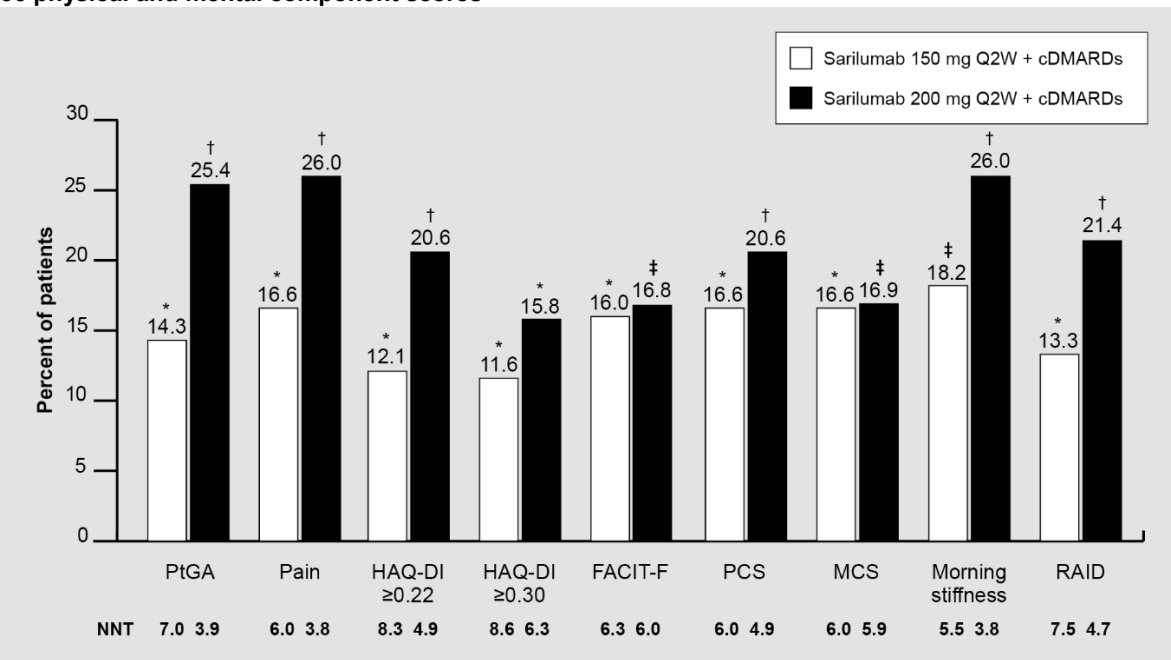
ACR50/70 = American College of Rheumatology 50%/70% improvement response; cDMARD=conventional disease-modifying anti-rheumatic drug

Figure 4.19 Least square mean change from baseline in Health Assessment Questionnaire Disability Index over time[57]



Dotted vertical line indicates the time point after which rescue was permitted.
cDMARD= Conventional disease-modifying anti-rheumatic drugs; HAQ-DI=Health Assessment Questionnaire Disability Index; LSM=least squares mean; SE=standard error; Q2W=once every 2 weeks

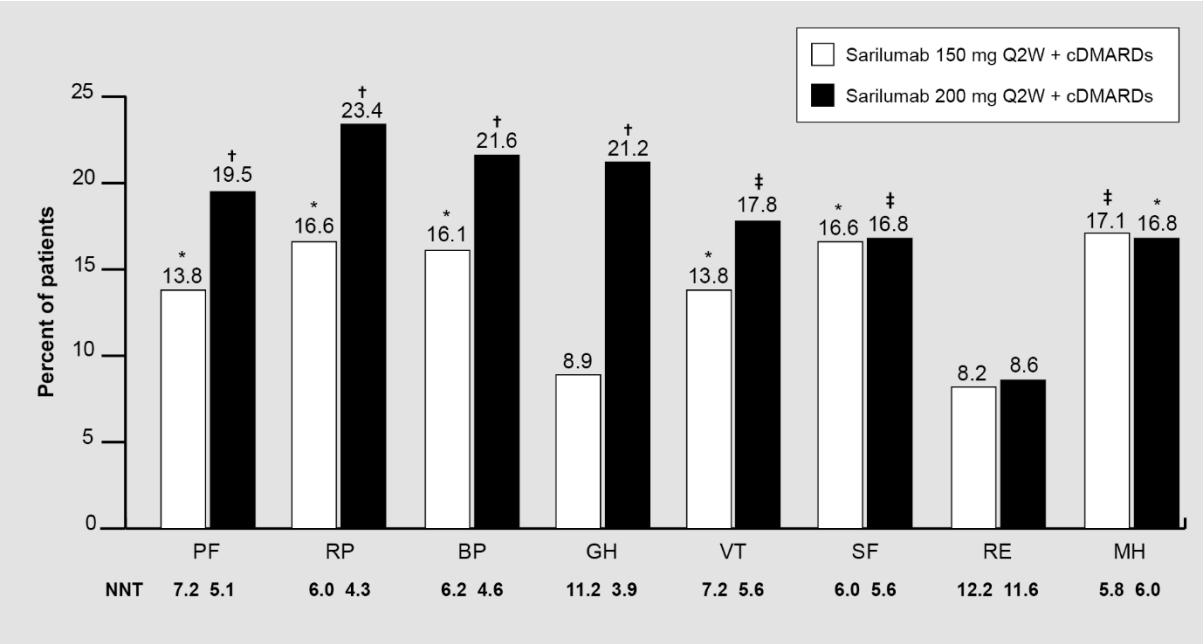
Figure 4.20 Responder analysis: Differences from placebo in the percentage of patients reporting improvement ≥MCID after 24 weeks of treatment according to PtGA, pain, FACIT-F, HAQ-DI, and the SF-36 physical and mental component scores[65]



*p<0.05, †p<0.0001 and ‡p<0.00 for response rate vs. placebo

BP=body pain; FACIT-F= Functional Assessment of Chronic Illness Therapy-Fatigue; GH=general health; HAQ-DI=Health Assessment Questionnaire Disability Index; MCS=SF-36 mental component scores; MH=mental health; NNT=number needed to treat; PCS=physical component scores; PF=physical functioning; PtGA=patient global assessment; RE=role emotional; RP=role physical; SF=social functioning; VT=vitality.

Figure 4.21 Responder analysis: Differences from placebo in the percentage of patients reporting improvements ≥MCID after 24 weeks of treatment in SF-36 domain scores[65]



*p<0.05, †p<0.0001 and ‡p<0.00 for response rate vs. placebo

BP=body pain; FACIT-F= Functional Assessment of Chronic Illness Therapy-Fatigue; GH=general health; HAQ-DI=Health Assessment Questionnaire Disability Index; MCS=SF-36 mental component scores; MH=mental health; NNT=number needed to treat; PCS=physical component scores; PF=physical functioning; PtGA=patient global assessment; RE=role emotional; RP=role physical; SF=social functioning; VT=vitality.

4.7.4 ASCERTAIN — sarilumab plus conventional disease-modifying anti-rheumatic drugs versus tocilizumab moderate-to-severe rheumatoid arthritis patients who were inadequate responders to or intolerant of methotrexate

ASCERTAIN was not designed to show statistical differences between treatments, but to establish additional context for safety of sarilumab and tocilizumab, at the time the only other approved IL-6 inhibitor. The primary objective of the ASCERTAIN study was to assess, in the same study, the safety and tolerability of sarilumab and tocilizumab in patients with RA who are inadequate responders to or intolerant of TNFis. The clinical effects of sarilumab and tocilizumab were investigated as an exploratory objective. The following discussions relate to exploratory efficacy endpoints[58,140]. Overall, efficacy results were [redacted] in signs and symptoms (ACR20/50/70), [redacted] in physical function (HAQ-DI), [redacted] disease activity (DAS28) and [redacted] rates of clinical remission from baseline to Week 24 between sarilumab 150 mg or 200 mg Q2W plus cDMARD and tocilizumab 4 mg/kg Q4W (standard dose) plus cDMARD (Table 4.21)[58].

4.7.4.1 Comparable improvements in signs and symptoms

The proportion of patients achieving an ACR20 response at Week 24 was [redacted] in patients treated with sarilumab 150 mg and 200 mg Q2W compared to tocilizumab 4–8

mg/kg Q4W [redacted] (Table 4.21) (ASCERTAIN CSR). In order to evaluate the impact of the higher discontinuation rate in the sarilumab groups compared to tocilizumab group, in the sensitivity analysis, missing data were imputed using the last value carried forward approach. In this analysis, the proportion of patients achieving an ACR20 response at Week 24 appeared to be [redacted][58].

The proportion of patients achieving an ACR50 response at Week 24 was [redacted] in patients treated with sarilumab 200 mg Q2W and tocilizumab 4–8 mg/kg Q4W [redacted] and [redacted] than in the group of patients treated with sarilumab 150 mg Q2W (36.7%) with the primary analysis approach (Table 4.21) (ASCERTAIN CSR). However, in the sensitivity analysis, the proportion of patients achieving an ACR50 response at Week 24 was [redacted] in the sarilumab 200 mg Q2W group [redacted] than in the tocilizumab 4–8 mg/kg Q4W group [redacted] and the sarilumab 150 mg Q2W group[58].

The proportion of patients achieving an ACR70 response at Week 24 was [redacted] in patients treated with sarilumab 150 mg and 200 mg Q2W compared to tocilizumab 4–8 mg/kg Q4W [redacted] in the primary analysis (Table 4.21) and similar results were obtained in the sensitivity analysis[58].

The mean change from baseline to Week 24 in both TJC and SJC were [redacted] in patients treated with 150 mg and 200 mg Q2W compared to tocilizumab 4–8 mg/kg Q4W [redacted] (Table 4.21)[58].

Baseline CRP values were [redacted] across all three treatment groups and the decrease in CRP from baseline to Week 24 were [redacted] in patients treated with 150 mg and 200 mg Q2W compared to tocilizumab 4–8 mg/kg Q4W [redacted] (Table 4.21)[58].

4.7.4.2 Comparable improvements in physical function

The mean change from baseline in HAQ-DI at Week 24 was [redacted] in patients treated with 150 mg and 200 mg Q2W compared to tocilizumab 4–8 mg/kg Q4W [redacted] (Table 4.21)[58].

4.7.4.3 Comparable reductions in disease activity

The decrease in the DAS28-CRP score at Week 24 was [redacted] in patients treated with 150 mg and 200 mg Q2W compared to tocilizumab 4–8 mg/kg Q4W [redacted] and the proportion of patients achieving DAS28-CRP remission <2.6 at

Week 24 was [redacted] in the three groups [redacted] (Table 4.21)[58].

The mean change from baseline to Week 24 in both physician and patient global assessment of disease activity were [redacted] in patients treated with 150 mg and 200 mg Q2W compared to tocilizumab 4–8 mg/kg Q4W [redacted] (Table 4.21)[58].

4.7.4.4 Comparable reductions in patient-reported outcome

The mean change from baseline to Week 24 in patient assessment of pain was [redacted] in patients treated with 150 mg and 200 mg Q2W compared to tocilizumab 4–8 mg/kg Q4W [redacted] (Table 4.21)[58].

4.7.4.5 Overall summary of efficacy results

This study was not designed to evaluate the comparative efficacy of sarilumab and tocilizumab and therefore, all efficacy endpoints were exploratory. Overall, efficacy results are generally similar across the three treatment groups[58].

For the primary efficacy analysis with discontinued patients imputed as non-responders, the ACR20 response rates were slightly lower in the sarilumab groups than in the tocilizumab group. However, when taking into account the discontinuation rate difference (due to no particular pattern of specific AEs leading to discontinuation) between the groups (i.e., with the sensitivity analysis), this difference disappeared and the response rates were similar across the three treatment groups[58].

Improvements in physical function, disease activity and patient assessment of pain were similarly comparable in sarilumab and tocilizumab treated patients[58].

.

Table 4.21 Efficacy results Week 24 — descriptive statistics only[58]

	Tocilizumab Q4W + cDMARD (N=102)	Sarilumab 150 mg Q2W + cDMARD (N=49)	Sarilumab 200 mg Q2W + cDMARD (N=51)
Signs and symptoms			
ACR20, %	[redacted]	[redacted]	[redacted]
ACR50, %	[redacted]	[redacted]	[redacted]
ACR70, %	[redacted]	[redacted]	[redacted]
TJC (0–68), LSM change from baseline	[redacted]	[redacted]	[redacted]
SJC (0–68), LSM mean change from baseline	[redacted]	[redacted]	[redacted]
Physical function			
HAQ-DI, LSM change from baseline (SE)	[redacted]	[redacted]	[redacted]
Disease activity			
Physician global assessment of disease activity (VAS), LSM change from baseline	[redacted]	[redacted]	[redacted]
Patient global assessment of disease activity (VAS), LSM change from baseline	[redacted]	[redacted]	[redacted]
CRP (mg/dL)	[redacted]	[redacted]	[redacted]
DAS28 remission <2.6, %	[redacted]	[redacted]	[redacted]
DAS28-CRP	[redacted]	[redacted]	[redacted]
Patient-reported outcomes			
Pain, LSM mean change from baseline	[redacted]	[redacted]	[redacted]

ACR50/70 = American College of Rheumatology 50%/70% improvement response; cDMARD=conventional disease-modifying anti-rheumatic drug; CRP=C-reactive protein; DAS28= 28-joint disease activity score; HAQ-DI=Health Assessment Questionnaire Disability Index; LSM=least square mean; MTX=methotrexate; Q2W=every 2 weeks; SE=standard error; SJC=swollen joint count; SF-36= Medical Outcomes Study: 36-Item Short Form Survey; TJC=tender joint count.

4.7.5 MONARCH—sarilumab monotherapy versus adalimumab monotherapy in moderate-to-severe rheumatoid arthritis patients who were inadequate responders to or intolerant of methotrexate

The MONARCH monotherapy study met its primary endpoint demonstrating that sarilumab was superior to adalimumab in improving signs and symptoms (DAS28- ESR) at Week 24 in severe RA patients who were inadequate responders to or intolerant of MTX (Table 4.22). The MONARCH study also met important secondary endpoints; superiority over adalimumab in improvements in signs and symptoms of RA and physical function[1].

4.7.5.1 Superior reductions in disease activity

Sarilumab 200 mg Q2W was significantly superior to adalimumab 40 mg Q2W in LSM change from baseline to Week 24 in DAS28-ESR (−3.28 vs. −2.20; p<0.0001) (Table 4.22 and Figure 4.22)[1]. Superior improvements in DAS28-ESR were apparent by Week 12 with sarilumab vs. adalimumab (−2.77 vs −1.88; nominal p<0.0001 (Figure 4.22)[1].

Sarilumab 200 mg Q2W was significantly superior to adalimumab 40 mg Q2W in terms of the proportion of patients achieving DAS28-ESR remission (26.6% vs. 7.0%; p<0.0001) (Table 4.22) and the odds of achieving DAS28-ESR remission with sarilumab were approximately three times greater than adalimumab at Week 12 (OR 2.6; 95% CI 1.31–5.19; nominal p=0.0051) and approximately five times greater at Week 24 (OR 4.88; 95% CI 2.54–9.39; p<0.0001)[1].

The change in DAS28-CRP at Week 24 was consistent with DAS28-ESR in terms of superiority of sarilumab versus adalimumab (−2.86 vs. −1.97; nominal p<0.0001) (Table 4.22 and Figure 4.22) and sensitivity analyses were consistent with the primary analysis[1].

Sarilumab 200 mg Q2W was significantly superior to adalimumab 40 mg Q2W in CDAI, a measure of clinical response independent of acute-phase reactants that may favour IL-6 inhibition. Sarilumab 200 mg Q2W was significantly superior in terms of least mean squares (LSM) improvements in CDAI score from baseline to Week 24 versus adalimumab 40 mg Q2W at Week 24 (−28.9 vs. −25.2; nominal p=0.0013) and a greater proportion of patients receiving sarilumab achieved CDAI remission versus adalimumab [redacted] (Table 4.22)[1,63].

4.7.5.2 Superior improvements in signs and symptoms

Sarilumab 200 mg Q2W was significantly superior to adalimumab 40 mg Q2W in the proportion of patients achieving an ACR20/50/70 response at Week 24 (71.7%/45.7%/23.4%

vs. 58.4%/29.7%/11.9%; all p≤0.0074), with differences observed as early as Week 8 (Table 4.22 and Figure 4.23)[1]

4.7.5.3 Improvements in physical function

Sarilumab 200 mg Q2W was significantly superior to adalimumab 40 mg Q2W in terms of LSM improvement in HAQ-DI score from baseline to Week 24 (−0.61 vs. −0.43; p=0.0037) (Table 4.22)[1].

4.7.5.4 Superior improvements in patient-reported outcomes and health-related quality of life

Sarilumab 200 mg Q2W was significantly superior to adalimumab 40 mg Q2W in terms of improvements in the SF-36 PCS at Week 24 (Table 4.22). Both groups demonstrated similar improvement in SF-36 MCS at Week 24. An improvement from baseline to week 24 in FACIT-Fatigue score was observed in both groups, with a trend towards greater improvement in the sarilumab group (Table 4.22)[1].

At Week 24, the mean change from baseline in the EQ-5D index score in the sarilumab group [redacted] (Table 4.22). At Week 24, the mean change from baseline in the EQ-5D VAS score in the sarilumab group [redacted] (Table 4.22)[63].

4.7.5.5 Overall summary of results

Sarilumab monotherapy demonstrated superiority to adalimumab monotherapy by improving signs and symptoms and physical functions of patients with RA who are unable to continue treatment with MTX. Sarilumab was statistically superior to adalimumab in reduction of disease activity and improvement in the signs and symptoms of RA as demonstrated by a greater reduction in DAS28-ESR (p<0.001), CDAI (p<0.05) and ACR20 (p=0.0074). Greater efficacy with sarilumab versus adalimumab observed with CDAI illustrates that the benefits of sarilumab monotherapy extend beyond the pharmacodynamic effects on acute-phase reactants. The odds of DAS28 disease remission were greater with sarilumab compared with adalimumab, despite the allowance of adalimumab dose escalation. Additionally, there was no difference in the magnitude of response for patient populations intolerant to MTX versus those with inadequate response, indicating that the robust efficacy outcomes observed with sarilumab were independent of prior MTX use or response (Section 4.8)[1].

Relative to adalimumab, patients receiving sarilumab reported significantly greater improvement in their health status and physical function as reflected by differences in SF-36

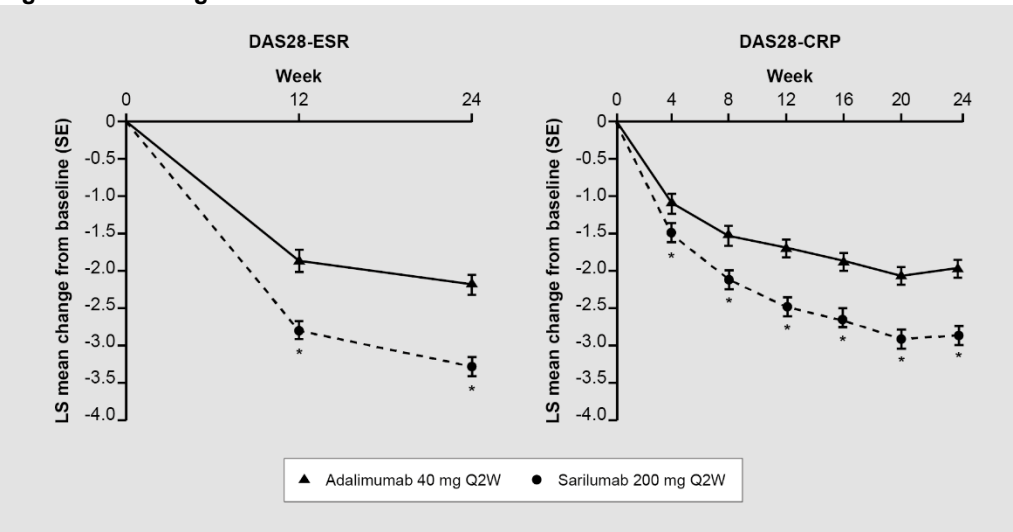
PCS (p=0.0006) and HAQ-DI (p=0.0037), along with a trend towards greater improvement in fatigue (p=0.0689)[1].

Table 4.22 Efficacy results Week 24[1,63]

	Adalimumab 40 mg Q2W (N=185)	Sarilumab 200mg Q2W (N=184)	p
Disease activity			
DAS28-ESR, mean (SD)	4.5 (1.4)	3.5 (1.4)	
DAS28-ESR, LSM change from baseline (SE)	−2.20 (0.106)	−3.28 (0.105)	<0.0001
DAS28-ESR <2.6 (remission), n (%)	13 (7.0)	49 (26.6)	<0.0001
CDAI, LS mean change from baseline (SE)	[redacted]	[redacted]	[redacted]
CDAI <2.8 (remission), n (%)	[redacted]	[redacted]	[redacted]
Signs and symptoms			
ACR20, n (%)	108 (58.4)	132 (71.7)	0.0074
ACR50, n (%)	55 (29.7)	84 (45.7)	0.0017
ACR70, n (%)	22 (11.9)	43 (23.4)	0.0036
Physical function and PROs			
HAQ-DI, mean (SD)	1.2 (0.7)	1.0 (0.7)	
HAQ-DI, LSM change from baseline (SE)	−0.43 (0.05)	−0.61 (0.05)	0.0037
SF-36 PCS, LSM change from baseline (SE)	6.1 (0.6)	8.7 (0.6)	0.0006
SF-36 MCS, LSM change from baseline (SE)	6.8 (0.8)	7.9 (0.8)	0.3319
FACIT-Fatigue, LSM change from baseline (SE)	8.4 (0.7)	10.2 (0.7)	0.0689
EQ-5D single index utility, LSM change from baseline (SE)	0.26 (0.35)	0.32 (0.35)	0.0382
EQ-5D VAS, LSM change from baseline (SE)	19.94 (1.720)	24.22 (1.686)	0.0699

ACR20/50/70=American College of Rheumatology 20%/50%/70% improvement; DAS28-ESR=28-joint disease activity score-erythrocyte sedimentation rate; EQ-5D= EuroQol five dimensions' questionnaire; FACIT=Functional Assessment of Chronic Illness Therapy; HAQ-DI=Health Assessment Questionnaire Disability Index; LSM=least square mean; Q2W=every 2 weeks; SF-36=Medical Outcomes Short Form 36 Health Survey.

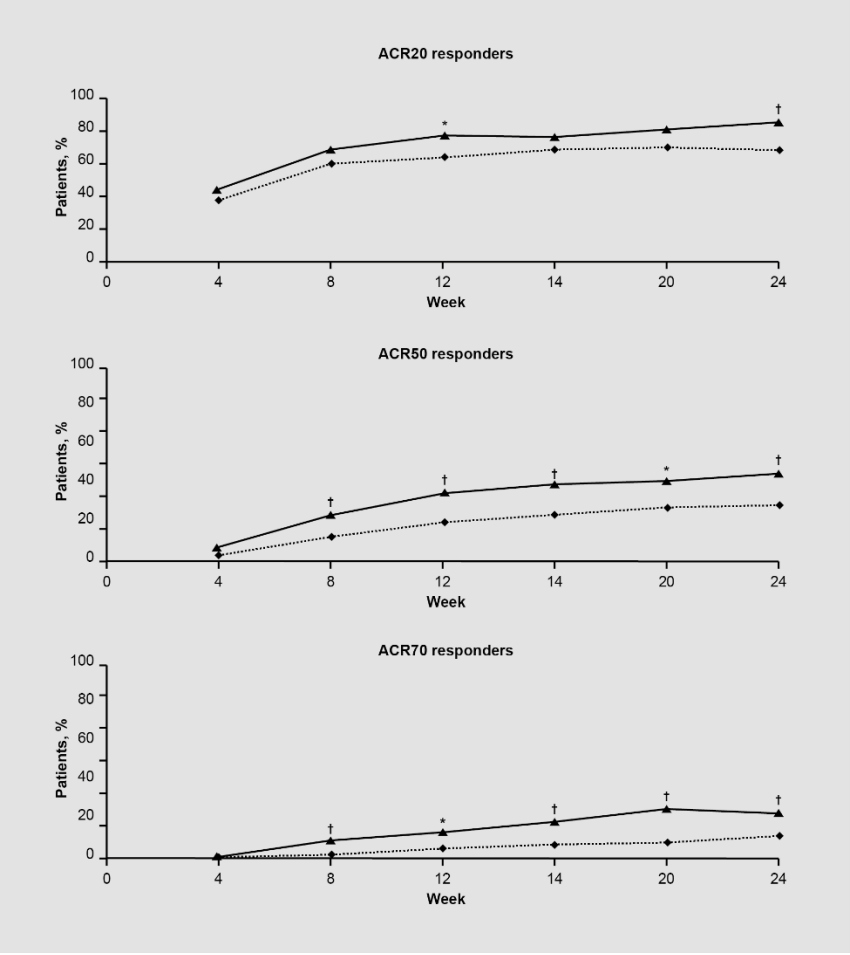
Figure 4.22 Change from baseline in DAS28 with ESR and with CRP[1]



*p<0.001 versus adalimumab

CRP=C-reactive protein; DAS28=28-joint count disease activity score; ESR=erythrocyte sedimentation rate; LS=least square; Q2W=once every 2 weeks.

Figure 4.23 American College of Rheumatology 20%/50%/70% improvement response over time[1]



*p<0.05 versus adalimumab; †p<0.01 versus adalimumab

ACR50/70 = American College of Rheumatology 50%/70% improvement

4.7.6 Overall summary of key efficacy endpoints

A summary table of efficacy endpoints is presented in Table 4.23.

Table 4.23 Overall summary of key efficacy endpoints[1,55-58]

	MOBILITY A			MOBILITY B			TARGET			ASCERTAIN			MONARCH	
	Placebo + MTX	Sarilumab 150 mg Q2W + MTX	Sarilumab 200 mg Q2W + MTX	Placebo+ MTX	Sarilumab 1 50 mg Q2W + MTX	Sarilumab 200 mg Q2W + MTX	Placebo + cDMARD	Sarilumab 150 mg Q2W+ cDMARD	Sarilumab 200 mg Q2W + cDMARD	Tocilizumab 4 mg/kg Q4W+ DMARD	Sarilumab 150 mg Q2W+ cDMARD	Sarilumab 200 mg Q2W + cDMARD	Adalimumab 40 mg Q2W	Sarilumab 200 mg Q2W
n	52	51	52	398	400	399	181	181	184	[redacted]	[redacted]	[redacted]	185	184
Signs and symptoms														
ACR20, %	46.2	67.0	65.0	33.4	58.0	66.4	33.7	55.8	60.9	[redacted]	[redacted]	[redacted]	58.4	71.7
Physical function														
HAQ-DI, LSM change from baseline	−0.26	−0.62	−0.57	−0.29	−0.53	−0.55	−0.34	−0.52	−0.58	[redacted]	[redacted]	[redacted]	−0.43	−0.61
Radiographic progression														
mTSS LSM change from baseline				2.78	0.90	0.25								
Disease activity														
DAS28-CRP/ESR remission, %				10.1	27.8	34.1	7.2	24.9	28.8	[redacted]	[redacted]	[redacted]	7.0	26.6
CDAI, LSM change from baseline				−14.50	−23.90	−25.79	[redacted]	[redacted]	[redacted]				[redacted]	[redacted]

ACR20 = American College of Rheumatology 20% improvement; CRP = C-reactive protein; DAS28-CRP = Disease Activity Score in 28 joints using CRP level; CDAI = Clinical Disease Activity Index; HAQ-DI = Health Assessment Questionnaire Disability Index; LSM=least squares mean; mTSS=modified Total Sharp Score; Q2W=once every 2 weeks; Q4W=once every 4 weeks

4.8 Subgroup analysis

Testing of treatment-by-subgroup interactions demonstrated that sarilumab efficacy was not influenced by gender, race, age, geographical region, weight, BMI, prior biological use, rheumatoid factor or cyclic citrullinated peptide antibody positivity, baseline CRP, smoking history, duration of RA disease or number of prior[1,55-58].

Further details of subgroup interaction analysis can be found in Appendix 7.

The superior efficacy (change from baseline in DAS28-ESR at Week 24) of sarilumab relative to adalimumab [redacted][63].

4.8.1 Subgroup analysis for MOBILITY

A pre-specified analysis of patients from MOBILITY demonstrated no significant difference in the incidence of ACR20 in patients with and without prior biological use (Table 4.24)[55].

Table 4.24 Incidence of American College of Rheumatology 20% improvement response at week 12 by prior biological use — MOBILITY-A[55]

	ACR20 at Week 12, n (%)	
	Prior biologic use	**No prior biologic use**
Placebo (n=52)	4 (33.3)	20 (50.0)
Sarilumab 100 mg Q2W (n=51)	7 (53.8)	18 (47.4)
Sarilumab 150 mg Q2W (n=51)	8 (66.7)	26 (66.7)
Sarilumab 100 mg QW (n=50)	5 (41.7)	26 (68.4)
Sarilumab 200 mg Q2W (n=52)	9 (64.3)	25 (65.8)
Sarilumab 150 mg QW (N=50)	7 (58.3)	29 (76.3)

ACR20 = American College of Rheumatology 20% improvement response; Q2W=once every 2 weeks

4.8.2 Subgroup analysis for TARGET

A pre-specified analysis of patients from TARGET demonstrated greater ACR20 response rates at Week 24 and improvements in HAQ-DI at Week 12 with sarilumab compared to placebo regardless of number of prior TNFis (Table 4.25)[57].

Table 4.25 American College of Rheumatology 20% improvement response at Week 24 and Health Assessment Questionnaire Disability Index at Week 12 by prior tumour necrosis factor inhibitor — TARGET[57]

	Sarilumab 150 mg Q2W + cDMARD(s) (n=181)	Sarilumab 200 mg Q2W + cDMARD(s) (n=184)
ACR20, OR (95% CI) vs. placebo at Week 24		
1 prior TNFi	3.11 (1.85–5.25)	2.90 (1.73–4.86)
> 1prior TNFi	1.82 (0.75–4.43)	4.66 (1.94–11.21)
HAQ-DI, difference in LS mean vs. placebo at Week 12 (95% CI)		
1 prior TNFi	-0.15 (−0.28 to −0.01)	−0.21 (−0.34 to −0.07)
> 1prior TNFi	-0.37 (−0.59 to −0.14)	−0.23 (−0.45 to −0.01)

ACR20=American College of Rheumatology 20% improvement; HAQ-DI=Health Assessment Questionnaire Disability Index; LS=least square; DMARD=disease-modifying anti-rheumatic drug; TNFi=tumour necrosis factor

4.8.3 Subgroups analysis for MONARCH

A pre-specified subgroup analysis of patients from MONARCH demonstrated greater a change from baseline in DAS28-ESR at Week 24 with sarilumab compared with adalimumab, regardless of previous MTX response (treatment-by-subgroup interaction: intolerant versus inadequate response, p=0.2163) (Table 4.26)[1].

Table 4.26 CFB in DAS28 with ESR at Week 24 by MTX response — MONARCH[1]

	Adalimumab 40 mg Q2W (n=185)	Sarilumab 200 mg Q2W (n=184)
MTX inadequate responders		
Change from baseline in DAS28-ESR at Week 24, mean (SD)	4.4 (1.4)	3.6 (1.5)
Mean difference, 95% CI vs. adalimumab	-	−0.891 (−1.293 to −0.489)
MTX intolerant		
Change from baseline in DAS28-ESR at Week 24, mean (SD)	4.7 (1.3)	3.2 (1.4)
Mean difference, 95% CI vs. adalimumab	-	−1.253 (−1.660 to −0.846)

CFB=change from baseline; CI=confidence interval; DAS28= 28 joint disease activity score; ESR=erythrocyte sedimentation rate; HAQ-DI=Health Assessment Questionnaire Disability Index; LS=least square; MTX= methotrexate; Q2W=once every 2 weeks; SD=standard deviation

4.9 Meta-analysis

In order to compare the efficacy of sarilumab to the comparators specified in the NICE scope, a NMA was conducted to analyse the evidence from pivotal Phase III studies as described in Section 4.10.

4.10 Network meta-analysis

Key points

- Direct head-to-head evidence for sarilumab versus all treatments specified in the NICE scope was not identified. Therefore, a Bayesian NMA was conducted to evaluate the relative effectiveness of sarilumab (200 mg Q2W) with these comparators.
- The NMA reported three separate networks for patients 1) cDMARD inadequate responders (cDMARD-IR) receiving combination therapies 2) cDMARD-IR receiving monotherapy and 3) TNFi inadequate responders (TNFi-IR). NMA were performed for the clinically relevant outcomes of ACR responses, Health Assessment Questionnaire Disability Index (HAD-QI) change from baseline, EULAR responses, 28 joint disease activity score remission (DAS28), modified Total Sharp Score (mTSS) change from baseline (CFB), serious infections (SI) and adverse events (AEs).
- For each population, a base-case analysis was carried out for the primary endpoint for each comparator between Weeks 24 and 52. NMA with baseline risk regression was used as the base-case for the cDMARD-IR combination therapy (with the exception of EULAR data, where too few studies were available to perform a meaningful regression). NMA with Risk Difference was used in the base-case analysis for the TNF-IR network or for binary outcomes where there was considerable variability in baseline risk. There were too few studies to perform a regression analysis. The base-case NMA evaluating the comparative efficacy and safety of sarilumab (200 mg Q2W) vs. licensed treatments demonstrates comparable efficacy and safety to other biologic combination therapies. Sarilumab shows significantly better efficacy vs. adalimumab monotherapy, consistent with head-to-head trial data[1,63].
- In the cDMARD-IR population sarilumab 200 mg demonstrates:
    - Similar (overlapping credible intervals[CrI]) efficacy to other biologic combination therapies (adalimumab, etanercept, certolizumab pegol,

golimumab, infliximab, abatacept, rituximab, tofacitinib) in terms of ACR responses at Week 24.

    - Superiority (CrI do not overlap) to cDMARDs HAQ-DI CFB, DAS28 remission (DAS28 <2.6), EULAR good response, EULAR moderate-to-good response and mTSS at Week 24.
    - Superiority (CrI do not overlap) to cDMARDs in mTSS at Week 52.
    - Similarity (overlapping CrI) safety to all comparators (cDMARD, TNFi, golimumab and abatacept) and the class at Week 52.

- In the TNFi-IR/intolerant population sarilumab 200 mg demonstrates:
    - Superiority (CrI do not overlap) to cDMARD/MTX for ACR 20/50/70 and DAS28 <2.6 at Week 24.
    - Superiority (overlapping CrI) to cDMARD/MTX for CFB in HAQ-DI, EULAR good response and EULAR moderate-to-good response at Week 24.
    - Similar (overlapping CrI) safety profile (including AE rate) to all comparators (cDMARD/MTX, TNFi, rituximab, abatacept, golimumab, and tocilizumab).
    - In a scenario analysis, TNFis were pooled as a class for ACR 20, 50 and 70 outcomes in cDMARD combination and monotherapy populations. Sarilumab 200 mg combination therapy was found statistically superior to cDMARD and comparable to all other combination therapies.
    - This extensive NMA included a considerable number of trials and a range of different efficacy and safety outcomes. Sarilumab in combination with cDMARD/ MTX shows comparable efficacy and safety to other biologic combination therapies. For the primary trial outcome, ACR 20, 50, 70, sarilumab monotherapy shows significantly better efficacy versus adalimumab monotherapy, consistent with head-to-head trial data. In comparison with the TNFi class and with the TNFis separately sarilumab shows similar and superior efficacy.

4.10.1 NMA search strategy

The objective of the NMA was to evaluate the comparative efficacy and safety of sarilumab (200 mg Q2W and 150 mg Q2W) versus licensed treatments at recommended doses, in the treatment of RA, for the following groups of patients:

1) Adult patients (≥18 years) with moderately to severely active RA who have had inadequate response to one or more cDMARDs

2) Adult patients (≥18 years) with moderately to severely active RA who have had inadequate response to one or more bDMARDs (TNFi or other mode of action)

3) Adult patients (≥18 years) intolerant to methotrexate (MTX) or for whom continued MTX is inappropriate

The search strategy is described in Section 4.1.1.

All treatments named in the decision problem were included in the NMA (sarilumab, tocilizumab, adalimumab, etanercept, certolizumab pegol, golimumab, infliximab, rituximab, and abatacept). In addition, tofacitinib (Xeljanz®), baricitinib (Olumiant®), and sirukumab were included in the analysis as comparators of interest. However, these were not included in the cost-effectiveness assessment in Section 5 because they are not yet licensed in the UK, nor is any information available on the cost of the interventions.

4.10.2 NMA study selection

For the scope of the NMA, the evidence collected by the SLR was filtered as comparators of interest include only licensed drugs at recommended doses by EMA with the following exceptions:

- Inclusion of sarilumab 150 mg every 2 weeks and 200 mg every 2 weeks, with or without MTX/cDMARD;

- Inclusion of Phase III molecules sirukumab 50 mg every 4 weeks and 100 mg every 2 weeks and baricitinib 2 mg once daily (OD) and 4 mg OD both with or without MTX/cDMARD, because it is close to receiving licence;

- Inclusion of rituximab for the cDMARD-IR population as it is of interest for the health economic model (rituximab is only licensed for the TNF-IR population);

- Exclusion of anakinra because despite being licensed it is not commonly used in daily practice. In addition, the Singh et al 2009 NMA concluded that anakinra was less effective than all of the other biologics[113].

- Each trial comparing one intervention of interest to at least one other intervention of interest or placebo or MTX or ≥1 cDMARD(s) were included in the NMA evidence base.

Two base networks of evidence were created assuming differences in clinical outcomes for patients who are cDMARD-IR (and receiving both combination and monotherapy in the reported studies) and those who are bDMARD- IR. The bDMARD- IR network included studies investigating bDMARDs in combination with MTX, no studies were identified investigating bDMARDs as monotherapy in this patient population.

The inclusion/exclusion details for the populations of interest are given below in summary. Details on the excluded studies for the NMA can be found in Appendix 8.1.

4.10.3 cDMARD-IR studies: Inclusion/exclusion

After excluding studies not in line with the protocol, we retrieved 89 trials to include in the NMA feasibility assessment for the cDMARD-IR population. Following feasibility assessment, 34 studies were excluded from cDMARD-IR network:

- Ten studies (ASSET[149], Chen 2009[150], Lan 2004[151], Weinblatt 1999[152], Taylor 2004[153], Maini 1998[154], Tam 2012[155], Tanaka 2011[156], Smolen, 2014 (part A)[157] and Smolen, 2014 (part B)[157] were excluded from the analyses as these studies were small studies with less than 30 patients per arm[149-157]. Nuesch et al. 2010[158] suggested that small studies may distort meta-analysis, however, the chosen threshold of 30 patients is arbitrary.

- Thirteen studies did not report the any outcome of interest (CHARISMA[159], Abe 2006[160], REALISTIC[161], MOBILITY-A[55], CAMEO[162,163], RED SEA[164], ADORE[165,166], ORAL solo[167], Tanaka 2015[168], Kim 2013[169], ASSET[149], APPEAL[170,171], Hobbs 2015[172]).

- Two studies (RACAT[173] and Machado 2014[174]) reported data on the outcomes of interest but could not be linked in the analyses networks.

- Three studies assessed monotherapy vs. combination treatment SURPRISE[175-177], ACT-RAY[131] and JESMR[178,179]), hence were not part of either of the population network diagrams.

- One study was excluded on study design: Open-label adalimumab arm and study not powered for comparison (AUGUST II[180]).

- Three studies assessed mixed monotherapy/combination treatments (HIKARI[181], SIRROUND-D[182] and SAMURI[183]).

- One sarilumab study was excluded due to different dose-response profile. The KAKEHASI trial was conducted in Japanese population and was included in the SLR as a relevant sarilumab Phase III trial. However, in this study, [redacted] [147]. The main licensed dose in Japan is likely to be the 150 mg dose. This dose-response profile is different to that observed in the other trial populations included in the FDA and EMA licence submissions, and including this study would have given potentially misleading results in the NMA for the majority of countries that will consider the NMA.

- One study was excluded on time point ≤12 weeks (Tanaka 2015[184]).

Therefore, the base cDMARD-IR network included a total of 55 studies for the cDMARD-IR network. Out of the 55 global cDMARD studies, monotherapy cDMARD network included ten studies and combination cDMARD network included 46 studies (1 study common in monotherapy and combination network (Etanercept 309 study[185,186]) as shown in Table 4.27 and Table 4.28.

4.10.4 TNF-IR studies: Inclusion/exclusion

For the TNF-IR network 12 studies were identified, two of which were excluded based on patient populations in the trials (Schiff 2014[187] and Genovese 2014[188]). In addition to these studies, the researchers were aware of two trials identified as part of the cDMARD-IR network: (BREVACTA[189] and SIRROUND-D[182]) that reported subgroup data for TNF-IR population. These were excluded from TNF-IR analysis because the studies were not powered for TNF-IR population comparisons and there were limited details were provided on patient characteristics to make comparison possible.

Two studies were included in the TNF-IR network that did not strictly meet the inclusion/exclusion criteria, however were deemed too important not to include: in the GO-

AFTER study, about 30% of the patients were on monotherapy with golimumab, while golimumab is only licensed in combination with a cDMARD[190]. Another limitation of this study is that only 58% of patients had discontinued previous TNFi for lack of effectiveness. The other reasons of discontinuation were unrelated to effectiveness and included accessibility issues as well as intolerance. Therefore, not all of the included patients are truly inadequate responders to TNF-inhibitors. GO-AFTER was nevertheless included because it is the only study that specifically evaluates the use of a TNFi after a previous TNFi.

Also in the TNF-IR network, in SIRROUND-T study, around 25% patients were treated with sirukumab monotherapy or placebo[191]. Although there were a proportion of patients receiving sirukumab as monotherapy, this study was included in the TNF-IR network, similarly to the GO-AFTER study. All other studies in the TNF-IR network are pure combination therapy studies.

Therefore, in total, ten studies identified for inclusion in the TNF-IR network.

A full description of the study selection criteria is provided in Section 4.1.

4.10.5 Summary of resultant networks

The complete treatment networks of the cDMARD-IR combination therapy, CDMARD-IR monotherapy and TNF-IR are shown in the network diagrams (Figure 4.24, Figure 4.25 and Figure 4.26). Each node represents a treatment regimen included in the network and lines represent direct comparisons between nodes. The studies contributing to each comparison are also detailed along each line in the network diagrams. Network diagrams for the other outcomes of interest are presented Appendix 8.2.

Table 4.27 Summary of the studies contributing to the evidence base network for cDMARD-IR: Updated review

Intervention arm(s)	Control arm	Duration of study (weeks)	Number of patients	References
Monotherapy studies vs. (placebo or cDMARD)				
TNF studies				
Adalimumab SC 20 mg QW Adalimumab SC 20 mg Q2W Adalimumab SC 40 mg QW Adalimumab SC 40 mg Q2W	Placebo	26	544	Adalimumab efficacy and safety study (van de Putte 2004[192])
Adalimumab SC 20 mg Q2W Adalimumab SC 40 mg Q2W Adalimumab SC 80 mg Q2W	Placebo	24	352	CHANGE (Miyasaka 2008[193])
Certolizumab SC 400 mg Q4W	Placebo	24	220	FAST4WARD (Fleischmann 2009[194])
Etanercept SC 25 mg BIW Etanercept SC 25 mg BIW + sulfasalazine	sulfasalazine	104	254	Etanercept study 309 (Combe 2006, Combe 2009[185,186])
Etanercept SC 10 mg BIW Etanercept SC 25 mg BIW	Placebo	26	234	Etanercept monotherapy study (Moreland 1999[195])
IL-6 studies				
Tocilizumab SC 8 mg/kg Q4W	MTX	24	125	SARTORI (Nishimoto 2009[196])
Tocilizumab IV 8 mg/kg Q4W	Adalimumab SC 40 mg Q2W	32	325	ADACTA (GABAY 2013[33])
Sirukumab SC 50 mg Q4W Sirukumab SC 100 mg Q2W	Adalimumab SC 40 mg Q2W	24	559	SIRROUND-H (Taylor 2016[197])
Sarilumab SC 200 mg Q2W	Adalimumab SC 40 mg Q2W	24	369	MONARCH (Burmester 2016[1])
JAK inhibitors studies				
Tofacitinib oral 1 mg BID Tofacitinib oral 3 mg BID Tofacitinib oral 5 mg BID Tofacitinib oral 10 mg BID Tofacitinib oral 15 mg BID Adalimumab SC 40 mg QW for 12 weeks followed by oral tofacitinib 5 mg BID for 12 weeks	Placebo	24	384	Efficacy and safety of tofacitinib vs. adalimumab (Fleischmann 2012[198])

Intervention arm(s)	Control arm	Duration of study (weeks)	Number of patients	References
Combination studies vs. (placebo or cDMARD)				
TNF studies				
Adalimumab SC 20 mg QW + MTX Adalimumab SC 40 mg Q2W + MTX	MTX	52 (plus 10 year OLE)	619	DE019 (Keystone 2013[199], Keystone 2011[200], Keystone 2004[201])
Adalimumab SC 40 mg Q2W + MTX	MTX	24	128	Adalimumab efficacy and safety study (Kim 2007[202])
Adalimumab SC 20 mg Q2W + MTX Adalimumab SC 40 mg Q2W + MTX Adalimumab SC 80 mg Q2W + MTX	MTX	24	271	ARMADA (Weinblatt 2003[203])
Adalimumab SC 40 mg Q2W + standard treatment	Placebo + standard treatment	24	636	STAR (Furst 2003[204])
Certolizumab SC 200 mg Q2W + MTX Certolizumab SC 400 mg Q2W + MTX	MTX	52	982	RAPID (Keystone 2008[205], Strand 2009[206])
Certolizumab SC 100 mg Q2W + MTX Certolizumab SC 200 mg Q2W + MTX Certolizumab SC 400 mg Q2W + MTX	MTX	24	316	J-RAPID (Yamamoto 2014[207])
Certolizumab SC 200 mg Q2W + MTX Certolizumab SC 400 mg Q2W + MTX	MTX	24	619	RAPID-2 (Smolen 2009[208])
Certolizumab SC 400 mg Q2W + MTX	MTX	24	247	Certolizumab efficacy and safety study (Choy 2012[209])
Certolizumab SC 400 mg Q2W + cDMARD	cDMARD	24	194	CERTAIN (Smolen 2015[210])
Etanercept SC 25 mg BIW Etanercept SC 25 mg BIW + sulfasalazine	sulfasalazine	104	254	Etanercept 309 study (Combe 2006[186], Combe 2009[185])
Etanercept SC 25 mg BIW + MTX	MTX	104	222	ENCOURAGE (Yamanka 2016[211])
Golimumab SC 50 mg Q4W + MTX Golimumab SC 100 mg Q4W + MTX	MTX	24	269	GO-FORTH (Tanaka 2012[212])
Golimumab SC 50 mg Q2W + MTX Golimumab SC 50 mg Q4W + MTX Golimumab SC 100 mg Q2W + MTX	MTX	52	172	Golimumab efficacy and safety study (Kay 2008[213])

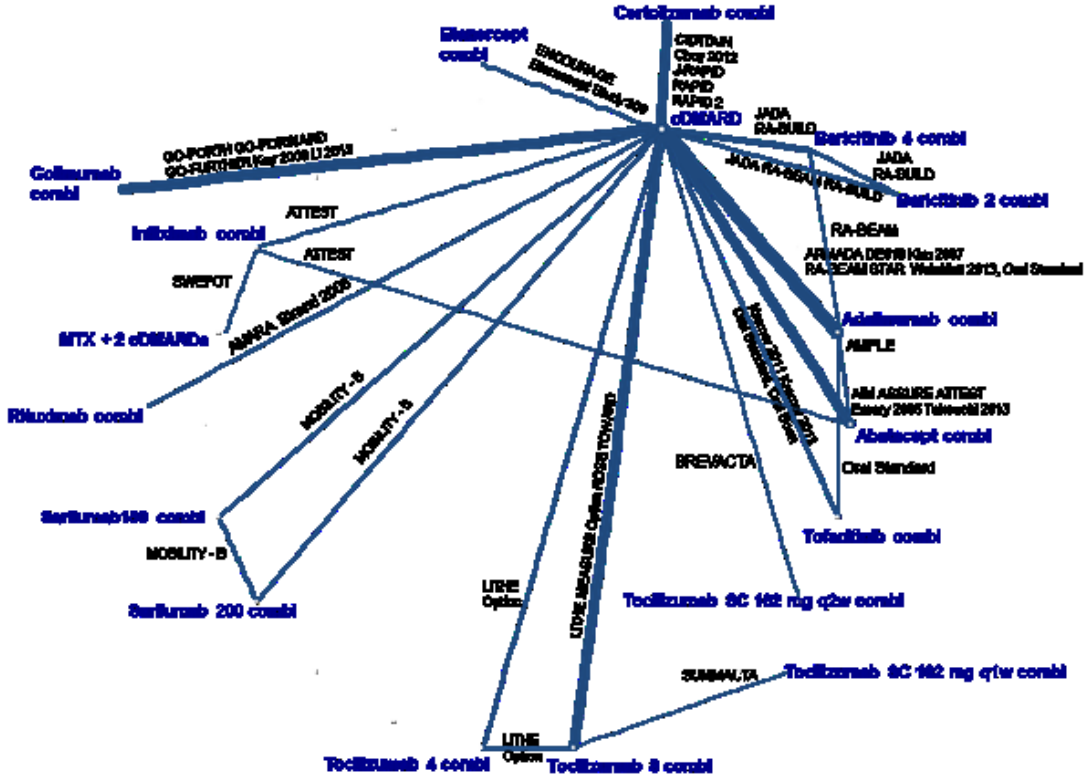
Intervention arm(s)	Control arm	Duration of study (weeks)	Number of patients	References
Golimumab SC 100 mg Q4W + MTX				
Golimumab SC 50 mg Q4W + MTX	MTX	52	264	Golimumab efficacy and safety study (Li 2016[214])
Golimumab SC 2 mg/kg Q8W+ MTX	MTX	112	592	GO-FURTHER (Weinblatt 2014[136], Bingham 2014[134], Weinblatt 2013[135])
Golimumab SC 100 mg Q4W Golimumab SC 50 mg Q4W + MTX Golimumab SC 100 mg Q4W + MTX	MTX	312	444	GO-FORWARD (Keystone 2016[215], Keystone 2013[216], Genovese 2012[217], Keystone 2010[218], Keystone 2009[219])
Infliximab IV 3 mg/kg Q8W + MTX Infliximab IV 3 mg/kg Q4W + MTX Infliximab IV 10 mg/kg Q8W + MTX Infliximab IV 10 mg/kg Q4W + MTX	MTX	54 (plus 1 year OLE)	428	ATTRACT (Maini 1999[220], Lipsky 2000[221], Maini 2004[222])
Infliximab IV 3 mg/kg Q8W + MTX Infliximab IV 10 mg/kg Q8W + MTX	MTX	54	1084	START (Westerhovens 2006[223])
Infliximab IV 3 mg/kg Q8W + MTX Abatacept IV 8–10 mg/kg + MTX	MTX	52	431	ATTEST (Schiff 2008[224])
Infliximab IV 3 mg/kg Q8W + MTX	sulfasalazine 1000 mg (oral) BID + HCQ 400 mg (oral) BID + MTX	104	245	SWEFOT (Karlsson 2013[225], Rezaei 2013[226], van Vollenhoven 2012[227], van Vollenhoven 2009[110], Eriksson 2013[228])
Non-TNF studies				
Abatacept IV 8–10 mg/kg Q4W + MTX	MTX	52	652	AIM (Russell 2007[229], Kremer 2006[230])
Abatacept IV 2 mg/kg Q4W + MTX Abatacept IV 10 mg/kg Q4W + MTX	MTX	52	339	Abatacept efficacy and safety study (Emery 2006[231], Kremer 2005[232], Kremer 2003[233])
Abatacept IV 2 mg/kg Q4W + MTX Abatacept IV 10 mg/kg Q4W + MTX	MTX	32	194	Abatacept efficacy and safety study (Takeuchi 2013[234])
Infliximab IV 3 mg/kg Q8W + MTX Abatacept IV 8–10 mg/kg + MTX	MTX	52	431	ATTEST (Schiff 2008[224])
Abatacept IV 8–10 mg/kg Q4W + cDMARD	cDMARD	52	1456	ASSURE (Weinblatt 2006[235])
Rituximab IV 2 x 500 mg at days 1 and 15 + MTX	MTX	48	511	SERENE (Emery 2010[236])

Intervention arm(s)	Control arm	Duration of study (weeks)	Number of patients	References
Rituximab IV 2 x 1,000 mg at days 1 and 15 + MTX				
Rituximab IV 2 x 500 mg at days 1 and 15 + MTX Rituximab IV 2 x 1000 mg at days 1 and 15 + MTX	MTX	24	367	DANCER (Mease 2008[237])
Rituximab IV 1,000 mg days 1 and 15 Rituximab IV 1,000 mg days 1 and 15 + MTX Rituximab IV 1,000 mg days 1 and 15 + cyclophosphamide 750 mg days 3 and 17	MTX	104	161	Rituximab efficacy and safety study (Strand 2006[238], Edwards 2004[239])
Rituximab IV 500 mg + MTX Rituximab IV 1,000 mg + MTX	MTX	52	185	RA-SCORE (Peterfy 2016[240])
Rituximab IV 1,000 mg + leflunomide	Leflunomide	52	140	AMARA (Behrens 2016[241])
IL-6 studies				
Sarilumab SC 150 mg Q2W + MTX Sarilumab 200 mg Q2W + MTX	MTX	52	1,197	MOBILITY B (Genovese 2015[56])
Tocilizumab IV 4 mg/kg Q4W + MTX Tocilizumab IV 8 mg/kg Q4W + MTX	MTX	24	623	OPTION (Smolen 2008[242])
Tocilizumab IV 8 mg/kg Q4W + MTX	MTX	24	132	MEASURE (McInnes 2015[243], Mirjafari 2013[244])
Tocilizumab IV 4 mg/kg Q4W + MTX Tocilizumab IV 8 mg/kg Q4W + MTX	MTX	104	1,196	LITHE (Fleischmann 2013[245], Kremer 2011[246])
Tocilizumab SC 162 mg Q2W + cDMARD	cDMARD	24	656	BREVACTA (Kivitz 2014[247], Kivitz 2013[189])
Tocilizumab IV 8 mg/kg Q4W + cDMARD	cDMARD	24	1,220	TOWARD (Genovese 2008[248])
Tocilizumab IV 8 mg/kg Q2W + cDMARD	cDMARD	24	619	ROSE (Yazici 2012[249])
JAK inhibitors studies				
Tofacitinib oral 1 mg BID + MTX Tofacitinib oral 3 mg BID + MTX Tofacitinib oral 5 mg BID + MTX	MTX	24	509	Tofacitinib efficacy and safety study (Kremer 2012[250])

Intervention arm(s)	Control arm	Duration of study (weeks)	Number of patients	References
Tofacitinib oral 10 mg BID + MTX Tofacitinib oral 15 mg BID + MTX Tofacitinib oral 20 mg BID + MTX				
Tofacitinib oral 5 mg BID + MTX Tofacitinib oral 10 mg BID + MTX	MTX	104	797	Oral Scan (van der Heijde 2013[251])
Tofacitinib oral 5 mg BID + MTX Tofacitinib oral 10 mg BID + MTX Tofacitinib oral 40 mg BID + MTX Adalimumab SC 40 mg Q2W + MTX	MTX	52	717	Oral Standard (Van Vollenhoven 2012[252])
Tofacitinib oral 5 mg BID + cDMARD Tofacitinib oral 10 mg BID + cDMARD	cDMARD	53	636	Tofacitinib efficacy and safety study (Kremer 2013[253])
Baricitinib oral 2 mg OD + cDMARD Baricitinib oral 10 mg OD + cDMARD	cDMARD	24	684	RA-BUILD (Dougados 2017[254])
Biologic vs. same biologic				
Comparisons of different routes of administration				
Tocilizumab SC 162 mg QW + cDMARD	Tocilizumab IV 4/8 mg Q4W + cDMARD	104	1262	SUMMACTA (Burmester 2014[255,256], Burmester 2013[257])
Head-to-head comparisons of bDMARDs				
TNF vs. non-TNF				
Adalimumab SC 40 mg Q2W + MTX	Abatacept SC 125 mg QW + MTX	104	646	AMPLE (Schiff 2014[258], Weinblatt 2013[259])
Adalimumab SC 40 mg Q2W + MTX	Baricitinib oral 4 mg OD + MTX	52	1307	RA-BEAM (Taylor 2017[260])
IL-6 vs. TNF				
Tocilizumab IV 8 mg/kg Q4W	Adalimumab SC 40 mg Q2W	32	326	ADACTA (Gabay 2013[33])
Sarilumab SC 200 mg Q2W	Adalimumab SC 40 mg Q2W	24	369	MONARCH (Burmester 2016[1])

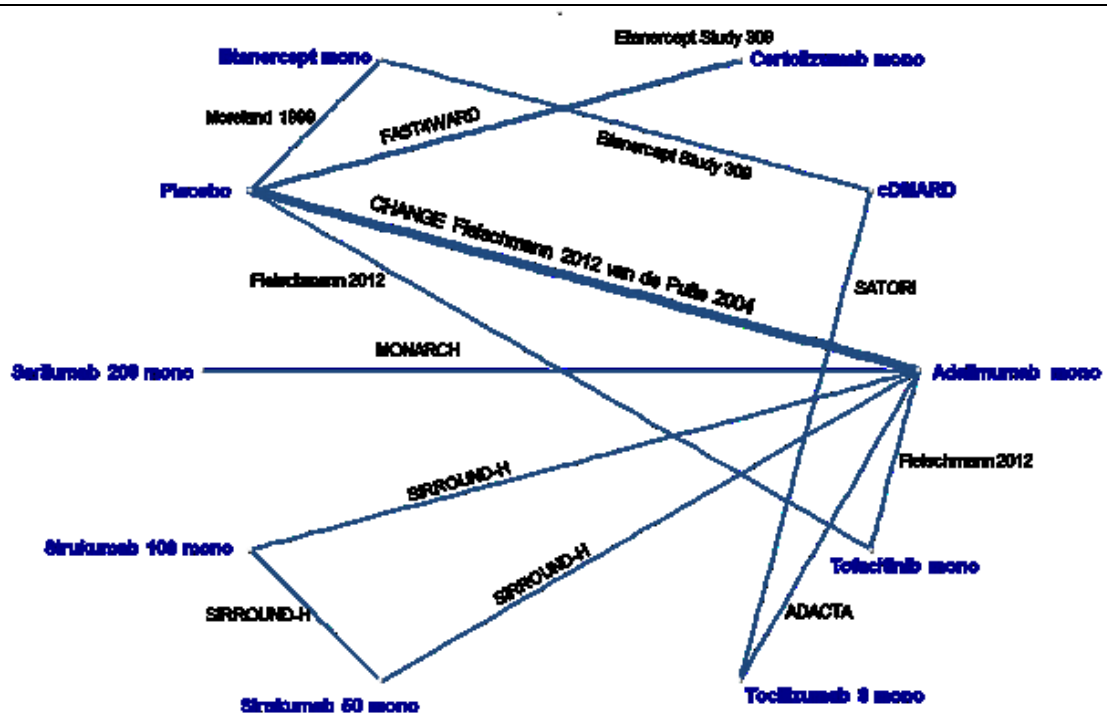
BID=Twice a day; BIW=twice weekly; cDMARD= disease-modifying anti-rheumatic drugs; HCQ= hydroxychloroquine; IL-6=interleukin-6; IV=intravenous; MTX=methotrexate; OD=once daily; OLE=open labelled extension; QW=once a week; Q2W=every 2 weeks; Q4W=every 4 weeks; Q8W=once every 8 weeks; SC=subcutaneous;

Figure 4.24 cDMARD-IR base network diagram



cDMARDs= conventional disease modifying anti-rheumatic drugs; IR=irresponsive; MTX=methotrexate; q1w=weekly; q2w=once every two weeks

Figure 4.25 cDMARD irresponsive monotherapy base network diagram



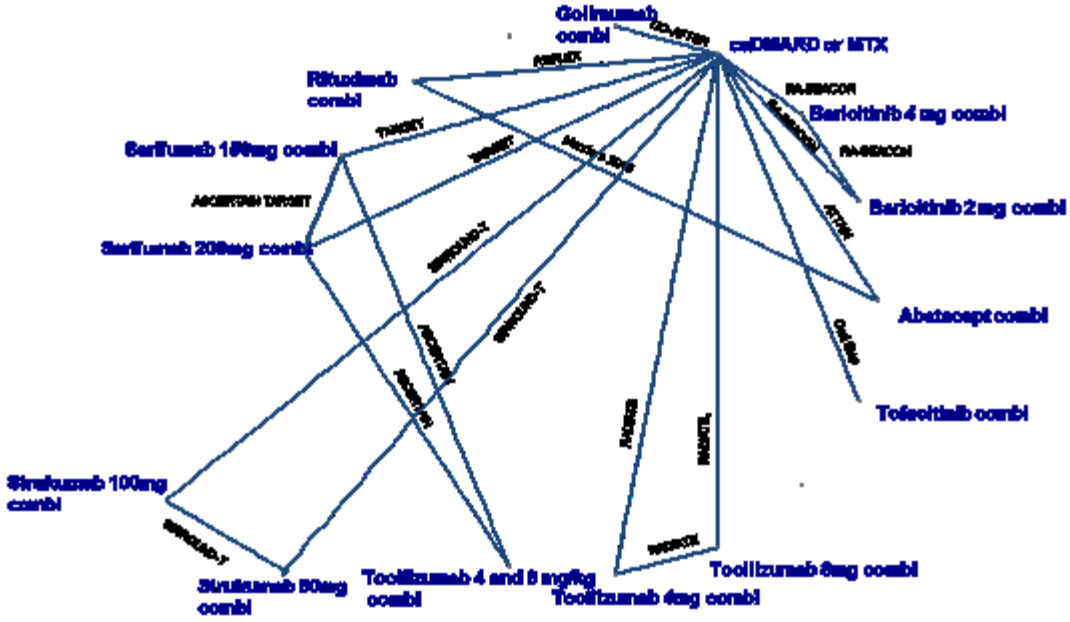
cDMARDs= conventional disease modifying anti-rheumatic drugs; IR=irresponsive;

Table 4.28 Summary of the studies contributing to the evidence base network for TNF-IR: Updated review

Intervention		Comparator(s)	Duration of study (weeks)	Number of patients	References
Monotherapy studies vs. placebo					
Golimumab SC 50 mg Q4W +/- cDMARD Golimumab SC 100 mg Q4W +/- cDMARD		cDMARDs	24	461	GO-AFTER (Smolen 2009[190])
Sirukumab SC 500 mg Q4W +/- cDMARD Sirukumab SC 1000 mg Q2W +/- cDMARD		cDMARD	NA	878	SIRROUND-T (Tanaka 2016[191])
Combination studies vs. cDMARD					
Non-TNF studies					
Abatacept IV 10 mg/kg Q4W + cDMARD		cDMARD	26	258	ATTAIN (Westhovens 2006[261], Genovese 2005[262])
Rituximab IV 1,000 mg at days 1 and 15 + MTX		MTX	104	520	REFLEX (Keystone 2009[263], Keystone 2008[264], Cohen, 2006[265])
Tofacitinib oral 5 mg BID + MTX Tofacitinib oral 10 mg BID + MTX		MTX	26	399	Oral Step (Strand 2015[266], Burmester 2013[267])
IL6 studies					
Tocilizumab IV 4 mg/kg Q4W + MTX Tocilizumab IV 8 mg/kg Q4W + MTX		MTX	24	489	RADIATE (Strand 2012[268], Emery 2008[269])
Sarilumab SC 150 mg Q2W + cDMARD Sarilumab SC 200 mg Q2W + cDMARD		cDMARD	24	546	TARGET (Fleischmann 2017[57])
JAK inhibitors studies					
Baricitinib oral 2 mg OD + cDMARD Baricitinib oral 4 mg OD + cDMARD		cDMARD	24	527	RA-BEACON (Genovese 2016[270])
Head-to-head comparisons of bDMARDs					
Sarilumab SC 150 mg Q2W + cDMARD Sarilumab SC 200 mg Q2W + cDMARD		Tocilizumab IV 4-8 mg/kg Q4W + cDMARD	24	202	ASCERTAIN (Sanofi Genzyme[58])
Abatacept (dose/frequency not stated)	Rituximab (dose/frequency not stated)	TNFi (dose/frequency not stated)	52	143	Open-label study (Manders 2015[271])

bDMARD= biological disease-modifying anti-rheumatic drugs; cDMARD=conventional disease-modifying anti-rheumatic drugs; IL-6=interleukin-6; IR=irresponsive; IV=intravenous; MTX=methotrexate; QW=once a week; Q2W=every 2 weeks; Q4W=every 4 weeks; Q8W=every 8 weeks; SC=subcutaneous; TNFi=tumour necrosis factor inhibitor.

Figure 4.26 TNF-IR network



bDMARD= biological disease-modifying anti-rheumatic drugs; cDMARDs= conventional disease modifying anti-rheumatic drugs; MTX=methotrexate

The available treatments were grouped and included in the networks, where the following important assumptions were made:

- MTX and cDMARD used as background therapies were considered similar and grouped.
- Arms with one cDMARD plus MTX were separated from arms including two cDMARDs plus MTX.
- Different licensed dosages of the same treatment were pooled in many cases (Appendix 8.3), on the basis of studies showing equivalence between different doses or based on clinical advice.
- Different routes of administration (e.g. IV vs. SC) for the same treatment were pooled together in many cases (Appendix 8.3).

The decisions listed above were explored by using forest plots (Appendix 8.4) and confirmed by the Sanofi Genzyme clinical team.

4.10.5.1 Methods and outcomes of included studies

The patient population of all included studies matched the population specified in the decision problem.

In the cDMARD-IR Network, patient's ages were quite similar between all studies (and study arms) in cDMARD combination population varying from 46.7 years (Li 2013[272]) to 57.3 years (DE019[199-201]). In all trials, except ATTEST (Schiff 2008[224]), the majority of the patients were female. In the trials reporting ethnicity, the majority of the patients were Caucasian and in six trials, the entire population was Asian (J-RAPID[207], The Etanercept Study 309[185,186], GO-FORTH[212], Kim 2013[169], Li 2013[272], and Takeuchi 2013[176]). At baseline, the RF positive % was above 60% in all studies reporting this value, with the exception of the ASSET trial (55.6% for abatacept 8mg/kg IV Q4W + MTX)[149]. The mean weight varied from 52.9 (J-RAPID[207] to 82 kilogram (kg) (MEASURE[243,244]). Disease duration ranged widely, from 0.5 (SWEFOT[110,225-228]) to 13.1 (ARMADA[203]) years.

Patient's ages were quite similar between all studies (and study arms) in cDMARD monotherapy population varying from 50.6 years (The Etanercept Study 309[185,186]) to 56.9 years (CHANGE[193]). In all trials, the majority of the patients were female. In the trials reporting ethnicity, the majority of the patients were Caucasian and in one trial, the entire population was Asian (The Etanercept Study 309[185,186]). At baseline, the RF positive % was above 60% in all studies reporting this value. The mean weight varied from 52.4 (CHANGE[193]) to 72.8 kilogram (kg) (The Etanercept Study 309[185,186]). Disease duration ranged widely, from 5.6 (The Etanercept Study 309[185,186]) to 13.0 (Moreland 1999[195]) years.

In the TNF-IR network, the patient population of the studies included in the NMA was similar in terms of age, ranging from 50.4 years (ASCERTAIN[58]) to 59.4 years (Genovese 2014[188]). In all trials, the majority of the population was female and Caucasian (when reported). The rheumatoid factor positive percentage varied from 56% (Manders 2014[273]) to 83% (ASCERTAIN[58]) and the mean weight ranged from 72.6 (ASCERTAIN[58]) to 79.4 (TARGET[57]). Disease duration ranged from 5.6 years (Manders 2014[273]) to 14.0 years (Schiff 2014[187]).

Baseline disease severity, as measured by the DAS28, differed between the studies. For the cDMARD or MTX arms, the mean baseline DAS28-CRP ranged from 5.4 (Oral Step[266,267]) and Schiff 2014[187]) to 6.9 (REFLEX[263-265]) the DAS28-ESR ranged from 4.7 (Manders 2015[271]) to 6.5 (Oral Step[266,267]); and the DAS28-unspecified ranged from 6.5 (ATTAIN[261,262]) to 6.8 (RADIATE[268,269]).

Details of the design, patient characteristics, and results of the studies can be found in Appendix 8.5, Appendix 8.6, and Appendix 8.10.

Several key outcomes of interest were extracted for the NMA on the basis of relevance to the decision problem and availability of data from the study reports, these are summarised in Table 4.29. Of particular relevance were ACR20, 50, and 70 scores, which were used to inform the treatment response of each comparator in the cost-effectiveness assessment.

Table 4.29 Outcomes used in the NMA per population and time point

Outcome	cDMARD-IR		TNF-IR
	24 weeks	52 weeks	24 weeks
ACR20, 50 and 70	✓		✓
HAQ-DI CFB	✓		✓
EULAR moderate-to-good, good	✓		✓
DAS28 remission	✓		✓
mTSS CFB	✓	✓	
SIs	✓	✓	✓
SAE	✓	✓	✓

ACR20/50/70=American College of Rheumatology 20%/50%/70% improvement; CFB=change from baseline; DAS28=28-joint disease activity score; HAQ-DI=Health Assessment Questionnaire Disability Index; mTSS=modified Total Sharp Score; NMA=network meta analysis; SAE=serious adverse event; SI=serious infections

4.10.5.2 Risk of bias assessment

Quality assessments of each trial included in the NMA were performed according to NICE guidelines. Results and a complete quality assessment can be found in Appendix 8.7.

4.10.5.2.1 cDMARD –IR population risk of bias assessment

The included studies were of good quality as assessed by the NICE questionnaire. Some RCTs mentioned rescue therapy allowance, while others did not report this information. The statistical method used to handle missing values was not always clearly explicit. This is however difficult to perform scenario analyses to explore if these study design aspects are treatment effects modifiers. The trials were sometimes located worldwide or restricted to a specific part of the world (North America, Asia or Europe). Some imbalances were also observed in the patients' characteristics, i.e. mean disease duration, proportion of positive RF status and mean weight/BMI. Only weight/BMI was identified as a potential treatment effect modifier by linear regression analyses and the Sanofi Genzyme clinical team. However this covariate was not consistently reported, thus could not be meaningfully used in a meta-regression scenario. It is however, explored in a sensitivity analysis in the economic section of this submission (Section 5.28).

A high variation of the proportion of response in the common comparator (i.e. cDMARD) was observed. The treatment effect expressed as log odds ratios has a negative relationship with the baseline risk, as discussed in the NICE DSU document for the certolizumab example in RA[274]. Methods explored and used to adjust for the variation in the common comparator responses are documented in Section 4.10.5.3.

4.10.5.2.2 Biological disease-modifying anti-rheumatic drug irresponsive network risk of bias assessment

The included studies were in general of good quality as assessed by the NICE questionnaire.

As discussed in the cDMARD-IR risk of bias assessment, some imbalances were also observed in the patients' characteristics, but no covariate was identified as a potential treatment effect modifier by the clinical expert. No linear regression was performed as the number of studies was too limited. Two studies (Schiff 2014[187]) and Genovese 2014[188]) were excluded from the analyses as these studies were small studies with less than 30 patients per arm. Small studies have been shown to distort meta-analysis in Nuesch et al. 2010[158]). The chosen threshold of 30 patients is arbitrary.

4.10.5.3 Methods of analysis

The selected outcomes, i.e. relative efficacy and safety of the treatments of interest were evaluated using a Bayesian NMA[275-277]. In this analysis, a linear model with normal likelihood distribution was used for continuous outcomes, and a binomial likelihood with a log link was used for the dichotomous outcomes[274,278]. A full description of the NMA methodology and rationale can be found in Appendix 8.8.

For binary efficacy outcomes, NMA with baseline risk regression was used for the base-case where there were sufficient studies in the network. This applied to all binary efficacy outcomes in the cDMARD-IR network, with the exception of EULAR response. Where there were too few studies to reliably perform this analysis, the risk difference NMA was used as the base-case. This applied to all binary efficacy outcomes in the TNF-IR network, and to EULAR response in cDMARD-IR. Standard linear CFB NMA was the base-case for continuous efficacy outcomes. A conventional NMA was used for safety outcomes. Where sufficient data were available, the random effects model was used as the base-case model to allow for heterogeneity, and when the numbers of studies were smaller (EULAR outcomes of the cDMARD-IR population and all outcomes of the TNFi-IR population), it was necessary to use the fixed effects model.

TNFα inhibitors are often viewed as a class; therefore, analyses were performed where all TNFα inhibitors are assumed to have similar efficacy and pooled together in addition to as separate agents in the cDMARD-IR network. For mTSS at 52 weeks, the ATTRACT study[220-222] was also included in a scenario analysis in this network.

The WINBUGS code and parameter inputs are provided in a separate attachment.

Pairwise results for sarilumab 200 mg versus all comparators for all outcomes of interest are presented below. Results of each pairwise comparison between each comparator for each outcome of interest are presented in Appendix 8.10, with the absolute median values of each comparator also presented.

4.10.5.4 Results of the NMA

4.10.5.4.1 cDMARD-IR combination population

ACR response at Week 24

- In the cDMARD-IR network, sarilumab 200 mg combination therapy shows superiority to cDMARD for ACR 20/50/70 endpoints
- Sarilumab 200 mg combination therapy shows similar efficacy to abatacept combination, baricitinib 2 mg OD combination and 4 mg OD combination, tofacitinib combination, adalimumab combination, certolizumab combination, etanercept combination, golimumab combination, infliximab combination, tocilizumab 4 mg/kg IV combination, tocilizumab 8 mg/kg IV combination, tocilizumab SC 162 mg QW combination, tocilizumab SC 162 mg Q2W combination, rituximab combination, and sarilumab 150 mg combination.

HAQ-DI at Week 24

- Sarilumab 200 mg combination therapy shows superiority to cDMARD, for the HAQ-DI CFB endpoint
- Sarilumab 200 mg combination therapy shows similar efficacy to baricitinib 2 mg OD combination, baricitinib 4 mg OD combination, etanercept combination, abatacept combination, adalimumab combination, certolizumab combination, golimumab combination, infliximab combination, tocilizumab 4 mg/kg IV combination, tocilizumab 8 mg/kg IV combination, tofacitinib combination, rituximab combination and sarilumab 150 mg combination.

DAS28 remission (DAS28 < 2.6) at Week 24

- In the cDMARD-IR network, sarilumab 200 mg combination therapy shows superiority to cDMARD for DAS28 remission endpoint

- Sarilumab shows similar efficacy to abatacept combination, baricitinib 2 mg OD combination, baricitinib 4 mg OD combination, adalimumab combination, certolizumab combination, etanercept combination, golimumab combination, infliximab combination, tocilizumab 4 mg/kg IV combination, tocilizumab 8 mg/kg IV combination, tocilizumab SC 162 mg QW, tocilizumab SC 162 mg Q2W, tofacitinib combination, rituximab combination and sarilumab 150 mg combination.

EULAR good response at Week 24

- Sarilumab 200 mg combination shows superiority to cDMARD, two cDMARDs plus MTX, abatacept combination, infliximab combination, tocilizumab 4 mg/kg IV combination, rituximab combination and sarilumab 150 mg combination for the EULAR good endpoint.

- Sarilumab 200 mg combination shows similar efficacy to golimumab combination and tocilizumab 8 mg/kg IV combination on EULAR good.

EULAR moderate-to-good response at Week 24

- Sarilumab 200 mg combination therapy shows superiority to cDMARD for the EULAR moderate-to-good endpoint.

- Sarilumab 200 mg combination therapy shows similar efficacy to golimumab combination, infliximab combination, tocilizumab 4 mg/kg IV combination, rituximab combination, tocilizumab 8 mg /kg IV combination, and sarilumab 150 combination on EULAR moderate-to-good.

- Sarilumab (both doses) shows inferiority to certolizumab. However, certolizumab data are only reported in one study (J-RAPID[207]) and this study only included Asian patients.

- Sarilumab (both doses) shows similar efficacy to all other comparators: golimumab, infliximab and rituximab for EULAR moderate-to-good.

Radiographic endpoint mTSS at Week 24

- Sarilumab 200 mg combination therapy shows superiority to cDMARD, baricitinib 2 mg OD combination, tofacitinib combination, and certolizumab combination therapy.
- Sarilumab 200 mg combination therapy shows similar efficacy to infliximab combination, baricitinib 4 OD mg combination, adalimumab combination, golimumab combination, tocilizumab 162 q2w combination and sarilumab 150 mg combination therapy.

Radiographic endpoint mTSS at Week 52

- Sarilumab 200 mg combination therapy shows superiority to cDMARD and sarilumab 150 mg combination.
- Sarilumab 200 mg combination therapy shows similar efficacy to abatacept combination, adalimumab combination, certolizumab combination and etanercept combination.

Serious infection at Week 52

- Sarilumab (both doses) shows similar safety to all comparators (cDMARD, abatacept combination, adalimumab combination, certolizumab combination, rituximab combination, infliximab combination, and sarilumab 150 mg combination).

Serious adverse event at Week 52

- Sarilumab 200 mg combination therapy shows similar safety to all comparators (cDMARD, abatacept combination, adalimumab combination, certolizumab combination, infliximab combination, rituximab combination, and sarilumab 150 mg combination)

4.10.5.4.2 cDMARD-IR monotherapy population

Only data for sarilumab 200 mg is available because the 150 mg dose was not evaluated in MONARCH[1].

ACR response rates at Week 24

- Sarilumab 200 mg was superior to adalimumab for all ACR endpoints in the head-to-head MONARCH trial[1] and in the NMA results.

- Sarilumab 200 mg monotherapy was also superior to placebo, cDMARD, pooled TNFs and sirukumab SC 50 mg Q4W monotherapy (only ACR20/50 data available for sirukumab).
- Sarilumab 200 mg shows similar efficacy to certolizumab monotherapy, etanercept monotherapy, sirukumab SC 100 mg Q2W, tocilizumab 8 mg/kg monotherapy (the only dose for which data were available in monotherapy) and tofacitinib monotherapy.

HAQ-DI at Week 24

- In the NMA, sarilumab 200 mg shows superiority efficacy to adalimumab for the HAQ-DI CFB endpoint, in line with the results from MONARCH[1]. Sarilumab 200 mg monotherapy was also superior to placebo.
- Sarilumab 200 mg shows similar efficacy to cDMARD, certolizumab monotherapy, etanercept monotherapy and tocilizumab 8 mg/kg IV monotherapy.

DAS28 remission (DAS28 < 2.6) at Week 24

- Sarilumab 200 mg monotherapy was superior to adalimumab for DAS28 remission in the head-to-head MONARCH trial[1] and also in the NMA results. Sarilumab 200 mg monotherapy was also superior to cDMARD and sirukumab SC 50 mg Q4W monotherapy.
- Sarilumab 200 mg shows similar efficacy to tocilizumab 8 mg/kg IV and sirukumab SC 100mg Q2W monotherapy for DAS28 remission.

EULAR good at Week 24

- Sarilumab 200 mg was superior to adalimumab on EULAR endpoints in the head-to-head MONARCH trial[1] and also in the NMA results.
- Sarilumab 200 mg monotherapy was statistically superior to placebo and cDMARD and comparable to tocilizumab 8 mg/kg IV monotherapy.

EULAR moderate-to-good at Week 24

- Sarilumab 200 mg shows superiority to placebo, to cDMARD and to adalimumab on the EULAR moderate-to-good endpoint, and similar efficacy to tocilizumab IV 8 mg/kg.

Serious infections and serious adverse events at Week 24

- Sarilumab shows similar safety to placebo and all active comparators (tofacitinib monotherapy, adalimumab monotherapy, certolizumab monotherapy, sirukumab SC 50 mg Q4W monotherapy and sirukumab SC 100mg Q2W).

4.10.5.4.3 TNF-IR population

ACR response at Week 24

- In the TNF-IR network, sarilumab 200 mg combination therapy shows superiority to cDMARD/MTX for ACR 20/50/70 using the NMA risk difference model.
- Sarilumab 200 mg combination therapy shows similar efficacy to abatacept combination, golimumab combination, rituximab combination, tocilizumab 4 mg/kg IV combination, tocilizumab 8 mg/kg IV combination, tocilizumab 4 and 8 mg/kg IV combination, sirukumab SC 100mg Q2W combination, baricitinib 4 mg OD combi and sarilumab 150 mg combination for the ACR 20/50/70 endpoints.
- Sarilumab shows superior efficacy to baricitinib 2mg OD combination and sirukumab SC 50 mg Q4W combination for ACR 50 outcome only (similar on ACR20 and ACR70).

HAQ-DI at Week 24

- Sarilumab 200 mg combination therapy shows superior efficacy to cDMARD and similar efficacy to abatacept combination, baricitinib 2 mg OD combination, baricitinib 4 mg OD combination, golimumab combination, sirukumab SC 50mg Q4W combination, sirukumab SC 100mg Q2W combination, rituximab combination, tocilizumab 4 mg/ kg combination, tocilizumab 8 mg /kg IV combination, tocilizumab 4 and 8 mg /kg IV combination and sarilumab 150 mg combination for the HAQ-DI CFB endpoint.

DAS28 remission (DAS28 < 2.6) at Week 24

- In the TNF-IR network, sarilumab 200 mg combination therapy shows superiority to cDMARD, abatacept combination, baricitinib 2 mg OD combination, golimumab combination, sirukumab SC 50 Q4W combination, rituximab combination and tocilizumab 4 mg/kg IV combination for DAS28 remission using the NMA risk difference model.

- Sarilumab 200 mg combination therapy shows similar efficacy to baricitinib 4 mg OD combination, sirukumab SC 100 mg Q2W combination, tocilizumab 8 mg/kg IV combination and sarilumab 150 mg combination.

EULAR at Week 24

- The results of EULAR need to be interpreted with caution due to very few data (e.g.; five studies for eight treatments for the EULAR moderate-to-good outcome), and considerable variability in observed data.

EULAR good at Week 24

- Sarilumab 200 mg combination therapy shows superiority to cDMARD and rituximab combination for the EULAR good endpoint.
- Sarilumab 200 mg combination therapy shows similar efficacy to abatacept combination and sarilumab 150 mg combination for the EULAR good endpoint.

EULAR moderate-to-good at Week 24

- Sarilumab 200 mg combination therapy shows superiority to cDMARD for the EULAR moderate-to-good endpoint.
- Sarilumab 200 mg combination therapy shows inferiority to tocilizumab IV 8 mg/kg and rituximab on EULAR moderate-to-good.
- Sarilumab 200 mg combination therapy shows similar efficacy to all other comparators: abatacept combination, golimumab combination, tocilizumab 4 mg/kg combination and sarilumab 150 mg combination for EULAR moderate-to-good.

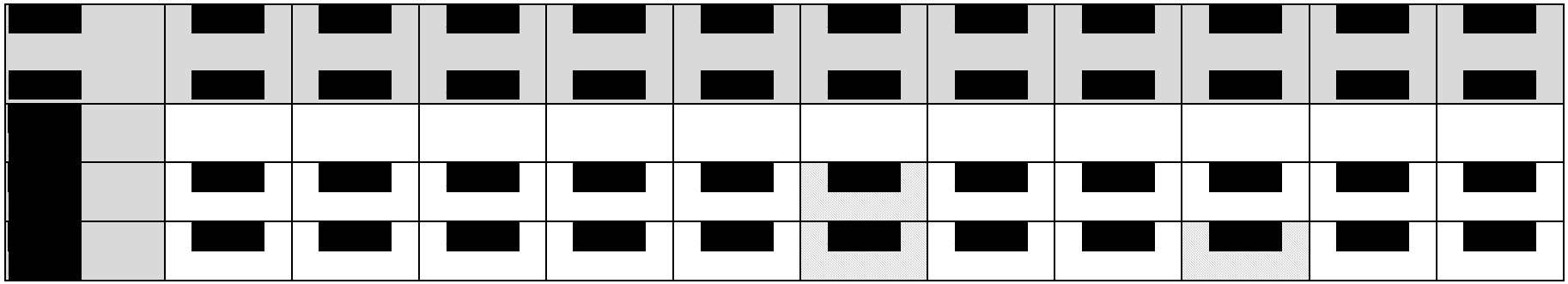
Serious infections and serious adverse events at Week 24

- Sarilumab 200 mg combination therapy shows similar safety to all comparators (cDMARD, abatacept combination, baricitinib 2mg OD combination, baricitinib 4mg OD combination, golimumab combination, sirukumab SC 50mg Q4W combination, sirukumab SC 100mg Q2W combination, rituximab combination, tocilizumab 4 mg/kg IV combination, tocilizumab 4mg/kg and 8mg/kg IV combination and sarilumab 150 mg combination).

The tables below provide a summary of the NMA evidence for cDMARD-IR, combination therapy (Table 4.30), monotherapy (Table 4.31) and TNF-IR combination therapy (Table 4.32) for sarilumab 200 mg versus comparators using the base-case models.

Table 4.30 Summary results for sarilumab 200 mg combination versus other combinations in the conventional disease-modifying anti-rheumatic drug irresponsive population

[redacted]



White cells mean comparable, hatched cells that sarilumab 200 mg was found better, grey cells that the comparator was found better, and – that the comparison was not available.

ACR20/50/70=American College of Rheumatology 20%/50%/70% improvement; cDMARD=conventional disease-modifying anti-rheumatic drug; combi=combination; DAS28 rem=28-joint disease activity score remission; DIC=Deviance Information Criterion; diff=difference; EULAR=European League Against Rheumatism; FEM=fixed effects model; HAQ=Health Assessment Questionnaire; mod=moderate; mTSS=modified Total Sharp Score; NMA=network meta-analysis; OR=odds ratio; QW=once a week; Q2W=once every 2 weeks; RD=risk difference; REM=random effects model; SAE=serious adverse event; SC=subcutaneous; SI=serious infection; TNF=tumour necrosis factor; TNFi=tumour necrosis factor inhibitor

Table 4.31 Summary results of efficacy and safety outcomes at week 24 for sarilumab 200 mg monotherapy versus other monotherapies in the cDMARD-IR population

[redacted]

White cells mean comparable, hatched cells that sarilumab 200 mg was found better, grey cells that the comparator was found better, and –that the comparison was not available.

Similarity hypothesis between anti-TNF treatments is verified

ACR20/50/70=American College of Rheumatology 20%/50%/70% improvement response; CFB=change from baseline; combi=combination; CrI=credibility interval; DAS28 rem=28-joint disease activity score remission; dif=difference; EULAR=European League Against Rheumatism; FEM=fixed effects model; HAQ-DI=Health Assessment Questionnaire Disability Index; mod=moderate; mono=monotherapy; NMA=network meta-analysis; OR=odds ratio; RD=risk difference, REM=random effects model; SAE=serious adverse event; SI=serious infection; TNF=tumour necrosis factor

Table 4.32 Summary results for sarilumab 200mg combinations versus other combinations in the tumour necrosis factor inhibitor irresponsive population

[redacted]

White cells mean comparable, hatched cells that sarilumab 200 mg was found better, grey cells that the comparator was found better, and –that the comparison was not available.

ACR20/50/70=American College of Rheumatology 20%/50%/70% improvement; cDMARD=conventional disease-modifying anti-rheumatic drug; CFB=change from baseline; combi=combination; CrI=credibility interval; DAS28 rem=28-joint disease activity score remission; diff=difference; EULAR=European League Against Rheumatism; FEM=fixed effects model; HAQ-DI=Health Assessment Questionnaire Disability Index; MTX=methotrexate; NMA=network meta-analysis; OR=odds ratio; RD=risk difference; REM=random effects model; SAE=adverse event; SC=subcutaneous; SI=serious infection.

4.10.5.5 Scenario analyses

In the base-case, all treatments were kept separate. However, because it was relevant to inform cost-effectiveness modelling, in a scenario analysis, TNFis were pooled together as a class for ACR 20, 50 and 70 outcomes in cDMARD combination and monotherapy populations. When this was done, checks were performed to assess whether this was valid (i.e. similar efficacy was observed between the individual TNFis). In addition to TNF-pooling, various other scenarios were also tested for all three populations.

4.10.5.5.1 cDMARD-IR combination population

ACR response at Week 24

As described above, a scenario analysis was run with TNFi treatments pooled together. A baseline adjustment model with random effects was used (DIC= 674.9). The coefficient of regression was estimated to be [redacted]. In total, 43 studies were included in the network and 13 interventions.

The TNFi combination class comparison should be interpreted with caution as there is uncertainty regarding the clinical meaningfulness of observed differences in the clinical trials and therefore NMA results.

As in the all treatments separated scenario, sarilumab 200 mg combination therapy was found statistically superior to cDMARD and comparable to all other combination therapies (Table 4.33).

4.10.5.5.2 cDMARD-IR monotherapy population

ACR response rates at Week 24

Sarilumab 200 mg monotherapy was found statistically superior to placebo, cDMARD, sirukumab SC 50mg Q4W monotherapy, TNF monotherapy and tofacitinib monotherapy whereas comparable to sirukumab SC 100mg Q2W monotherapy and tocilizumab 8 mg/kg IV monotherapy (Table 4.34)

Table 4.33 Cross-tabulations of all pairwise combination comparisons as OR for ACR20 response at 24 weeks – TNF class (43 studies included for 13 treatments)

[redacted]

Values in hatched cells are in favour of the intervention; values in grey cells are in favour of the comparator; value without colour means that the two treatment options are comparable.

ACR20=American College of Rheumatology 20% improvement; cDMARD=conventional disease modifying anti-rheumatic drug; IV=intravenous; QW=once a week; Q2W=every 2 weeks; SC=subcutaneous; TNFi=tumour necrosis factor inhibitor;

Table 4.34 Cross-tabulations of all pairwise monotherapy comparisons as OR for ACR20 response at 24 weeks – TNFi class (10 studies included for 8 treatments)

[redacted]

Values in hatched cells are in favour of the intervention; values in grey cells are in disfavour of the intervention; value without colour means that the two treatment options are comparable
ACR20=American College of Rheumatology 20% improvement; cDMARD=conventional disease modifying anti-rheumatic drug; IV=intravenous; OR=odds ratio TNFi=tumour necrosis factor inhibitor.

The network of studies and results for ACR 20, 50 and 70 responses at 24 weeks for all populations are presented in Appendix 8.10. Absolute results of ACR20, 50 and 70 responders for all population is presented in Appendix 8.10.

4.10.5.6 Heterogeneity and inconsistency

4.10.5.6.1 Inconsistency model

Inconsistency in the network was examined using the "back-calculation method" as suggested by Bucher.

The inconsistency model is presented in Appendix 8.13.

4.10.5.6.2 Variation in the baseline treatment arms, odds ratios, and risk difference models

A high degree of variation was observed between the baseline treatment arms for the efficacy outcomes of cDMARD-IR combination and TNF-IR population. In the monotherapy network, there was considerably less variability where the common comparator was an active comparator (adalimumab), with some degree of variability where placebo was the control arm.

The NICE Technical Support Document on adjusting for heterogeneity within evidence synthesis, described that the treatment effect expressed as log ORs has a negative relationship with the baseline risk, using an example of certolizumab pegol in RA[274]. We explored this and also found that the baseline treatment arm odds of response correlated negatively with the ORs of the active treatment arm versus the baseline arm (Table 4.35). Given this relationship and the degree of heterogeneity observed in the baseline response, it was considered important to explore and adjust for this heterogeneity in the NMA.

Network meta-analysis with baseline risk regression

The NMA with regression on baseline risk is a NMA with a constant treatment and covariate interaction; the covariate being the trial-specific baseline for the control arm in each trial. This methodology adjusts for potential bias introduced by variability in the control response rate across the different studies. This model was used as the base-case for the cDMARD-IR population (with the exception of EULAR data, for which too few studies were available to perform a meaningful regression).

As with any regression, to apply this method, a relatively high number of studies per covariate is necessary. Usually, regression is thought to be meaningless with fewer than ten studies[279]. The TNF-IR outcomes network is small — with at most seven studies — and it

was therefore difficult to get the model converging. To address this issue, less vague priors were used: (1) for relative treatment effect, called logodds (under the belief of OR=[0,500], d~*Normal* [0,10]) and study effect (under the belief of p[0.005, 0.995], mu~*Normal* [0,10]), based on the work of Spiegelhalter and colleagues; and (2) for coefficient of regression, it was estimated from baseline risk regression of ACR20/50/70 in cDMARD-IR with variance less than 1 (sd=[0.13;0.85]) and with the mean of zero in order to give the chance for both negative and positive sides: B~*Normal* (0,1). However, even with informative priors, very wide CrIs were obtained. The NMA with baseline risk regression results for the TNF-IR population were highly uncertain (e.g. the OR of the ACR20 of sarilumab 200 mg combination versus MTX observed in the TARGET trial was [redacted] [57], whereas the NMA regression result was [redacted].

Network meta-analysis based on risk difference

As an alternative scenario, a NMA based on risk differences was conducted based on the approach suggested by Spiegelhalter and colleagues[280], in which a risk difference scale was used instead of a log OR scale. In this model, the responder levels were treated as continuous outcomes following a normal distribution and a model for continuous data was used.

To explore the suitability of this approach, correlation analyses were performed on the TNF-IR population. A Pearson correlation coefficient was calculated between the outcome values for the baseline arm (cDMARD) and the comparative effect of the treatment arm versus the baseline arm. The comparative effects were calculated using ORs and risk differences. Eight treatment arms from six studies were included in the analyses. These analyses were performed on ACR20, 50, and 70 and DAS28 remission at 24 weeks. The Pearson correlation coefficients (rho) were estimated to be between [redacted] between the baseline values and the log ORs, and they were statistically different from 0 (Table 4.35). This is in line with the observation in the NICE Technical Support Document of a negative relationship between the baseline risk and the log OR. However, Pearson correlation coefficients (rho) were estimated to be between [redacted] for the baseline values versus the risk difference, and they were not statistically different from zero. Moreover, there was a weak and not statistically significant correlation between logodds of treatment response and logOR [redacted], indicating that the OR is correlated with the control arm response, but not the active arm response.

Table 4.35 Coefficients of correlation between baseline values and risk difference and between log odds of baseline response, log odds of treatment response, and log odds ratios for ACR 20/50/70 improvement response (number of active treatment arms=8) and DAS28 remission

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ACR20/50/70=American College of Rheumatology 20%/50%/70% improvement; DAS28=28-joint disease activity score; logOR=log odds ratio; log(oddsbsl)=log odds of baseline response; log(oddstrt)=log odds of treatment response; p_bls=baseline values; RD=risk difference, rho=coefficient of Pearson correlation

Compared with a conventional logistic NMA, the risk difference NMA significantly better predicted the observed risk difference from the studies.

Figure 4.27 shows that in TNF-IR, conventional logistic NMA (OR NMA) underestimated the relative treatment effect, expressed as risk difference, for sarilumab versus cDMARD such that it was significantly different to that observed in the TARGET study (the 95% CrIs do not contain the true value). Based on this, together with the fact that the risk difference is not significantly correlated with the baseline values, the risk difference model seems to be an appropriate alternative model when the number of studies included in the analysis is too small to perform a meaningful regression analysis.

Therefore, the risk difference NMA was used in the base-case for analyses of binary outcomes where there was considerable variability in baseline risk, but where there were too few studies to perform a regression analysis. This included all binary efficacy outcomes for the TNF-IR network, and the EULAR outcome in cDMARD-IR.

Figure 4.27 Extract of comparison between ACR20/50/70 Risk Difference between observed (direct results) and estimated from NMA using RD or OR approaches (indirect estimate) at Week 24.

ACR20/50/70=American College of Rheumatology 20%/50%/70% improvement response; cDMARD=conventional disease-modifying anti-rheumatic drug; CrI=credibility interval; NMA=network meta-analysis; OR=odds ratio; RD=risk difference;

Continuous outcomes

The impact of heterogeneity in baseline response is much greater on binary outcomes than on continuous outcomes because the latter uses a linear model with comparative treatment effects, expressed using a difference scale. A standard linear CFB NMA was performed for all continuous efficacy outcomes.

Safety outcomes

For safety outcomes, much less variability was observed in the baseline response as compared with efficacy outcomes. A conventional OR-based NMA was used for safety outcomes.

4.10.6 Overall summary of network meta-analysis evidence

In summary, sarilumab in combination with cDMARD/ MTX shows comparable efficacy and safety to other biologic combination therapies, with some outcomes showing advantages over lower doses of sirukumab and baricitinib in TNF-IR. Sarilumab monotherapy shows significantly better efficacy versus adalimumab monotherapy, consistent with head-to-head trial data, and this was also reflected in comparison versus the TNFi class in scenario analyses of ACR responses, although not versus the other individual TNFis.

Overall, this was an extensive NMA including a considerable number of trials and a range of different efficacy and safety outcomes.

4.11 Non-randomised and non-controlled evidence

4.11.1 EXTEND

4.11.1.1 Study design

EXTEND (NCT01146652) is an ongoing, Phase III, multi-national, open-label extension study to assess long-term efficacy and long-term safety associated with long-term use of sarilumab with or without concomitant DMARDs, including MTX[59,142].

All patients who completed the double-blind treatment period of MOBILITY [redacted], TARGET [redacted], ASCERTAIN [redacted], ONE (see below) [redacted] and [redacted] (study investigating clinical benefit of sarilumab plus cDMARD in patients who are inadequate responders to or intolerant of up to [redacted] were eligible for inclusion in the long-term OLE safety study EXTEND [redacted] where they would receive open-label sarilumab until commercial availability of sarilumab in their country, or until 2020 at the latest [redacted] when the study is to be closed[59]. At the time of the EXTEND data cut, MONARCH had not yet reached completion and patients had not entered the OLE phase.

At the time of their inclusion in the initial study, patients were either inadequate responders to MTX (MOBILITY), inadequate responders to or intolerant of TNFis (TARGET, ASCERTAIN), inadequate responders to TNFα antagonists who had failed up to 2 TNF-α antagonists (ACR115575) or inadequate responders to or intolerant of non-biologic DMARDs (ONE). Patients were allowed to continue their background medication as per the initial study. Patients who received sarilumab monotherapy in ONE continued sarilumab monotherapy in EXTEND[59].

Only subjects who fulfilled all the inclusion criteria and did not meet any of the exclusion criteria were included in the clinical trial. The full inclusion and exclusion criteria for MOBILITY, TARGET and ASCERTAIN are provided in Table 4.5.

The primary endpoint of EXTEND was to evaluate the long-term safety of sarilumab. The secondary objective was to evaluate the long-term efficacy of sarilumab on moderate-to-severe RA patients and the study included assessments of the ACR core set and X-rays.

Figure 4.28 Schematic of patient populations who entered EXTEND[59]

4.11.1.2 Endpoints

Table 4.36 describes outcome measures assessed in EXTEND. Analysis of PROs was not performed in this interim analysis.

Table 4.36 EXTEND: Outcome measures[59,142]

Efficacy	Proportion of patients achieving ACR20/50/70, DAS28 remission, EULAR response and DAS28-CRP over time mTSS over time (patients entering EXTEND from MOBILITY) Progression of mTSS over time (patients entering EXTEND from MOBILITY) HAQ-DI over time Each component of the ACR over time
Safety	AEs, laboratory safety, vital signs, physical examination, TB assessment, and ECG

ACR20/50/70=American College of Rheumatology 20%/50%/70% improvement; AE=adverse event; DAS28-CRP=28-joint count disease activity score-C-reactive protein; EULAR=European League Against Rheumatism; HAQ-DI=Health Assessment Questionnaire Disability Index; mTSS=modified Total Sharp Score; TB=tuberculosis

4.11.1.3 Interim analysis

Data for the interim analysis presented in this submission were extracted on 25 January 2016[59].

The following efficacy endpoints were assessed in the interim report of this study[59]:

- ACR20/50/70 response over time

- CFB in ACR components
- DAS28-CRP response over time
- DAS28 remission over time
- EULAR response over time
- CFB in the mTSS (X-ray population) at Weeks 48 and 96
- Incidence of radiographic progression of the mTSS at Weeks 48 and 96
- CFB in HAQ-DI over time

The analyses were performed separately for the sarilumab + DMARD and sarilumab monotherapy groups. X-ray analyses summarise 3 years of data (1 year from MOBILITY and 2 years from the OLE [EXTEND]). This interim analysis included a specific X-ray during which X-rays from EXTEND baseline as well as Week 48 and Week 96 were read for all eligible patients. The data in this document constitutes the final Week 96 X-ray data for the study[59].

4.11.1.4 Baseline characteristics

An overview of patient characteristics at baseline of initial studies is described in Table 4.37.

Table 4.37 EXTEND: Baseline characteristics[59]

	Sarilumab + DMARD (N=1912)	Sarilumab monotherapy (N=111)
Age, mean (SD)	[redacted]	[redacted]
Males, %	[redacted]	[redacted]
Race, %		
Caucasian/White	[redacted]	[redacted]
Black	[redacted]	[redacted]
Asian/Oriental	[redacted]	[redacted]
Other	[redacted]	[redacted]
Weight kg, mean (SD)	[redacted]	[redacted]
BMI kg/m^2, mean (SD)	[redacted]	[redacted]
Duration of RA since diagnosis in years, mean (SD)	[redacted]	[redacted]
RA functional class, %		
I	[redacted]	[redacted]
II	[redacted]	[redacted]
III	[redacted]	[redacted]
IV	[redacted]	[redacted]
RF +ve, %	[redacted]	[redacted]

	Sarilumab + DMARD (N=1912)	Sarilumab monotherapy (N=111)
Anti-CCP +ve, %	[redacted]	[redacted]
TJC (0–68), mean (SD)	[redacted]	[redacted]
SJC (0–66), mean (SD)	[redacted]	[redacted]
CRP in mg/L, mean (SD)	[redacted]	[redacted]
HAQ-DI (0–3), mean (SD)	[redacted]	[redacted]
DAS28-CRP, mean (SD)	[redacted]	[redacted]
Prior cDMARD use, %	[redacted]	[redacted]

BMI=body mass index; CDAI=Clinical Disease Activity Index; cDMARDs=conventional synthetic disease-modifying anti-rheumatic drug; CRP= C-reactive protein; DAS28-CRP=28-joint count disease activity score-C-reactive protein; HAQ-DI=Health Assessment Questionnaire Disability Index; RA=rheumatoid arthritis; RF=rheumatoid factor

4.11.1.5 Results

4.11.1.5.1 Improvements in signs and symptoms

[redacted] [59]. For patients receiving sarilumab plus DMARD, the proportions of patients achieving ACR20, ACR50, and ACR70 at Week 24 and Week [redacted], respectively (Table 4.38)[59].

4.11.1.5.2 Improvements in physical function

For patients receiving both sarilumab plus DMARD or sarilumab monotherapy, after an [redacted] between Week 0 and Week 36, [redacted] [59].

4.11.1.5.3 Inhibition of structural damage

X-ray data were [redacted] [59].

In the 2-year analysis of mTSS, [redacted] (Table 4.39)[59].

A CFB in the mTSS score of ≤ 0 is considered as no progression.

In the 2-year analysis, [redacted] (Table 4.40). In the 3-year analysis, [redacted] (Table 4.40)[59].

4.11.1.5.4 Reduced disease activity (DAS)

For patients receiving sarilumab plus DMARD, [redacted] (Figure 4.29)[59].

Similarly, for patients receiving sarilumab monotherapy, [redacted][59].

4.11.1.5.5 Clinical remission and clinical response

After an initial increase from Week 0 to Week 24, [redacted] (Table 4.38). For patients receiving sarilumab plus DMARD, the proportions of patients achieving DAS28 remission [redacted] For patients receiving sarilumab monotherapy, proportions of patients [redacted][59].

At Week 0, [redacted]. At Week 24, [redacted][59].

At Week 0, [redacted]. At Week 36, [redacted][59].

Table 4.38 EXTEND: Proportion of patients with ACR20/50/70 response and DAS-28 remission (DAS-CRP<2.6) over time[59]

	ACR20	ACR50	ACR70	DAS28 remission
Sarilumab + DMARD				
Week 0, %	[redacted]	[redacted]	[redacted]	[redacted]
Week 24, %	[redacted]	[redacted]	[redacted]	[redacted]
Week 48, %	[redacted]	[redacted]	[redacted]	[redacted]
Week 96, %	[redacted]	[redacted]	[redacted]	[redacted]
Week 144, %	[redacted]	[redacted]	[redacted]	[redacted]
Week 192, %	[redacted]	[redacted]	[redacted]	[redacted]
Week 216, %	[redacted]	[redacted]	[redacted]	[redacted]
Week 240, %	[redacted]	[redacted]	[redacted]	[redacted]
Week 264, %	[redacted]	[redacted]	[redacted]	[redacted]
Sarilumab monotherapy				
Week 0, %	[redacted]	[redacted]	[redacted]	[redacted]
Week 24, %	[redacted]	[redacted]	[redacted]	[redacted]
Week 48, %	[redacted]	[redacted]	[redacted]	[redacted]

ACR20/50/70=American College of Rheumatology 20%/50%/70% improvement; DAS28-CRP=28-joint count disease activity score-C-reactive protein

Table 4.39 EXTEND: CFB in mTSS at Year 2 and Year 3[59]

	2-year analysis Sarilumab + DMARD (n=889)	3-year analysis Sarilumab + DMARD (n=796)
CFB in mTSS, mean (SD)		
Week 0 (52 weeks from baseline)	[redacted]	[redacted]
Week 48 (100 weeks from baseline)	[redacted]	[redacted]
Week 96 (148 weeks from baseline)	[redacted]	[redacted]

CFB=change from baseline; DMARD=disease-modifying anti-rheumatic drug; mTSS=modified Total Sharp Score; SD=standard deviation

Table 4.40 EXTEND: Rates of radiographic nonprogression at Year 2 and Year 3[59]

	2-year analysis Sarilumab + DMARD (n=889)	3-year analysis Sarilumab + DMARD (n=796)
No progression in mTSS, %		
Week 0 (52 weeks from baseline)	[redacted]	[redacted]
Week 48 (100 weeks from baseline)	[redacted]	[redacted]
Week 96 (148 weeks from baseline)	[redacted]	[redacted]

DMARD=disease-modifying anti-rheumatic drug; mTSS=modified Total Sharp Score; SD=standard deviation

Figure 4.29 EXTEND: DAS28-CRP response over time in sarilumab plus DMARD patients[59]

4.11.1.6 EXTEND: Efficacy conclusions

4.11.1.6.1 Sarilumab + DMARD

The increase in the proportion of patients with ACR20/50/70 responses and DAS28 remission of patients who received placebo in the initial studies.

In the interim analysis were evaluated. The combined sarilumab population

In the Year 3 analysis of mTSS[59]:

[redacted]

[redacted]

Initial results from this open-label extension study demonstrate that [redacted]

4.11.1.6.2 Sarilumab monotherapy

Efficacy data for patients in the sarilumab monotherapy group were [redacted]

The proportion of patients with ACR20/50/70 responses, and DAS28 remission [redacted] The initial improvement in response and remission rates between [redacted]

Initial data of patients receiving sarilumab monotherapy [redacted]

4.12 Adverse reactions

4.12.1 Summary of adverse events in Phase II and III randomised controlled trials

Based on the safety profile of other biologics used in the treatment of RA, including IL-6 inhibitors, potential AEs that should be considered include infections, neutropenia, elevations in hepatic enzymes (alanine aminotransferase [ALT], aspartate aminotransferase [AST] and transaminases) and malignancies.

Overall, sarilumab was generally well tolerated in the clinical trial programme and exhibited a safety profile consistent with IL-6 blockade and that observed previously with other anti-IL-6 therapy[1,56-58,131,242,247,269,281].

No clinically meaningful differences in safety profiles were observed between patients treated with sarilumab, tocilizumab, and adalimumab[1,58].

4.12.1.1 Summary of adverse events in MOBILITY A

Incidences of AEs and SAEs were higher with sarilumab than placebo; AEs occurred in 43.1–72.0% of the sarilumab plus MTX groups versus 47.1% of the placebo plus MTX group (Table 4.41). Treatment discontinuation due to an AE occurred in 24 patients; 13 of whom were in the 100 mg QW dose group with between one and four patients in each of the other groups. Infections and infestations were the most common AEs, and the incidence in patients treated with doses of 150 mg Q2W and higher was greater than placebo. There were no serious infections[55].

Injection site reactions occurred in 5.5% of patients receiving sarilumab and in 2.0% of patients receiving placebo. These events were generally mild to moderate in intensity, with the exception of one patient receiving sarilumab 100 mg QW who experienced a severe reaction, which led to permanent treatment discontinuation[55].

Overall, sarilumab was generally well tolerated, with changes in neutrophil counts and trends for other safety and laboratory parameters such as ALT elevations favouring Q2W dosing[55].

Table 4.41 MOBILITY A: Summary of safety[55]

	Placebo + MTX (n=51)	Sarilumab 100 mg Q2W + MTX (n=51)	Sarilumab 150 mg Q2W + MTX (n=52)	Sarilumab 100 mg QW + MTX (n=50)	Sarilumab 200 mg Q2W + MTX (n=51)	Sarilumab 150 mg QW + MTX (n=50)
Any AE, n (%)	24 (47.1)	22 (43.1)	28 (53.8)	36 (72.0)	33 (64.7)	27 (54.0)
Any SAE, n (%)	2 (3.9)	3 (5.9)	0	3 (6.0)	0	0
Any AE leading to treatment discontinuation, n (%)	2 (3.9)	4 (7.8)	2 (3.8)	13 (26.0)	4 (7.8)	3 (6.0)
Deaths, n	0	1	0	0	0	0
SAEs by system/organ class						
Basal cell carcinoma, n (%)	1 (2.0)	0	0	0	0	0
Plasmacytoma, n (%)	0	1 (2.0)	0	0	0	0
Squamous cell carcinoma, n (%)	1 (2.0)	0	0	0	0	0
Neutropenia, n (%)	0	0	0	1 (2.0)	0	0
Hypersensitivity, n (%)	0	0	0	1 (2.0)	0	0
Cerebrovascular event, n (%)	0	1 (2.0)	0	0	0	0
Acute respiratory distress syndrome, n (%)	0	1 (2.0)	0	0	0	0
Alcoholic pancreatitis, n (%)	0	0	0	1 (2.0)	0	0
Arthralgia, n (%)	1 (2.0)	0	0	0	0	0

	Placebo + MTX (n=51)	Sarilumab 100 mg Q2W + MTX (n=51)	Sarilumab 150 mg Q2W + MTX (n=52)	Sarilumab 100 mg QW + MTX (n=50)	Sarilumab 200 mg Q2W + MTX (n=51)	Sarilumab 150 mg QW + MTX (n=50)
AEs occurring in ≥5% of patients						
Infections and infestations, n (%)	7 (13.7)	6 (11.8)	12 (23.1)	13 (26.0)	12 (23.5)	10 (20.0)
Nasopharyngitis, n (%)	3 (5.9)	2 (3.9)	2 (3.8)	2 (4.0)	2 (3.9)	1 (2.0)
Upper respiratory tract infection, n (%)	2 (3.9)	0	0 2 (3.8)	1 (2.0)	3 (5.9)	2 (4.0)
Urinary tract infection	1 (2.0)	1 (2.0)	1 (1.9)	3 (6.0)	1 (2.0)	0
Blood and lymphatic system disorders, n (%)	0	1 (2.0)	1 (1.9)	9 (18.0)	11 (21.6)	6 (12.0)
Neutropenia, n (%)	0	0	1 (1.9)	7 (14.0)	10 (19.6)	5 (10.0)
Musculoskeletal/ connective tissue, n (%)	5 (9.8)	5 (9.8)	1 (1.9)	1 (2.0)	2 (3.9)	5 (10.0)
ALT increases, n (%)	0	0	3 (5.8)	2 (4.0)	2 (3.9)	2 (4.0)

AE=adverse event; ALT=alanine aminotransferase; Q2W=every 2 weeks; QW=every week; SAE=serious adverse event

4.12.1.2 Summary of adverse events in MOBILITY B

In the double-blind treatment period, incidences of AEs and SAEs were higher with sarilumab plus MTX than with placebo plus MTX. In the double-blind period, AEs occurred in 74.5% and 78.1% of patients in the sarilumab 150 mg and 200 mg groups versus 61.6% in the placebo group (Table 4.34). Most AEs were mild or moderate in intensity. In the double-blind period, treatment discontinuation due to an AE occurred in 12.5% and 13.9% of patients receiving sarilumab 150 mg and 200 mg versus 4.7% of those on receiving and the discontinuations were generally attributable to infections, neutropenia, or increased ALT levels (Table 4.42)[56].

Injection site reactions occurred in 9.0% and 10.1% of patients receiving sarilumab 150 mg and 200 mg and in 1.2% of patients receiving placebo. These events were generally mild to moderate in intensity, with the exception of one patient who developed severe urticaria at the injection site. Injection site reactions resulted in permanent treatment discontinuation in three patients[56].

In the double-blind treatment period, infections and infestations were the most common AEs, occurring in 40.1% and 39.6% of patients receiving sarilumab 150 mg and 200 mg versus 31.1% of those receiving placebo (Table 4.42) and serious infections were reported in 2.6% and 4.0% of those on sarilumab 150 mg and 200 mg versus 2.3% of those on placebo[56]. Opportunistic infections were reported in

three patients receiving sarilumab 150 mg (0.7%), four patients receiving sarilumab 200 mg (0.9%), and two patients receiving placebo (0.5%)[56].

In the double-blind treatment period, neutropenia occurred in 9.3% and 14.4% of patients receiving sarilumab 150 mg and 200 mg versus 0.2% of those on placebo; however, there was no apparent association between neutropenia and the incidences of infections (Table 4.34)[56].

In the double-blind treatment period, ALT elevations occurred in 8.6% and 7.5% of patients receiving sarilumab 150 mg and 200 mg versus 3.3% of those on placebo (Table 4.42) leading to discontinuation in [redacted] of patients receiving sarilumab 150 mg and 200 mg[56,61].

Eight neoplasms were reported during the study. Four of these occurred in patients receiving sarilumab 150 mg (melanoma in one patient, breast cancer in two patients, and cancer of the appendix in one patient), three occurred in those receiving sarilumab 200 mg (basal cell carcinoma in one patient, melanoma in one patient, and breast cancer in one patient), and one occurred in a patient in the placebo group (squamous cell carcinoma). No cases of lymphoma were reported[56].

Table 4.42 MOBILITY B: Summary of safety[56]

	Double-blind period			Open-label rescue period		
	Placebo + MTX (n=427)	Sarilumab (150 mg Q2W) + MTX (n=431)	Sarilumab (200 mg Q2W) + MTX (n=424)	From placebo + MTX to sarilumab (200 mg Q2W) + MTX (n=168)	From sarilumab (150 mg Q2W) + MTX to sarilumab (200 mg Q2W) + MTX (n=61)	From sarilumab (200 mg Q2W) + MTX to sarilumab (200 mg Q2W) + MTX (n=55)
Any AE, n (%)	263 (61.6)	321 (74.5)	331 (78.1)	110 (65.5)	43 (70.5)	31 (56.4)
Any SAE, n (%)	23 (5.4)	38 (8.8)	48 (11.3)	16 (9.5)	8 (13.1)	5 (9.1)
Any AE leading to treatment discontinuation, n (%)	20 (4.7)	54 (12.5)	59 (13.9)	12 (7.1)	9 (14.8)	5 (9.1)
Deaths, n (%)	2 (0.5)	2 (0.5)	1 (0.2)	1 (0.6)	0 (0)	1 (1.8)
Most frequent AEs by system/organ class						
Infections and infestations, n (%)	133 (31.1)	173 (40.1)	168 (39.6)	54 (32.1)	22 (36.1)	14 (25.5)
Upper respiratory infection, n (%)	24 (5.6)	36 (8.4)	37 (8.7)	6 (3.6)	3 (4.9)	2 (3.6)
Bronchitis, n (%)	17 (4.0)	14 (3.2)	24 (5.7)	9 (5.4)	5 (8.2)	1 (1.8)
Urinary tract infection, n (%)	16 (3.7)	22 (5.1)	23 (5.4)	6 (3.6)	1 (1.6)	1 (1.8)
Blood and lymphatic disorders, n (%)	11 (2.6)	51 (11.8)	80 (18.9)	20 (11.9)	8 (13.1)	6 (10.9)
Neutropenia, n (%)	1 (0.2)	40 (9.3)	61 (14.4)	19 (11.3)	6 (9.8)	5 (9.1)
Leukopenia, n (%)	0	9 (2.1)	18 (4.2)	6 (3.6)	2 (3.3)	1 (1.8)
Anaemia, n (%)	7 (1.6)	1 (0.2)	3 (0.7)	0	0	0
Laboratory investigations, n (%)	36 (8.4)	65 (15.1)	68 (16.0)	19 (11.3)	2 (3.3)	5 (9.1)
ALT levels increased, n (%)	14 (3.3)	37 (8.6)	32 (7.5)	13 (7.7)	1 (1.6)	2 (3.6)
Transaminase levels increased, n (%)	3 (0.7)	10 (2.3)	15 (3.5)	1 (0.6)	0	0
AST levels increased, n (%)	3 (0.7)	3 (0.7)	5 (1.2)	2 (1.2)	1 (1.6)	0
GI disorders, n (%)	46 (10.8)	49 (11.4)	64 (15.1)	17 (10.1)	8 (13.1)	3 (5.5)
Diarrhoea, n (%)	9 (2.1)	12 (2.8)	17 (4.0)	6 (3.6)	4 (6.6)	0
Nausea, n (%)	9 (2.1)	9 (2.1)	13 (3.1)	0	1 (1.6)	0
Dyspepsia, n (%)	5 (1.2)	4 (0.9)	6 (1.4)	0	2 (3.3)	0

AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; GI=gastrointestinal; MTX=methotrexate; Q2W=once every 2 weeks; SAE=serious adverse event

4.12.1.3 Summary of adverse events in TARGET

Incidences of AEs and SAEs were higher with sarilumab plus cDMARD than with placebo plus cDMARD. AEs occurred in 65.7% and 65.2% of patients receiving sarilumab 150 mg and 200 mg versus 49.7% of those receiving placebo, and SAEs occurred in 3.3% and 5.4% of those on sarilumab 150 mg and 200 mg versus 3.3% of those on placebo (Table 4.43). Treatment discontinuation due to an AE occurred in 7.7% and 9.2% of patients receiving sarilumab 150 mg and 200 mg versus 4.4% of those on placebo (Table 4.35) and these discontinuations were generally attributable to infections, neutropenia, and increased transaminase levels[57].

Injection site reactions occurred in 7.2% and 8.2% of patients receiving sarilumab 150 mg and 200 mg versus 1.1% of those on placebo. These events were generally mild to moderate in intensity, with no patients discontinuing treatment because of an injection site reaction[57].

Infections and infestations as the most common AE occurred in 22.1% and 30.4% of patients receiving sarilumab 150 mg and 200 mg versus 26.5% of those on placebo (Table 4.43). Infections and infestations were also the most frequently reported SAE across treatment groups and occurred in one patient receiving sarilumab 150 mg (0.5%), two patients receiving sarilumab 200 mg (1.0%), and two patients receiving placebo (1.0%)[57].

SAEs included decreased neutrophil counts, elevated transaminase levels, and cardiovascular disorders. Serious cardiovascular events occurred in three patients receiving sarilumab 200 mg (1.6%): one patient developed non-infectious endocarditis of the mitral valve, one patient with a prior episode of syncope developed an atrioventricular block, and one patient had venous thrombosis[57].

Neutropenia occurred in 12.7% and 12.5% of patients receiving sarilumab 150 mg and 200 mg versus 1.1% of those on placebo (Table 4.32). Decreases in the absolute neutrophil count were generally self-limited and returned toward baseline and neutropenia was not associated with a between-group difference in the incidences of infections or serious infections[57].

ALT elevations occurred in 2.8% and 5.4% of patients receiving sarilumab 150 mg and 200 mg versus 1.1% of those on placebo (Table 4.43). These events were generally asymptomatic and resolved during continued treatment or after dose delays, with one patient (sarilumab 150 mg) discontinuing treatment[57].

Malignancy was diagnosed in three patients: in one patient receiving sarilumab 150 mg (renal cell carcinoma), one patient receiving sarilumab 200 mg (skin carcinoma), and one patient receiving placebo (ureter carcinoma)[57].

Table 4.43 TARGET: Summary of safety[57]

	Placebo + cDMARD (n=181)	Sarilumab 150 mg Q2W + cDMARD (n=181)	Sarilumab 200 mg Q2W + cDMARD (n=184)
Any AE, n (%)	90 (49.7)	119 (65.7)	120 (65.2)
Any SAE, n (%)	6 (3.3)	6 (3.3)	10 (5.4)
Any AE leading to treatment discontinuation, n (%)	8 (4.4)	14 (7.7)	17 (9.2)
Deaths, n (%)	1 (0.6)	0	0
Most frequent AEs by system/organ class			
Infections and infestations, n (%)	48 (26.5)	40 (22.1)	56 (30.4)
Urinary tract infection, n (%)	12 (6.6)	6 (3.3)	13 (7.1)
Nasopharyngitis, n (%)	9 (5.0)	11 (6.1)	7 (3.8)
Pharyngitis, n (%)	3 (1.7)	2 (1.1)	6 (3.3)
Upper respiratory infection, n (%)	6 (3.3)	4 (2.2)	6 (3.3)
Blood and lymphatic disorders, n (%)	9 (5.0)	25 (13.8)	29 (15.8)
Neutropenia, n (%)	2 (1.1)	23 (12.7)	23 (12.5)
Thrombocytopenia, n (%)	0	0	5 (2.7)
Leukopenia, n (%)	0	2 (1.1)	3 (1.6)
Anaemia, n (%)	5 (2.8)	0	1 (0.5)
Laboratory investigations, n (%)	8 (4.4)	19 (10.5)	30 (16.3)
ALT levels increased, n (%)	2 (1.1)	5 (2.8)	10 (5.4)
Transaminase levels increased, n (%)	0	2 (1.1)	6 (3.3)
AST levels increased, n (%)	0	2 (1.1)	3 (1.6)

AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; cDMARD=conventional disease-modifying anti-rheumatic drug; Q2W=once every 2 weeks; SAE=serious adverse event

4.12.1.4 Summary of adverse events in ASCERTAIN

Incidences of AEs and SAEs [redacted] in patients treated with sarilumab plus cDMARD and tocilizumab plus cDMARD. AEs occurred in [redacted] of patients receiving sarilumab 150 mg and 200 mg versus [redacted] of those on tocilizumab, and SAEs occurred in [redacted] of patients receiving sarilumab 150 mg and 200 mg versus [redacted] of those on tocilizumab (Table 4.44). Treatment discontinuation due to an AE occurred in [redacted] of patients receiving sarilumab 150 mg and 200 mg versus [redacted] of those on tocilizumab and [redacted][58].

Injection site reactions occurred in [redacted] of patients receiving sarilumab 150 mg and 200 mg versus [redacted] of those on tocilizumab. These events were generally mild to moderate in intensity, with the exception of two patients receiving sarilumab 200 mg who experienced a severe reaction, which led to permanent treatment discontinuation[58].

Infections and infestations as the most common AE occurred in [redacted] of patients receiving sarilumab 150 mg and 200 mg versus [redacted] of those on tocilizumab (Table 4.36). Infections and infestations were also the most frequently reported SAE across treatment groups and occurred in [redacted] receiving sarilumab 150 mg [redacted] and two patients receiving tocilizumab [redacted][58].

Other SAEs included neutropenia in [redacted] receiving tocilizumab [redacted], vascular disorders in [redacted] receiving sarilumab 150 mg [redacted], elevated transaminase levels in [redacted] receiving sarilumab 200 mg [redacted], and cardiovascular disorders in [redacted] receiving sarilumab 200 mg [redacted][58].

ALT elevations occurred in [redacted] of patients receiving sarilumab 150 mg and 200 mg versus [redacted] of those on tocilizumab (Table 4.44) and there were no cases of diverticulitis, gastrointestinal perforation, malignancy, or demyelinating disorders[58].

Table 4.44 ASCERTAIN: Summary of safety[58]

	Tocilizumab IV 4–8 mg/kg Q4W + cDMARD (n=102)	Sarilumab 150 mg Q2W + cDMARD (n=49)	Sarilumab 200 mg Q2W + cDMARD (n=51)
Any AE, n (%)	[redacted]	[redacted]	[redacted]
Any SAE, n (%)	[redacted]	[redacted]	[redacted]
Any AE leading to treatment discontinuation, n (%)	[redacted]	[redacted]	[redacted]
Deaths, n (%)	[redacted]	[redacted]	[redacted]
Most frequent AEs by system/organ class			

	Tocilizumab IV 4–8 mg/kg Q4W + cDMARD (n=102)	Sarilumab 150 mg Q2W + cDMARD (n=49)	Sarilumab 200 mg Q2W + cDMARD (n=51)
Infections and infestations, n (%)	[redacted]	[redacted]	[redacted]
Urinary tract infection, n (%)	[redacted]	[redacted]	[redacted]
Nasopharyngitis, n (%)	[redacted]	[redacted]	[redacted]
Upper respiratory infection, n (%)	[redacted]	[redacted]	[redacted]
Gastroenteritis, n (%)	[redacted]	[redacted]	[redacted]
Blood and lymphatic disorders, n (%)	[redacted]	[redacted]	[redacted]
Neutropenia, n (%)	[redacted]	[redacted]	[redacted]
Laboratory investigations,			
ALT levels increased, n (%)	[redacted]	[redacted]	[redacted]
Transaminase levels increased, n (%)	[redacted]	[redacted]	[redacted]

AE=adverse event; ALT=alanine aminotransferase; cDMARD=conventional disease-modifying anti-rheumatic drug; IV=intravenous; Q2W=once every 2 weeks; Q4W=once every 4 weeks; SAE=serious adverse event

4.12.1.5 Summary of adverse events in MONARCH

Incidences of AEs, SAEs, and discontinuations due to AEs were comparable in patients treated with sarilumab 200 mg Q2W and adalimumab 40 mg Q2W. AEs occurred in 64.1% of patients receiving sarilumab versus 63.6% of those receiving adalimumab, and SAEs occurred in 4.9% of patients receiving sarilumab versus 6.5% of those receiving adalimumab (Table 4.45). Treatment discontinuation due to an AE occurred in 6.0% of patients receiving sarilumab versus 7.1% of those receiving adalimumab (Table 4.45) and the discontinuations were generally attributable to [redacted][1,63].

Injection site reactions occurred in 9.2% of patients receiving sarilumab versus 4.3% of those receiving adalimumab. All events were reported to be mild to moderate in intensity by the investigator, and the majority of patients were able to continue study treatment [redacted][1,63].

Infections and infestations as the most common AE occurred in 28.8% of patients receiving sarilumab versus 27.7% of those on adalimumab (Table 4.45)[1]. Two patients receiving sarilumab (one mastitis and one infective bursitis) and two patients receiving adalimumab (one bacterial arthritis and one upper respiratory tract infection) experienced a serious infection[1].

Neutropenia occurred in 13.6% of patients receiving sarilumab versus 0.5% of those on adalimumab (Table 4.37) but was not associated with a between-group difference in the incidences of infections or serious infections[1].

ALT elevations were similar, occurring in 3.8% of patients receiving sarilumab or adalimumab (Table 4.45) and [redacted] was diagnosed only in [redacted] receiving adalimumab [redacted][1,63].

Table 4.45 MONARCH: Summary of safety[1,63]

	Adalimumab 40 mg Q2W (n=184)	Sarilumab 200 mg Q2W (n=184)
Any AE, n (%)	117 (63.6)	118 (64.1)
Any SAE, n (%)	12 (6.5)	9 (4.9)
Any AE leading to treatment discontinuation, n (%)	13 (7.1)	11 (6.0)
Deaths, n (%)	0	1 (0.5)
Most frequent AEs by system/organ class		
Infections and infestations, n (%)	51 (27.7)	53 (28.8)
Nasopharyngitis, n (%)	14 (7.6)	11 (6.0)
Bronchitis, n (%)	7 (3.8)	12 (6.5)
Urinary tract infection, n (%)	4 (2.2)	5 (2.7)
Pharyngitis, n (%)	5 (2.7)	3 (1.6)
Upper respiratory infection, n (%)	7 (3.8)	3 (1.6)
Sinusitis, n (%)	0	2 (1.1)
Blood and lymphatic disorders, n (%)	3 (1.6)	27 (14.7)
Neutropenia, n (%)	1 (0.5)	25 (13.6)
Anaemia, n (%)	0	2 (1.1)
Nervous system disorders, n (%)	20 (10.9)	14 (7.6)
Headache, n (%)	12 (6.5)	7 (3.8)
Laboratory investigations, n (%)		
ALT levels increased, n (%)	7 (3.8)	7 (3.8)
AST levels increased, n (%)	3 (1.6)	1 (0.5)

AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; Q2W=once every 2 weeks; SAE=serious adverse event

4.12.1.6 Additional studies reporting adverse events

There are no appropriate additional studies to be assessed.

4.13 Interpretation of clinical effectiveness and safety evidence

Collectively, evidence from the NMA (Section 4.10.6) and data from MOBILITY A, MOBILITY B, TARGET, ASCERTAIN, and MONARCH (Section 4.7.3) demonstrate that sarilumab is well tolerated and improves signs and symptoms and functional disability in patients with moderate-to-severe RA including patients who are inadequate responders to or intolerant of cDMARDs or TNFis[1,55-58]. Sarilumab is therefore an appropriate and effective treatment in combination with MTX or as a monotherapy for patients who are unsuitable candidates for continued treatment with MTX/TNFi due to intolerance or an inadequate response.

The results of the NMA demonstrate that sarilumab is comparable to other bDMARDs and more effective than cDMARDs with the additional benefits of safety and tolerability versus MTX and TNFis (Section 3.5.2, 3.5.3 and 3.5.5), a new mode of action (Section 3.5.4), dose flexibility and ease of use (Section 2.5.3).

4.13.1 Clinical effectiveness

As discussed in Section 3.5, despite the availability of multiple cDMARDs and bDMARDs, lack of disease control remains a significant clinical issue, with only a minority of patients with RA achieving and maintaining acceptable clinical outcomes and up to 30% of patients discontinuing cDMARDs or TNFis due to loss of response or intolerance[24,41-47].

Considering the suboptimal outcomes associated with TNFi cycling, the use of a bDMARD with an alternative MoA is an increasingly attractive treatment strategy. Studies suggest that RA patients switching from a TNFi to a drug with an alternative MoA are less likely to switch again and have better outcomes, and current clinical guidelines suggest that switching from one class of bDMARDs to another with a different mechanism of action may provide better clinical benefit[25,26,36-38,81,122].

Alternative therapies that improve signs and symptoms, effectively reduce disease activity, and improve physical function are needed for those patients who are irresponsive or intolerant to cDMARDs and/or TNFis.

4.13.2 Outcome measures

4.13.2.1 Primary outcome measures.

The primary outcome measure from MOBILITY A (ACR20 at Week 12) demonstrated that the Q2W dosing regimens (150 mg and 200 mg Q2W) were as effective as the QW dosing regimens (100 mg and 150 mg QW). Changes in neutrophil counts and trends for other safety and laboratory parameters favoured Q2W dosing, and as a result the 150 mg and

200 mg Q2W doses were subsequently assessed in multiple Phase III clinical trials. These included MOBILITY B, TARGET, ASCERTAIN, and MONARCH, in which sarilumab demonstrated statistically significant improvements in all primary and co-primary efficacy endpoints (Table 4.7) [1,55-58]. The data from these studies demonstrate that sarilumab has the ability to improve signs and symptoms and physical function (assessed by ACR20/50/70, change in HAQ-DI, change in DAS28-CRP/ESR, and change in mTSS) in patients with moderate-to-severe RA[1,55-58].

4.13.2.2 Secondary outcome measures

From the patient's perspective, the most important benefits of RA treatment are to improve pain, functional disability, and fatigue. Patients receiving sarilumab reported a greater improvement in their health status as reflected by differences in SF-36 PCS, HAQ-DI, and pain VAS scores, along with improvement in fatigue[1,55-58,64,65]. These show that the objective clinical outcomes observed with sarilumab translate into patient benefits as assessed across a range of PROs.

4.13.2.3 Subgroup analysis

Subgroup analyses demonstrate that sarilumab efficacy is independent of whether a patient is an inadequate responders to or intolerant of TNFi/MTX and the number of prior DMARDs/TNFis[1,55-58].

4.13.2.4 Comparative efficacy

Evidence from the sarilumab clinical trials programme demonstrated that, in addition to being well tolerated with a safety profile consistent with IL-6 blockade, sarilumab (in combination with MTX or as a monotherapy) is an appropriate and effective treatment for patients who are unsuitable candidates for continued treatment with cDMARD/TNFi due to intolerance or an inadequate response, thus providing sustained efficacy regardless of patient treatment history[1,55-58]. Sarilumab monotherapy has demonstrated superiority to adalimumab monotherapy in improving signs and symptoms and physical function, with no unexpected safety signals[1,63].

4.13.2.5 Safety

Sarilumab is generally well tolerated, with a safety profile consistent with IL-6 blockade and that observed previously with other anti-IL-6 therapy, and, as observed with other bDMARDs, non-serious infections were the most commonly reported AEs. There were no

clinically meaningful differences in safety profiles between patients treated with sarilumab, tocilizumab, and adalimumab[1,55-58,242,247,269,281].

4.13.3 Strengths of the randomised controlled trials in the sarilumab clinical trial programme

In the context of evidence-based medicine, RCTs are considered the gold standard level of scientifically proven evidence and the sarilumab clinical trial programme benefits from the utilisation of both placebo-controlled and active-controlled study designs.

Another key strength of the sarilumab clinical trial programme lies in the study design, with all five key studies being large, global, multicentre studies with substantial representation of patients from Europe, North America, South America, and Asia. In addition, stringent inclusion criteria (Table 4.5) ensured that patients in the studies had moderate-to-severe longstanding RA, and, consistent with the increasing use of bDMARDs in patients with active RA, a substantial proportion (24.5% in MOBILITY A, 27.9% in MOBILITY B, and 100% in TARGET and ASCERTAIN [Table 4.12]) of the patients had previously been treated with bDMARDs[1,55-58].

Improvements in physical function are as important to patients as improvement in signs and symptoms and the sarilumab clinical trial programme demonstrates that sarilumab significantly improved physical function through 24 and 52 weeks of treatment[1,55-58]. In addition, MOBILITY B, TARGET and MONARCH demonstrate significant improvements in CDAI illustrating that the benefits of sarilumab extend beyond its pharmacodynamic effects on CRP[1,55-58].

In addition to increased ACR20 responses and improvements in the HAQ-DI, the observation that sarilumab resulted in improvements in the ACR core set components, including the TJC, SJC, physician's assessment of global status, and patient's assessment of pain, indicates that sarilumab provides consistent clinically meaningful benefits[1,55-58]

Sarilumab clinical efficacy is complemented by clinically meaningful improvements in pain, fatigue and general health status. There is a concordance across all PROs studied and durable responses were apparent as early as 2 weeks[1,64].

Although the primary objective of ASCERTAIN was to evaluate the safety of sarilumab, this study included efficacy as an exploratory endpoint. ASCERTAIN added value both to the sarilumab clinical trial programme and the bDMARD knowledge base as it established additional context for the efficacy and safety of sarilumab compared with tocilizumab, at

present the only approved IL-6R blocking agent with the same mechanism of action as sarilumab.

A summary of the strengths of the individual studies are described in Table 4.46.

4.13.4 Limitations of the randomised controlled trials in the sarilumab clinical trial programme

The sarilumab Phase III clinical trial population included adult patient (≥18 years), with moderate-to-severe, active RA with disease duration ≥3 months who were inadequate responders to or intolerant of MTX/TNFi. Overall, patient demographics and characteristics (Table 4.12) were similar to those of populations included in comparative RA studies identified in the NMA (Section 4.10).

Although the patient populations involved in the sarilumab Phase III clinical trial programme may not be fully 'generalisable' due to the exclusion of patients with comorbidity, extra-articular manifestations, functional class IV disease, and other inflammatory joint diseases, comparison to historical data sets demonstrate that these patients reflect those in other RA trial programmes (please refer to Appendix 8.6). Thus, the results of the sarilumab trial programme can be applied to a clinical RA population.

A summary of the limitations of the individual studies are described in Table 4.46.

Table 4.46 Summary of randomised controlled trial strengths and limitations[1,55-58]

STUDY	MOBILITY A/B	TARGET	ASCERTAIN	MONARCH
Strengths	Operationally seamless, Phase II/III design[a] Primary efficacy analyses confirmed by sensitivity analyses that included radiographic data from patients who received rescue therapy and therefore were receiving active treatment at the time of the radiographic measurements	HAQ-DI evaluated at week 12 to reduce the amount of missing data Although not powered to evaluate statistical differences between sarilumab 150 mg and 200 mg Q2W, results indicate a trend toward greater responses with sarilumab 200 mg vs. 150 mg Q2W	Double-blind, double-dummy design prevented recall and reporting bias of safety events	Head-to-head study in a clinically relevant population Expands on the results from ADACTA, a Phase IV trial investigating tocilizumab monotherapy vs. adalimumab monotherapy (Gabay 2013)
Limitations	Inclusion and exclusion criteria specific to MOBILITY may have contributed to the relatively high rate of radiographic progression observed in the placebo group Because patients in MOBILITY B had not been categorised as biological non-responders, the population may not have been fully aligned to RA populations characterised by inadequate response to bDMARDs	Approximately three-quarters of the patients in TARGET had been unsuccessfully treated with one prior TNFi. Therefore, comparison of response rates according to the number of prior TNFis is limited Benefit of sarilumab in patients with an inadequate response to biological therapies with non-TNFi not evaluated	As a non-hypothesis testing study, ASCERTAIN was not powered to demonstrate statistically significant differences between treatments and all efficacy analyses were performed descriptively Although the recommended posology of tocilizumab is 8 mg/kg body weight, Q4W, in ASCERTAIN IV infusion of tocilizumab Q4W were initiated at 4 mg/kg and increased to 8 mg/kg, if needed, based on clinical response (as assessed by the investigator)	Absence of radiographic data

bDMARD=biological disease-modifying anti-rheumatic drug; HAQ-DI=Health Assessment Questionnaire Disability Index; Q2W=once every 2 weeks; RA=rheumatoid arthritis; TNFi=tumour necrosis factor inhibitor

[a.] This is particularly relevant as approaches to seamless design are a current topic of discussion in the literature and with regulators as the research community seeks to improve the efficiency of drug development.

4.14 Other studies and ongoing data analysis

4.14.1 Other studies in the sarilumab clinical Phase III clinical trial programme

Although trials are complete, data analyses remain ongoing for three additional trials from the Phase III clinical trial programme (EASY, ONE and KAKEHASI). The OLE trial EXTEND remains active but not recruiting additional patients (Table 4.47).

These studies included patients with moderate-to-severe active RA patients who were inadequate responders to or intolerant of MTX/cDMARD/TNFi.

The objective of EASY (NCT02057250) was to provide usability assessment of the sarilumab pre-filled pen and provide data to bridge to the pre-filled syringe, which was used in the clinical development programme, in support of registration. The open-label design was appropriate to collect objective measures including product technical complaints and assessment of PK parameters. No control group was included as there are no direct comparisons except assessment of PKs[144].

The ONE trial (NCT02121210) was designed as an open-label immunogenicity and safety study. As the primary assessment of the study was based on objective laboratory measurement for the development of adalimumab, consequently, blinding was considered unnecessary. A placebo group was not included as this was a monotherapy study, without background RA DMARD therapy, and given that the primary endpoint related to adalimumab incidence with active sarilumab treatment[143].

KAKEHASI (NCT02293902) is a Phase III, randomised, double-blind, multicentre study with a placebo-controlled period assessing the efficacy and safety of sarilumab added to MTX in Japanese patients with moderate-to-severe active RA who are inadequate responders to MTX[145].

EXTEND (NCT01146652) is an ongoing, Phase III, multi-national, open-label extension study to assess long-term efficacy and long-term safety associated with long-term use of sarilumab with or without concomitant DMARDs, including MTX (Section 4.11.1)[59]. All patients who completed the double-blind treatment period of MOBILITY, TARGET, ASCERTAIN, ONE and ACT11575 (study investigating clinical benefit of sarilumab plus cDMARD in patients who are inadequate responders to or intolerant of up to 2 TNFis) were eligible for inclusion in the long-term OLE safety study EXTEND where they would receive open-label sarilumab until commercial availability of sarilumab in their country, or until 2020 at the latest (maximum 276 weeks of open-label treatment) when the study is to be closed[59].

At the time of the EXTEND data cut, MONARCH had not yet reached completion and patients had not entered the OLE phase.

Sarilumab is also currently being investigated in paediatric populations with polyarticular-course juvenile idiopathic arthritis and systemic juvenile idiopathic arthritis (Table 4.47)[282,283].

Table 4.47 Other studies in the sarilumab clinical trial programme[59,78,142-144,146,282,283]

	ONE NCT02121210	EASY NCT02057250	EXTEND NCT01146652	KAKEHASI (NCT02293902)	Open-label, ascending, repeated dose-finding study in pcJIA NCT02776735	Repeated dose-finding study in sJIA NCT02991469
Phase	III	III	III	III	II	II
N	132	217	Sarilumab + DMARD 1910 Sarilumab monotherapy 111	243	Estimated enrolment 36	Estimated enrolment 36
Treatment	Sarilumab monotherapy	Sarilumab PFP + MTX Sarilumab PFS + MTX	Sarilumab + MTX/cDMARD OLE of TARGET, MOBILITY, ASCERTAIN, and ONE	Sarilumab + MTX	Open-label sarilumab	Open-label sarilumab
Population	cDMARD irresponsive/ intolerant adults	cDMARD irresponsive/ intolerant adults	cDMARD/TNFi irresponsive/ intolerant adults	MTX irresponsive	Children and adolescents (≥2 and ≤17 years) with pcJIA with inadequate response to current treatment and considered a candidate for bDMARDs as per investigator's judgement	Children and adolescents (1–17 years) with sJIA with inadequate response to current treatment and considered a candidate for bDMARDs as per investigator's judgement
Length	24 weeks	12 weeks	Ongoing At least 264 weeks	52 weeks	12 weeks	12 weeks core (plus 92-week extension)
Trial design	Multicentre, randomised, open-label Phase III study	Multicentre, randomised, open-label, Phase III study followed by 1-	Ongoing, multicentre, Phase III, OLE study	Multicentre, randomised, open-label Phase III study	Open-label, ascending, repeated dose-finding study	Open-label, ascending, repeated dose-finding study

	ONE NCT02121210	EASY NCT02057250	EXTEND NCT01146652	KAKEHASI (NCT02293902)	Open-label, ascending, repeated dose-finding study in pcJIA NCT02776735	Repeated dose-finding study in sJIA NCT02991469
		year OLE				
Intervention(s)	Sarilumab 150 mg Q2W (n=65) Sarilumab 200 mg Q2W (n=67)	Sarilumab 150 mg + cDMARD Q2W via PFP (n=56) Sarilumab 150 mg + cDMARD Q2W via PFS (n=53) Sarilumab 200 mg + cDMARD Q2W via PFP (n=52) Sarilumab 200 mg + cDMARD Q2W via PFS (n=56)	Sarilumab 150/200 mg Q2W + cDMARD (n=1,910) Sarilumab 150/200 mg Q2W monotherapy (n=111)	Sarilumab 150/200 mg Q2W + MTX	Sarilumab three ascending doses (weight dependant)	Sarilumab three ascending doses (weight dependant)
Disease activity	cDMARD irresponsive/intolerant adults (≥18 years) with moderate to severely active RA (SJC ≥4, TJC ≥4, hs-CRP ≥4 mg/L/) and an inadequate response or intolerance to cDMARDs for a minimum of 12 weeks at a stable dosage	[redacted]	MTX/TNFi irresponsive/intolerant adults (≥18 years) with moderate to severely active RA (SJC ≥6, TJC ≥8, hs-CRP ≥0.6 mg/dL), disease duration ≥3 months, and an inadequate response or intolerance to MTX or at least one TNFi as defined by the investigator	NR	NR	NR
Efficacy endpoints	Efficacy ACR20/50/70 at	[redacted]	ACR20/50/70, DAS28, EULAR response over	ACR20 Week 24 Safety parameters to	PK parameters	PK parameters

	ONE NCT02121210	EASY NCT02057250	EXTEND NCT01146652	KAKEHASI (NCT02293902)	Open-label, ascending, repeated dose-finding study in pcJIA NCT02776735	Repeated dose-finding study in sJIA NCT02991469
	week 12	[redacted]	time DAS28 remission over time Change in ACR components and mTSS BL to weeks 48 and 96 Proportion of patients with change in mTSS weeks 48 and 96 Change in HAQ-DI from BL over time	Week 52	Safety parameters JIA ACR30 week 12 Change from BL in JIA ACR components at week 12 Changes in IL-6 biomarkers at week 12	Safety parameters JIA ACR30 week 12 Change from BL JIA ACR components including physician global assessment of disease activity, CHAQ, number of joints with active arthritis/limitation of motion, hs-CRP, ESR and changes in IL-6 biomarkers at week 12
Statistical analyses	Descriptive statistics only Efficacy variables summarised using counts, proportions, mean, SE, and the corresponding 95% CI	[redacted]	Descriptive stats only Efficacy variables summarised using counts, proportions, mean, SE, and the corresponding 95% CI	NR	NR	NR
Location of data collection	28 study locations in seven countries: the US, Chile, Czech Republic, Estonia, Hungary, Poland, and	53 study locations in six countries: the US, Chile, Mexico, Poland, Russia, and South Africa	334 study locations in 28 countries (as per MOBILITY, TARGET, and MONARCH [Table 4.8])	96 study locations in Japan	31 study locations in 14 countries: Argentina, Canada, Chile, Czech Republic, Estonia, Finland, France,	Undisclosed number of study locations in five countries; Estonia, Finland, Italy, Poland, and Spain

	ONE NCT02121210	EASY NCT02057250	EXTEND NCT01146652	KAKEHASI (NCT02293902)	Open-label, ascending, repeated dose-finding study in pcJIA NCT02776735	Repeated dose-finding study in sJIA NCT02991469
	Russia				Italy, Mexico, Netherlands, Poland, Russia, Spain, and the UK	
Assessments	ADA immunoassay at randomisation and weeks 4, 8, 12, and 24 Components of ACR core set and associated measures determined at randomisation and weeks 4, 8, 12, and 24	[redacted]	Components of ACR core set and associated measures determined at randomisation, year 1, year 2 and year 3 Radiographs of hands/wrists and feet at randomisation, year 2 and year 3 Interim data analysis of ongoing study 25 January 2016 — week 96	NR	NR	NR

ACR20/50/70=American College of Rheumatology 20%/50%/70% improvement response; ADA=anti-drug antibodies; AI=auto-injector; bDMARD=biological disease-modifying anti-rheumatic drug; BL=baseline; cDMARD=conventional disease-modifying anti-rheumatic drug; CHAQ=Childhood Health Assessment Questionnaire; DAS28=28-joint disease activity score; ESR=erythrocyte sedimentation rate; EULAR=European League Against Rheumatism; HAQ-DI=Health Assessment Questionnaire Disability Index; HCG=human chorionic gonadotropin; hs-CRP=high-sensitivity C-reactive protein; IL-6=interleukin 6; JIA=juvenile idiopathic arthritis; LEF=leflunomide; mTSS=modified Total Sharp Score; MTX=methotrexate; NCT=national clinical trial; NR=not reported; OLE=open-label extension; pcJIA=polyarticular-course juvenile idiopathic arthritis; PFP=pre-filled pen;PFS=pre-filled syringe; Q2W=once every 2 weeks; RA=rheumatoid arthritis; SC=subcutaneous; SJC=swollen joint count; sJIA=systemic juvenile idiopathic arthritis; SSZ=sulfasalazine; TJC=tender joint count; TNFi=tumour necrosis factor inhibitor

5 Cost-effectiveness

Summary of cost-effectiveness

- An economic analysis is presented that estimates the cost-effectiveness of sarilumab compared with bDMARDs from the perspective of the NHS in the following three broad patient populations with moderate-to-severe RA:
    - Inadequate responders to cDMARDs
    - Intolerant to cDMARDs
    - Inadequate responders to bDMARDs (at least one TNFi)

- A *de novo* model was developed for the economic analysis drawing influence from the most appropriate sources identified in in a systematic literature review (SLR). The model also aligned with assessment group models from TA375[a] and TA195[b]. Key features of the model were as follows:
    - **Model structure:** Individual patient-level simulation with a six-month cycle length to reflect RA patient variability and NICE-recommended timing of treatment decisions
    - **Model inputs:**
        - **Clinical inputs:**
            - **Treatment response:** EULAR response was estimated by mapping the NMA output of ACR response to EULAR categories (none, moderate, good response) to align with NICE continuation rules
            - **HAQ-DI change:** Improvement in HAQ-DI was applied as a relative change from baseline (CFB) and dependent on the level EULAR response (i.e. better EULAR response returned greater improvement in HAQ-DI)
            - **HAQ-DI trajectory:** HAQ-DI remained constant following initial response equally for all bDMARDs based on the long-term extension analysis of HAQ-DI in the EXTEND trial
            - **Time to treatment discontinuation:** Drug retention probabilities were applied to the IL-6 inhibitor class, TNFi class, and other modes of action. These were informed by the respective retentions observed in

[a] Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed
[b] Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor

the RHUMADATA dataset

- **Adverse event inputs:** Serious infection was the only AE with significant costs and effects and was applied according to the rate observed in MOBILITY B for all bDMARDs
- **Mortality:** Hazard ratios were applied to UK life tables to according to patient baseline HAQ-DI score to reflect the disease associated mortality risk
- **Utility inputs:** EQ-5D utility was estimated from patient HAQ-DI using the algorithm developed by Malottki et al (2011) used in TA195[9,68]. The algorithm developed by Hernandez Alava et al (2013) used in TA375 was tested in sensitivity analysis[17,284]
- **Costs and resource use inputs:** Published drug acquisition costs were applied taking into account any non-confidential PAS and an exploratory 15% discount for any confidential PAS. Infusion, nurse visit, monitoring and HAQ-DI dependent routine care costs were applied as reported in Stevenson et al (2016)[67]

- Sarilumab is shown to be cost-effective in incremental analysis compared with all bDMARDs in all severe populations evaluated with ICERs ranging from £7,583 to £18,394 per QALY gained with the exception of RTX tolerant patients in the TNFi inadequate responder subgroup where the ICER was £104,012 per QALY gained vs. rituximab

- Sarilumab is shown to be cost-effective in a restricted population of patients with moderate (>4.0 DAS28 ≤5.1) active disease compared with best supportive care, reporting an estimated ICER of £22,275

- The marginal QALY differences between some of the comparators and the non-statistically significant differences in response from the NMA that contribute to them mean that the cost-effectiveness estimates should be interpreted with caution

- In a cost-minimisation scenario using the national list prices for comparators (15% discount assumed for tocilizumab and abatacept), sarilumab is associated with cost-savings to the NHS vs. all comparators over 12 months except certolizumab pegol due to its complex PAS which provides the first 12 weeks of treatment at no cost

- Deterministic and probabilistic sensitivity analyses were performed testing major assumptions and parameter uncertainty. These demonstrated that sarilumab

remained cost-effective compared with all bDMARDs under alternate assumptions

- The economic evidence suggests sarilumab is an efficient use of NHS resources that would result in similar clinical outcomes and cost savings vs bDMARDs with no additional risk to patient safety

5.1 Published cost-effectiveness studies

5.1.1 Methodology

A systematic literature review (SLR) was undertaken to identify relevant cost-effectiveness studies. The SLR was designed to identify economic evaluations of biological disease-modifying anti-rheumatic drugs (bDMARDs) used to treat patients with moderate-to-severe rheumatoid arthritis (RA). Economic evaluations reporting measures of cost-effectiveness and cost-utility were considered eligible for inclusion. Searches were run in MEDLINE, Embase, Health Economic Evaluation Database (HEED) and NHS Economic Evaluation Database (NHS EED).

The review was carried out in two stages, the first round of searches was conducted on 7th March 2014 and an update was performed to capture additional studies published to 23rd December 2016. The searches from the original review yielded 1,798 records (479 from MEDLINE, 815 from Embase, 118 from HEED, and 386 from NHS EED), with some overlap across the four databases. Removal of duplicates, resulted in 1,580 unique citations. Full-text publications of the studies deemed relevant for further review were screened.

The updated searches for the review yielded 607 records (106 from MEDLINE, 492 from Embase, and nine from NHS EED). NHS EED results were restricted to citations published to March 2015 as this database did not index citations after that date. In addition, HEED which was retired in December 2014, was not searched because the database is no longer publicly available. Removal of duplicates resulted in 511 unique citations for screening.

Studies were considered for inclusion if they were English language cost-benefit analysis (CBA) studies, cost-effectiveness analysis (CEA) studies or cost-utility analysis (CUA) studies that reported results separately for adult patients with moderate-to-severe RA who were refractory or intolerant to conventional DMARDs (cDMARD) or tumour necrosis factor inhibitors (TNFis). In addition, included studies had to have evaluated the use of at least one bDMARD. There were no limitations with regards to study location or date of publication. Conference proceedings were not included due to the limited reporting of methodologies in

such publications. If it was unclear whether the publication assessed the population of interest, the abstract was included if the study participants had RA. The PICOS for inclusion are described in Table 5.1 and PRISMA diagrams of the original and updated SLRs are shown in Figure 5.1.

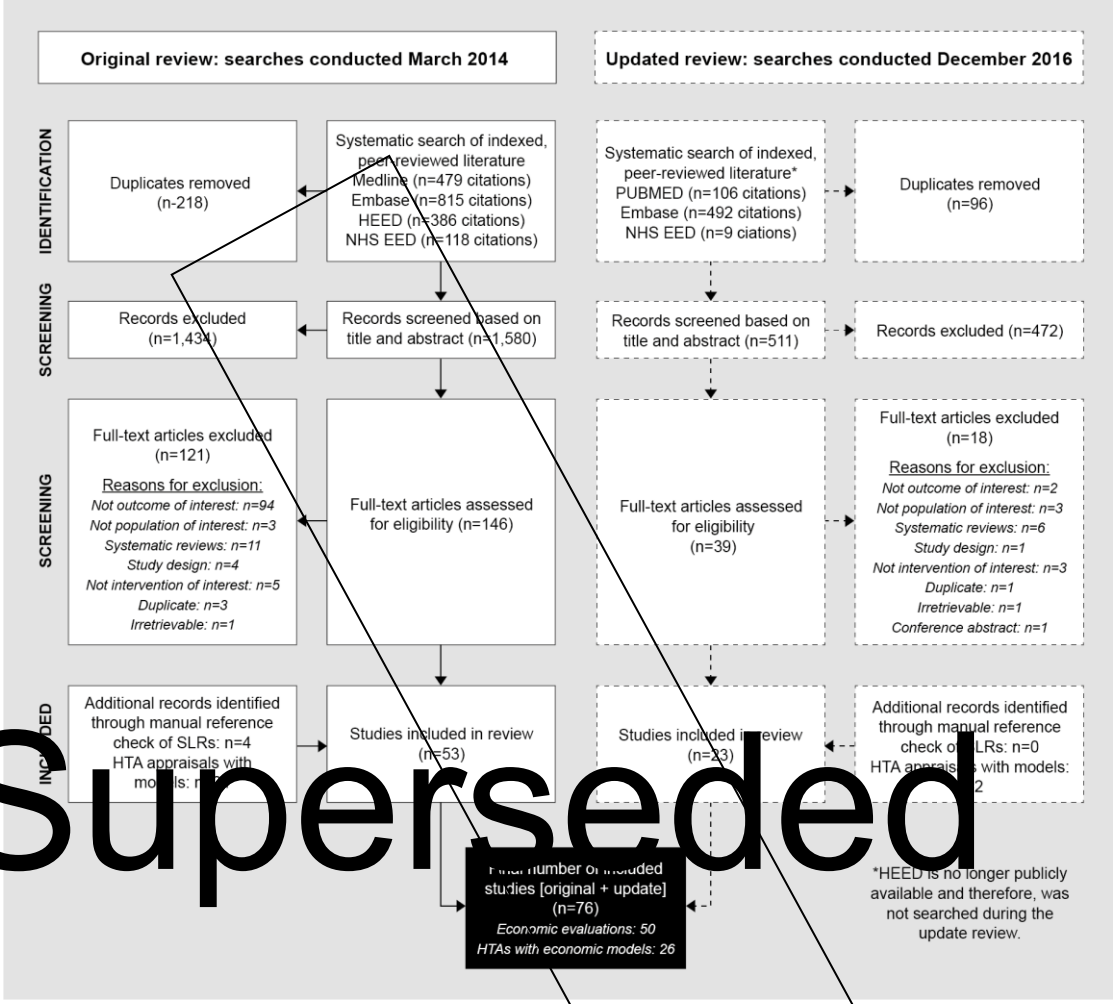
The search strategies used to identify studies in the indexed databases are provided in Appendix 9.

Table 5.1 PICOS inclusion criteria

Domain	Inclusion criteria	Exclusion criteria
Population	Adult patients with moderate-to-severe RA • Refractory to cDMARD or TNFi therapy • Or • Intolerant to cDMARD or TNFi therapy	• Any patient population other than adult patients with moderate-to-severe RA • Studies that do not report separate results for moderate-to-severe RA patients
Intervention/comparators	bDMARDs	Any treatment other than bDMARDs
Outcomes	• Model characteristics • Costs/utilities/disutilities • LYs/QALYs • CERs/ICERs	• Epidemiologic outcomes • Clinical efficacy and safety outcomes • PROs • Other economic outcomes
Study designs	Economic evaluations: trial-based economic analyses and economic models • Cost-benefit analyses • Cost-effectiveness analyses • Cost-utility analyses	The following study designs without an economic evaluation component • Cross-sectional studies • RCTs • Longitudinal observational studies Economic evaluations: trial-based economic analyses and economic models • Cost-minimisation analyses • Cost-consequence analyses • Budget impact analyses
Geography	No limitation in regards to geography	
Time period	No date restrictions were applied	
Language	English language	Non-English language

bDMARD=biologic disease-modifying anti-rheumatic drug; cDMARD= disease-modifying anti-rheumatic drug; CER = cost-effectiveness ratio; DMARD = disease-modifying anti-rheumatic drugs; ICER = incremental cost-effectiveness ratio; LYs = life years; PRO=patient-reported outcomes; RA=rheumatoid arthritis; RCTs=randomised controlled trials; TNFi=tumour necrosis factor inhibitor; QALYs = quality-adjusted life years

Figure 5.1 PRISMA diagram of included studies



HEED=Health Economic Evaluation Database; HTA=Health Technology Assessment; NHS EED=NHS Economic Evaluation Database; SLR=systematic literature review

An additional non-systematic search of technology appraisals involving bDMARDs in patients with moderate-to-severe RA irresponsive/intolerant to cDMARDs or bDMARDs was performed to further inform the model.

5.1.2 Results

The SLR identified 50 published economic evaluations and 26 HTA reports (with economic models) that were relevant to all licensed biologics in RA. The original review identified 29 published economic evaluations and 24 HTA reports (three which were resubmissions to the SMC), while the update of the SLR identified 21 published economic evaluations and 2 HTA reports. Findings are summarised in Table 5.2

Table 5.2 Studies included in the review of economic evaluations

Publication	TNFis					B- and T-cell Inhibitors		IL Inhibitors		JAK Inhibitor	cDMARD	Mixed or Unspecified Biologics	Related Model
	ADA	CZP	ETN	GOL	IFX	ABT	RTX	ANA	TCZ	TFC	MTX, Others		
Original SLR (search conducted in March 2014)													
Barbieri et al. (2005)[285]					✓						✓		None identified
Barton et al. (2004)[286]			✓		✓			✓			✓		Birmingham RA model
Beresniak et al. (2011)[287]	✓		✓		✓	✓	✓						None identified
Beresniak et al. (2013)[288]	✓		✓		✓	✓							None identified
Brennan et al. (2004)[289]			✓								✓		Sheffield RA model
Brennan et al. (2007)[290]											✓	TNFis	Sheffield RA model
CADTH 2010[291]	✓		✓	✓	✓	✓	✓				✓		None identified
Chen et al. (2006)[292]											✓	TNFis	Birmingham RA model
Chiou et al. (2004)[293]	✓		✓		✓			✓					None identified
Choi et al. (2000)[294]			✓								✓		None identified
Cimmino et al. (2011)[295]	✓		✓		✓	✓	✓						None identified
Coyle et al. (2006) (CADTH)[296]			✓		✓						✓		None identified
Diamantopoulos et al. (2012)[297]	✓		✓		✓	✓	✓		✓				None identified
Gissel and Repp (2013)[298]			✓		✓						✓		None identified
Jobanputra et al. (2002)[299]			✓		✓						✓		Birmingham RA model
Kielhorn et al.	✓				✓		✓						None identified

Publication	TNFis					B- and T-cell Inhibitors		IL Inhibitors		JAK Inhibitor	cDMARD	Mixed or Unspecified Biologics	Related Model
	ADA	CZP	ETN	GOL	IFX	ABT	RTX	ANA	TCZ	TFC	MTX, Others		
(2008)[300]													
Kobelt et al. (2003)[301]					✓						✓		None identified
Kobelt et al. (2005)[302]			✓								✓		None identified
Kobelt et al. (2009)[303]	✓		✓		✓								None identified
Lindgren et al. (2009)[304]							✓					TNFi	None identified
Marra et al. (2007)[305]					✓						✓		None identified
Merkesdal et al. (2010)[306]	✓				✓		✓						None identified
Nguyen et al. (2012)[307]	✓	✓	✓	✓	✓						✓		None identified
NICE TA126 (ERG model)[308]	✓				✓		✓				✓		None identified
NICE TA130[309]	✓		✓		✓						✓		Birmingham RA model
NICE TA141[310]						✓					✓	TNFi	None identified
NICE TA186[311]	✓	✓	✓		✓		✓						None identified
NICE TA195 (ERG model)[9]	✓		✓		✓	✓	✓				✓		Birmingham RA model
NICE TA198[312]			✓				✓		✓				Birmingham RA model
NICE TA225[103]	✓	✓	✓	✓	✓		✓				✓		None identified
NICE TA234[312]	✓	✓	✓	✓	✓	✓					✓		None identified
NICE TA247[101]			✓				✓		✓				Birmingham RA model
NICE TA280[313]	✓	✓	✓	✓	✓	✓					✓		None identified
PBAC 2005[314]			✓								✓		None identified

Publication	TNFis					B- and T-cell Inhibitors		IL Inhibitors		JAK Inhibitor	cDMARD	Mixed or Unspecified Biologics	Related Model
	ADA	CZP	ETN	GOL	IFX	ABT	RTX	ANA	TCZ	TFC	MTX, Others		
PBAC 2008[314]			✓								✓		None identified
Puolakka et al. (2012)[315]	✓		✓		✓	✓	✓						None identified
Russell et al. (2009)[316]	✓		✓		✓	✓					✓		None identified
Saraux et al. (2010)[317]	✓		✓		✓	✓	✓						None identified
SMC 323/06[318]			✓		✓		✓						None identified
SMC 400/07[319]						✓			✓			TNFis	None identified
SMC 590/09[320]	✓	✓	✓		✓								None identified
SMC 590/09 Resubmission (related to SMC 590/09)[321]	✓	✓	✓		✓								None identified
SMC 593/09[322]			✓				✓		✓		✓		Birmingham RA model
SMC 719/11[323]	✓	✓	✓	✓	✓	✓			✓		✓		None identified
SMC 719/11 Resubmission (related to SMC 719/11)[324]	✓	✓	✓	✓	✓	✓			✓		✓		None identified
SMC 733/11[325]	✓	✓	✓	✓	✓						✓		None identified
SMC 774/12[326]	✓	✓	✓						✓				Birmingham RA model
SMC 774/12 Resubmission (related to SMC 774/12)[327]	✓	✓	✓						✓				Birmingham RA model
Soini et al. (2012)[328]	✓		✓		✓		✓		✓		✓		None identified

Publication	TNFis					B- and T-cell Inhibitors		IL Inhibitors		JAK Inhibitor	cDMARD	Mixed or Unspecified Biologics	Related Model
	ADA	CZP	ETN	GOL	IFX	ABT	RTX	ANA	TCZ	TFC	MTX, Others		
Tanno et al. (2006)[329]			✓								✓		None identified
Wailoo et al. (2008)[330]	✓		✓		✓			✓			✓		None identified
Wong et al. (2002)[331]					✓						✓		None identified
Wu et al. (2012)[332]	✓		✓		✓		✓						None identified
Updated SLR (search conducted in December 2016)													
Ahmadiani et al. (2016)[333]							✓					cDMARDs	None identified
Athanasakis et al. (2016)[334]	✓		✓						✓		✓		None identified
Cardenas et al. (2016)[335]	✓		✓		✓								None identified
Carlson et al. (2015)[336]	✓								✓				None identified
Claxton et al. (2016)[337]	✓	✓	✓			✓	✓		✓	✓	✓		None identified
Diamantopoulos et al. (2014)[338]	✓	✓	✓		✓	✓	✓		✓				None identified
Eriksson et al. (2014)[339]					✓							cDMARDs	None identified
Hashemi-Meshkini et al. (2016)[340]													None identified
Jalal et al. (2016)[341]					✓				✓		✓		None identified
Joensuu et al. (2016)[342]	✓		✓		✓	✓	✓		✓		✓		None identified
Lee et al. (2015)[343]	✓									✓		TNFis Non-TNFis	None identified
NICE MTA375[344]	✓	✓	✓	✓	✓	✓			✓		✓		None identified

Publication	TNFis					B- and T-cell Inhibitors		IL Inhibitors		JAK Inhibitor	cDMARD	Mixed or Unspecified Biologics	Related Model
	ADA	CZP	ETN	GOL	IFX	ABT	RTX	ANA	TCZ	TFC	MTX, Others		
Stevenson et al. (2016) (related to NICE MTA375)[67]	✓	✓	✓	✓	✓	✓			✓		✓		None identified
NICE TA415[104]		✓									✓		None identified
Manders et al. (2015)[271]						✓	✓					TNFis	None identified
Park et al. (2016)[345]	✓		✓				✓		✓		✓		None identified
Porter et al. (2016)[346]	✓		✓				✓						None identified
Quatuccio et al. (2015)[347]							✓						None identified
Scott et al. (2014)[348]												cDMARDs TNFis	None identified
Tanaka et al. (2015)[349]									✓		✓		None identified
Tanaka et al. (2016)[350]	✓		✓		✓				✓				None identified
Tran-Duy et al. (2014)[351]					✓	✓			✓				None identified
Wu et al. (2015)[352]			✓ biosimilar				✓				✓		None identified

ABT=abatacept; ANA=anakinra; ADA=adalimumab; CADTH=Canadian Agency for Drugs and Technologies in Health; cDMARD=conventional disease-modifying anti-rheumatic drug; CZP=certolizumab; ETN=etanercept; GOL=golimumab; IFX=infliximab; IL=Interleukin; JAK=Janus kinase; MTX=methotrexate; RA= rheumatoid arthritis; RTX=rituximab; TCZ= tocilizumab; TFC= tofacitinib; TNFi=tumour necrosis factor inhibitor.

None of the studies or HTAs identified included sarilumab. The SLR provided insights and guidance on the optimal approach to the economic evaluation presented here. The model specifications including clinical parameters, utility equation, mortality equation, resource use and costs of care associated with RA and bDMARDs, were largely informed by previous models with special consideration to the independent assessment group model in TA375. Summary details of the relevant UK studies identified in the review and a quality assessment of included studies are provided in Appendix 10 and Appendix 11.

5.2 De novo analysis

5.2.1 Patient population

A *de novo* model was developed to assess the cost-effectiveness of sarilumab compared with bDMARDs in three broad populations with active, moderate-to-severe RA as follows: after inadequate response to cDMARDs in combination therapy, after inadequate response to cDMARDs in monotherapy, and after inadequate response to bDMARDs (including at least one TNFi) in combination therapy. These patient populations are within the licensed indication for sarilumab, align with the population eligible for inclusion in the final NICE scope, the systematic review of clinical evidence (see Table 4.1 and Table 4.2), and the population eligible for the MOBILITY, MONARCH and TARGET trials of sarilumab (see Section 4.2).

The model considers moderate active RA and severe active RA patients as separate populations, defined by baseline 28-joint count disease activity score (DAS28) and place in treatment pathway. For the moderate population, analysis is presented for those most at risk of progression to severe disease who have not responded adequately to, or are intolerant of cDMARDs, in line with the NICE scope. These patients are reflected in the model by restricting the population to those with a DAS28 >4.0 ≤5.1 (moderate RA ranges from >3.2 ≤5.1). As discussed in Section 3, some patients with moderate active disease are at risk of rapid disease progression and feedback from UK clinicians suggest that these patients are often maintained on intense cDMARD therapy due to a lack of alternative options (Appendix 12). Likewise, the NICE committee as part of the recent MTA (TA375) acknowledged the importance of having a variety of bDMARDs made available for patients whose disease does not respond to cDMARDs and are likely to progress rapidly with worse outcomes (TA375). However, due to the unacceptable ICERs produced for this patient group, they remain unable to access bDMARDs through the NHS despite a

recognised significant unmet need in UK clinical practice (TA375). By focussing on moderate patients who have not responded adequately to cDMARDs and most risk of rapid progression, as opposed to all moderate patients as evaluated in TA375, we have addressed the greatest unmet need in the moderate RA population where currently there is no NICE-recommended biological treatment.

RA patients with severe disease are defined in the model as having a baseline DAS28 of > 5.1. Current NICE guidance recommends bDMARDs in severe RA populations only and guidance is issued for multiple treatments in several places in the treatment pathway, within the severe population. In line with NICE guidance and the scope for this appraisal, the majority of analyses presented are for the severe patient group and the results are considered to be applicable only in the specific population analysed.

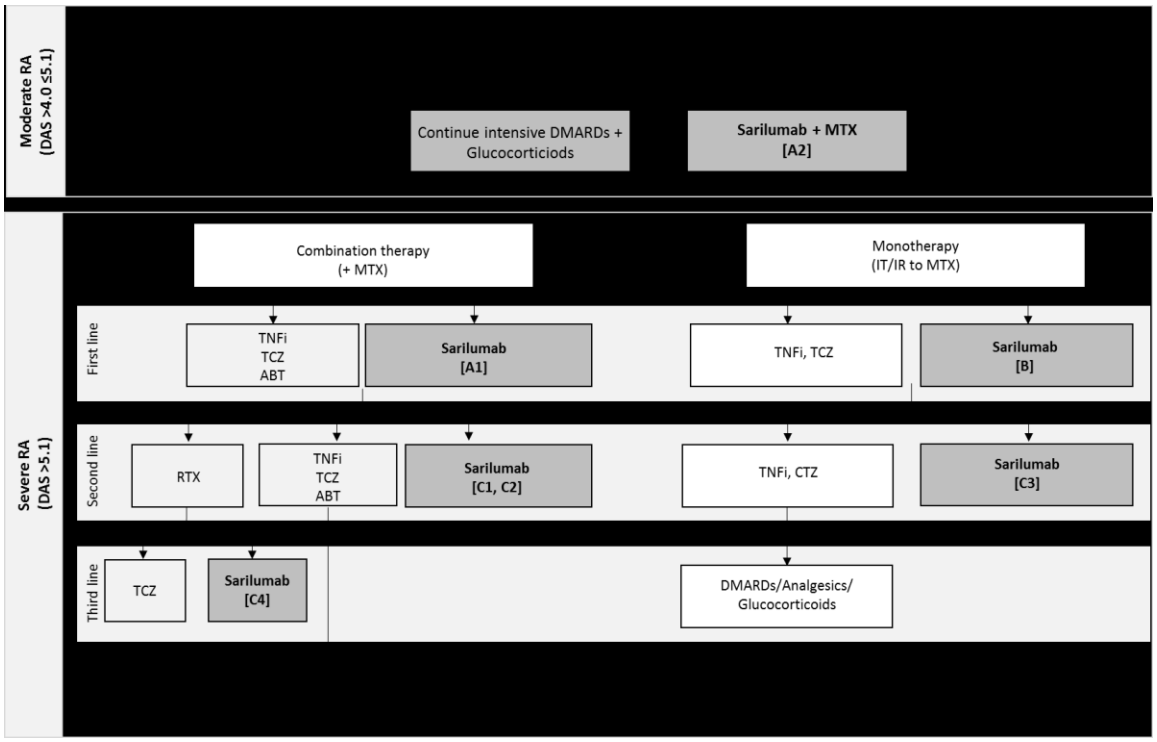
The populations considered as per the scope are described in Table 5.3

Table 5.3 Populations assessed in the de novo analysis

Population	Description	Patient Profile Source
A1	Patients with severe active RA that has not responded adequately to, or are intolerant of therapy with cDMARDs (combination with MTX)	MOBILITY B
A2	Patients with moderate active RA that has not responded adequately to, or are intolerant of therapy with cDMARDs (combination with MTX)	MOBILITY B
B	Patients with severe active RA that has not responded adequately to, or are intolerant of therapy with cDMARDs (monotherapy)	MONARCH
C1	Patients with severe active RA that has not responded adequately to, or are intolerant of therapy with DMARDs including at least one TNFi (RTX intolerant in combination with MTX)	TARGET
C2	Patients with severe active RA that has not responded adequately to, or are intolerant of therapy with DMARDs including at least one TNFi (RTX tolerant in combination with MTX)	TARGET
C3	Patients with severe active RA that has not responded adequately to, or are intolerant of therapy with DMARDs including at least one TNFi (RTX intolerant in monotherapy)	TARGET
C4	Patients with severe, active disease despite treatment with bDMARDs recommended according to NICE guidance (combination with MTX)	TARGET

bDMARD=Biological disease-modifying anti-rheumatic drugs; cDMARD=Conventional disease modifying anti-rheumatic drugs; DMARD=disease-modifying anti-rheumatic drugs; MTX=methotrexate; RA=rheumatoid arthritis; RTX=rituximab; TNFi=tumour necrosis factor inhibitor;

Figure 5.2 Anticipated place in therapy for sarilumab within the UK showing population assessed within the cost-effectiveness



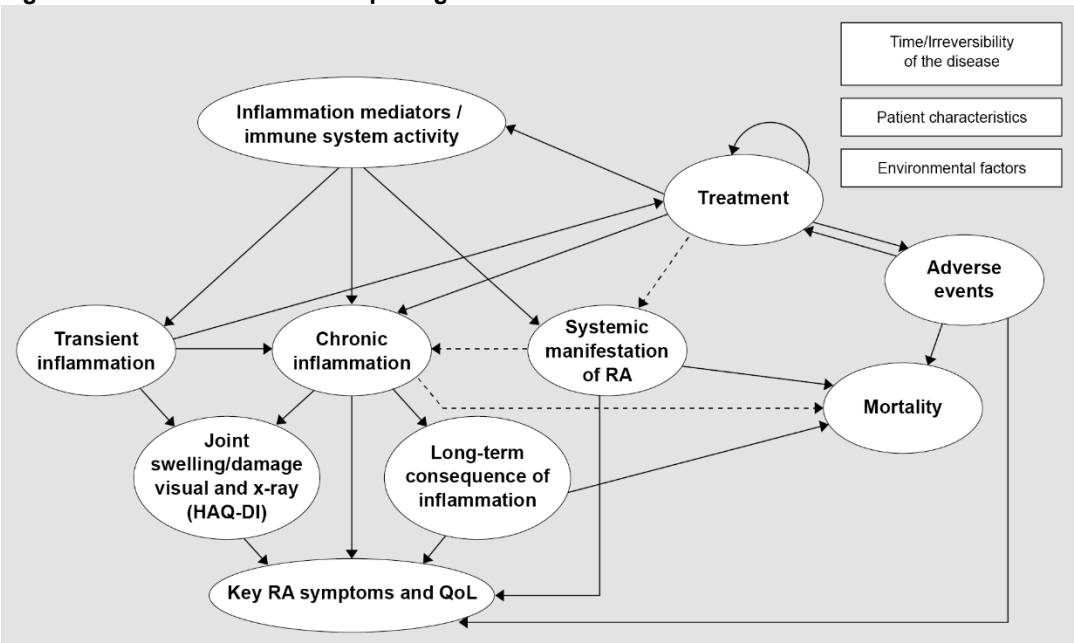
MOBILITY B, MONARCH and TARGET provided individual patient data for use in this patient-level simulation model. These trial data are representative of the UK RA patient populations that are the focus of this assessment. The baseline characteristics of the study populations were compared to those of UK cohorts reported in the British Society for Rheumatology Biologics Register (BSRBR) and were found to be similar (see Section 5.3.1). Base-case analysis is presented for all of the above populations. Sensitivity analyses are presented for only one population within each place in the treatment pathway, based on an assumption that response to treatment is constant within each trial population. The populations for which sensitivity analysis is provided are A1, B, and C1. These represent the patients in the trial that most reflect the patients in UK clinical practice, and those identified in the scope of this assessment.

5.2.2 Model structure

In RA, autoimmune activation leads to inflammation (transient or chronic) and systemic manifestations such as cardiovascular disease, lung fibroses, pleural and pericardial effusions all of which contribute to the disease burden[4,7,52,71]. Progressive and debilitating inflammation can lead to joint swelling, damage and disability usually measured by the HAQ-DI. Chronic inflammation can also have additional long-term consequences, for example tendon rupture, anaemia, severe joint damage

necessitating replacement and vasculitis. These affect quality of life and increase morbidity and mortality[85,86,88,97]. To be effective, treatment must modify disease progression and target both inflammation and irreversible joint destruction[7]. The concept diagram mapping the disease for our de novo model is shown in Figure 5.3.

Figure 5.3 De novo model concept diagram



HAQ-DI=Health Assessment Questionnaire Disability Index; RA=rheumatoid arthritis; QoL=quality of life

For many years, the HAQ-DI has been the gold standard measure of functional disability in rheumatology and is used to measure current level of difficulty in performing activities of daily living[353]. Through many demonstrations of its reliability, validity, adaptability, and ease of use, the HAQ-DI has played a major role in the paradigm shift from reliance on biochemical and physical measurements to emphasis on outcomes that are relevant to the patient[353,354]. Disease progression in RA is often assessed using the HAQ-DI score and the measure has also been found to correlate to differences in QoL, mortality and costs associated with the disease and so it is usually a key driver within cost-effectiveness models[355]. Response to treatment is a key driver for improvements in HAQ-DI score and an important factor in medication compliance and persistence[356].

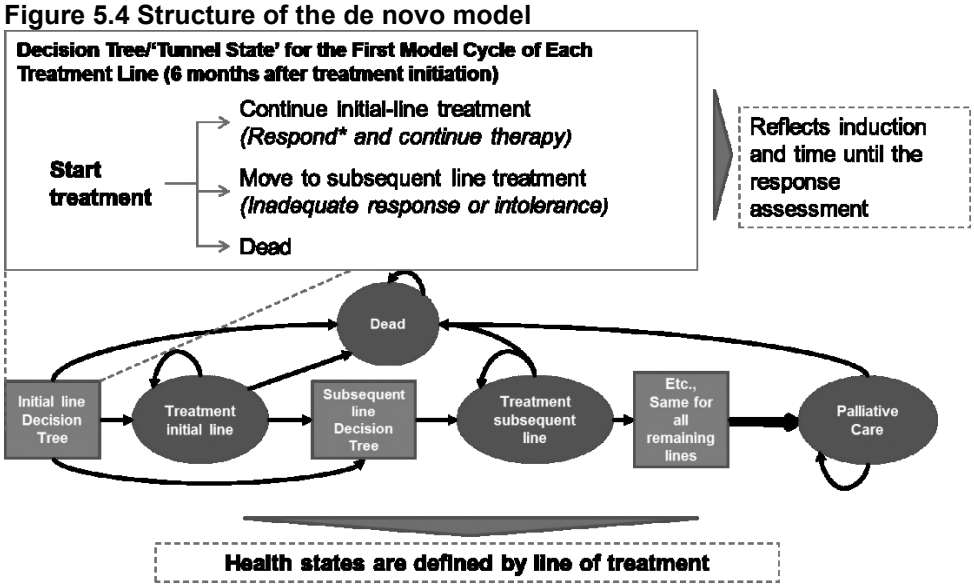
This model is an individual patient-level state transition model in line with the majority of models identified in the SLR. This approach enables the experience and progression of patients to be captured using mutually exclusive 'health states' whilst accounting for patient heterogeneity and the individual factors that influence their risk of worsening disease. Transient inflammation, long-term consequences of chronic

inflammation and systemic manifestations are not modelled explicitly as their consequences are considered to be part of the overall cost of care and the HAQ-DI dependent utility data.

This model employs a six-month cycle length to mirror the frequency of treatment decisions in the UK as per NICE guidance and as has been used in the majority of economic models for RA[289,290,300,338]. In the model, patients follow a sequence of treatments. The model can compare a number of sequences at the same time. The first treatment option in each of the sequences being compared represents the decision problem in terms of which treatment option is the most efficient at that point in the treatment pathway. The approach builds on established and accepted approaches to RA modelling identified in the SLR, most notably the assessment group models in TA375 and TA195 which have been used and accepted by NICE[67,68].

The model structure and major assumptions were externally validated by clinical and health economic experts in an Advisory Board during model development and further validated by a health economist involved in the TA375 AG model during the quality checking stages. Details of the Advisory Board can be found in Appendix 13. A schematic of the structure and flow of the de novo model are described in Figure 5.4 and Figure 5.5.

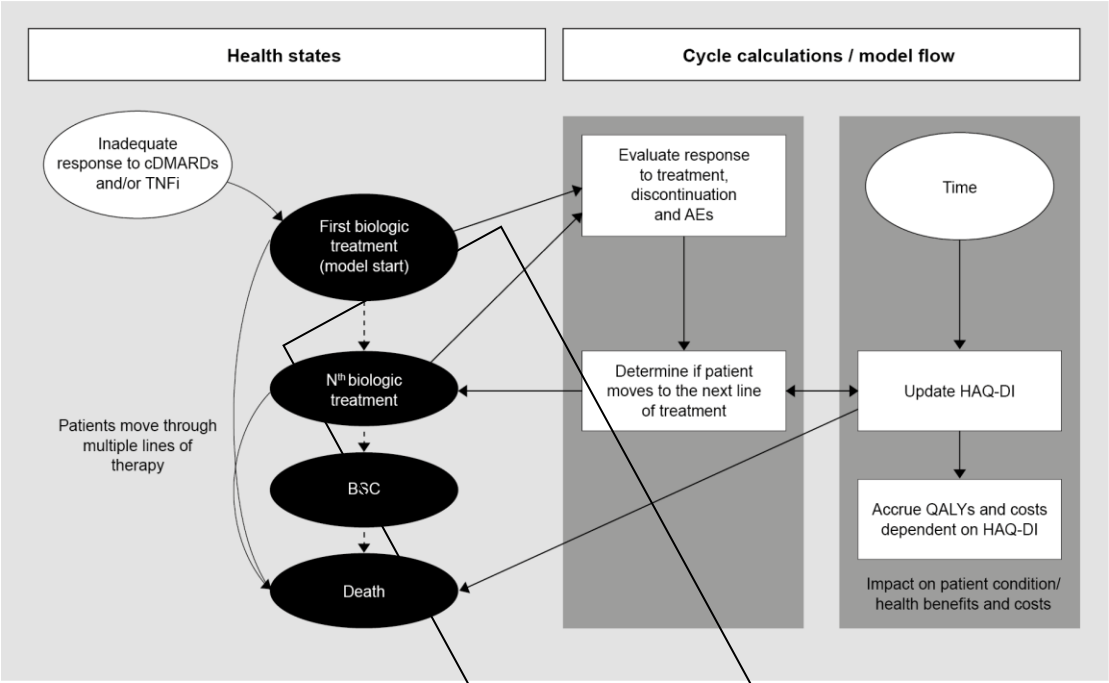
Figure 5.4 Structure of the de novo model



*Response defined by EULAR moderate response

BSC=best supportive care; HAQ-DI=Health Assessment Questionnaire Disability Index; TNFi=tumour necrosis factor inhibitor

Figure 5.5 Model flow schematic



BSC=best supportive care; HAQ-DI=Health Assessment Questionnaire Disability Index; TNFi=tumour necrosis factor inhibitor

Comparators are assessed within a sequence of treatments representing typical pathways followed by patients with RA in the UK. It should be noted that the sequence of treatments patients receive in clinical practice is made on a case-by-case basis and considers multiple factors including patient suitability, preference and clinician judgement. The sequences used in these analyses therefore represent a simplified pathway to enable evaluation, as is common practice in RA modelling. The first treatment in a sequence signifies the comparator being assessed for the sequence in question, the treatments in subsequent lines of therapy are held constant wherever possible for all comparator sequences being assessed (see Table 5.8–Table 5.14).

The economic model aimed to reflect the clinical care pathway and uses a decision tree/'tunnel state' structure until the first assessment of treatment response at the end of the initial six months for each treatment line. At this point the model decision tree assigns one of three possible outcomes to each patient:

Cycle 1 of each treatment:

- Response: Patients achieve at least moderate European League Against Rheumatism (EULAR) response and continue with the treatment. If so, the

patient moves to the 'Continue initial line treatment' health state and stays in this health state until either discontinuation or death

- Non-response: Patients do not achieve at least moderate EULAR response. In this case, the patient starts the subsequent-line treatment, i.e., transitions to the decision tree structure for the next line of treatment

- Death: Patients can die, i.e., can transition to the 'dead' health state

Cycle 2+ of each treatment:

If response is achieved, patients can stay on treatment, discontinue treatment or die at the end of each six-month cycle. This is modelled using a Markov structure with the following transitioning options:

- Stay on treatment

- Move to subsequent-line of treatment, or,

- Move to Best Supportive Care (BSC) consisting of cDMARD/non-biologic treatment

- Death

In clinical practice, patients discontinue treatment for a variety of reasons however the most commonly cited reasons are inadequate response and treatment-emergent adverse events (AEs)[14,105,106,119]. In the initial six months in this model, patients can discontinue treatment due to AEs and if so, they are assumed not to have adequate response as is modelled by the AG in TA375. In subsequent cycles, the model does not distinguish between reasons for discontinuation as discontinuation is captured as a function of the time to treatment discontinuation which encapsulates all reasons for subsequent termination of therapy. Treatment-emergent AEs (TEAEs) are not accounted for by separate health states, their effect on costs and quality of life are assumed to be included in the RA specific utilities and costs linked to patient HAQ-DI. However, the most influential AE, severe infection, is included separately for each line of treatment as a discrete event with management costs and associated disutility.

Each patient is computed through each comparator sequence and at the end of the time horizon, costs and quality-adjusted life years (QALYs) for each sequence are

recorded and the next patient profile is computed. The model repeats this process until all selected profiles have been evaluated and results summed.

Key features of this analysis are presented in Table 5.4

Table 5.4 Features of the de novo analysis

Factor	Chosen values	Justification
Analytical method	Cost-utility analysis with fully incremental analysis	Reference case
Software	Microsoft Excel	Reference case
Time horizon	Lifetime	Reference case
Cycle length	6 months	In line with NICE treatment continuation rules
Half-cycle correction	Yes	Reference case
Were health effects measured in QALYs; if not, what was used?	QALYs	Reference case
Discount of 3.5% for utilities and costs	3.5%	Reference case
Perspective (NHS/PSS)	NHS/PSS	Reference case

PSS=personal social services; QALYs=quality-adjusted life years

5.2.3 Intervention technology and comparators

The only other bDMARD with a similar mode of action to sarilumab i.e., inhibition of IL-6 signalling, recommended by NICE in the UK for the treatment of RA, is tocilizumab. According to expert clinical opinion, it is anticipated that in clinical practice, sarilumab would be considered in the same patient populations and at the same points in the treatment pathway as tocilizumab. Tocilizumab is therefore regarded as the most relevant comparator for sarilumab (and the product most likely to be displaced by sarilumab) in this HTA. All NICE-recommended bDMARDs are included in the scope, therefore the analysis presented compares with the full range of comparators with a particular focus on the comparison with tocilizumab.

All treatments were implemented in the model as per their licensed indication and sarilumab was implemented as per the summary of product characteristics (Appendix 1) as described in Table 5.5. Due to ambiguity in the rituximab label regarding the retreatment schedule, the same assumption used in TA375 i.e., a 9-month retreatment interval, was implemented (i.e. 0.67 2000 mg doses per cycle).

Table 5.5 Treatment schedules and dosages of comparators

Drug	Dose	Frequency
Sarilumab SC[b]	200 mg	Every other week
Abatacept IV[a]	500 mg if <60 kg, 750 mg if 60–100 kg, 1000 mg if > 100 kg	Week 0, 2, 4, then every 4 weeks
Abatacept SC[a]	125 mg SC injections	Once per week
Golimumab SC[a]	50 mg	Once per month
Etanercept SC[a]	25 mg	Twice weekly
Etanercept (biosimilar)SC[a]	50mg	Every week
Adalimumab SC[a]	40 mg	Every other week
Rituximab IV[c]	2,000 mg	Two 1000 mg IV infusions separated by 2 weeks (one course) every 9 months
Certolizumab pegol SC[a]	400 mg induction dose, 200 mg maintenance dose	400 mg dose at week 0, 2, and 4, followed by maintenance dose every other week
Tocilizumab IV[a]	8 mg/kg	Every 4 weeks
Tocilizumab SC[a]	162 mg SC	Every week
Infliximab IV[a] + infliximab biosimilar IV[a]	3 mg/kg	Week 0, 2 and 6, then every 8 weeks.

a https://www.medicines.org.uk/emc/

b Draft SmPC

c. TA375

IV = intravenous; RA = rheumatoid arthritis; Q2W, once every 2 weeks; SC = subcutaneous

The dose of methotrexate (MTX) used in combination with bDMARDs was the mean dose from MOBILITY B as shown in Table 5.6.

Table 5.6 Methotrexate dose used in combination therapy

	Mean	Standard Deviation
MOBILITY B trial	16.6 mg/week	3.8 mg/week

In the base-case, sarilumab is compared with the TNFis as a class (TNFi bundle) as described in Section 4.10 primarily due to the accepted common effect of the class. The market shares of each TNFi were identified from a freedom of information (FOI) request. All UK hospital trusts were asked to provide the number of RA patients treated with each named bDMARD during September – December 2016. A response was obtained from all trusts and the resultant breakdown of TNFi market shares are shown in Table 5.7. It should be noted that the FOI request did not return data for specific lines of therapy, rather overall usage therefore an assumption was made that the total shares apply across all lines of therapy. This assumption is thought to have

negligible impact because it affects only the TNFi class and there are no known reasons for differential prescribing habits among the TNFis between therapy lines.

Table 5.7 Market share of TNFis

TNFi	Market share
Etanercept (Enbrel®)	[redacted]
Etanercept biosimilar (Benepali ®)	[redacted]
Adalimumab (Humira®)	[redacted]
Infliximab (Remicade®)	[redacted]
Infliximab biosimilar (Remsima®/Inflectra®)	[redacted]
Golimumab (Simponi ®)	[redacted]
Certolizumab pegol (Cimzia®)	[redacted]
Total	**100%**

There are a number of local RA treatment guidelines (e.g. Calderdale Clinical Commissioning Group commissioning statement for bDMARDs in the treatment of RA) suggest clinicians/patients have a choice regarding the therapeutic sequence used in used in the treatment of RA[357]. Table 5.8 to Table 5.14 present the treatment sequences used in this economic evaluation. The approach to modelling of sequential treatments in this analysis aimed to take account of the differences in sequencing of biologic therapies in clinical practice. While there is variation in treatment sequences, tocilizumab and abatacept are more commonly used in later lines of therapy by UK rheumatologists (Appendix 12).

It is thought unlikely that both sarilumab and tocilizumab would be used in the same patient at different points in the pathway, i.e., there would not be IL-6 cycling despite the sub-optimal practice of TNFi cycling. Therefore, abatacept (rather than tocilizumab) is used as the common latter line treatment in populations A1 (evaluating first-line bDMARDs in combination therapy), C1 (evaluating second-line bDMARDs [less rituximab] in combination therapy) and C2 (evaluating second-line rituximab in combination therapy) to aid in the isolation of the decision problem and allow sarilumab and tocilizumab to be compared with the same trailing sequence. Where abatacept is compared as the first treatment in a sequence, tocilizumab is used in the third line position.

Rituximab was positioned as the second-line comparator for population A1 (evaluating first-line bDMARDs in combination therapy) due to its clear preferential positioning post TNFi failure from NICE guidance (TA195). An advantage of using the TNFi bundle in population B (evaluating first-line bDMARDs in monotherapy) is that it negates the need for a specific treatment to be placed at second-line and therefore enables consistency of sequencing across comparators. This is also a limitation because not all TNFis have NICE recommendations in monotherapy and there is effective 'double treatment' in the TNFi comparator arm. However, the limitation becomes negligible with the assumption that TNFis are equivalent. The impact of comparing against each individual TNFi is conservatively tested in sensitivity analysis. Populations A2 (evaluating sarilumab following cDMARD failure in moderate disease), C3 (evaluating second-line bDMARDs in monotherapy) and C4 (evaluating third-line (and beyond) bDMARDs in combination therapy) do not present a challenge in constructing comparator sequences because there is no bDMARD trailing sequence to follow the initial comparator. The last therapy in all treatment sequences is BSC which consists of a mix of cDMARDs/non-biologic therapies. The mix of treatments in BSC were combined to simplify the treatment sequences as there is severely limited data to inform treatment patterns post bDMARD and intense cDMARD failure in patients with severe and moderate disease respectively. The sequences for each population are described in Table 5.8 to Table 5.14.

Table 5.8 Treatment sequence comparisons for population A1 (patients with severe active RA that have not responded adequately to therapy with cDMARDs (combination with MTX))

Line 1	Line 2	Line 3	Line 4
Sarilumab + MTX	> Rituximab + MTX	> Abatacept IV + MTX	> BSC
Tocilizumab IV + MTX	> Rituximab + MTX	> Abatacept IV + MTX	> BSC
Tocilizumab SC + MTX	> Rituximab + MTX	> Abatacept IV + MTX	> BSC
TNFi Bundle + MTX	> Rituximab + MTX	> Abatacept IV + MTX	> BSC
Abatacept SC + MTX	> Rituximab + MTX	> Tocilizumab IV + MTX	> BSC

BSC=best supportive care; cDMARD=conventional disease modifying anti-rheumatic drug; IV=intravenous; MTX=methotrexate; SC=subcutaneous; TNFi=tumour necrosis factor inhibitor

Table 5.9 Treatment sequence comparisons for population A2 (patients with moderate active RA that have not responded adequately to or are intolerant of therapy with cDMARDs)

Line 1	Line 2
Sarilumab + MTX	> BSC
BSC	

BSC = best supportive care; cDMARD=conventional disease modifying anti-rheumatic drug; MTX=methotrexate

Table 5.10 Treatment sequence comparisons for population B (patients with severe active RA that have not responded adequately to therapy with cDMARDs (monotherapy))

Line 1	Line 2	Line 3
Sarilumab	> TNFi Bundle	> BSC
Tocilizumab IV	> TNFi Bundle	> BSC
Tocilizumab SC	> TNFi Bundle	> BSC
TNFi Bundle	> TNFi Bundle	> BSC

BSC=best supportive care; cDMARD=conventional disease modifying anti-rheumatic drug; IV=intravenous; SC=subcutaneous; TNFi=tumour necrosis factor inhibitor

Table 5.11 Treatment sequence comparisons for population C1 (patients with severe active RA that have not responded adequately to therapy with DMARDs including at least one TNFi (rituximab intolerant in combination with MTX))

Line 1	Line 2	Line 3
Sarilumab + MTX	> Abatacept IV + MTX	> BSC
Tocilizumab IV + MTX	> Abatacept IV + MTX	> BSC
Tocilizumab SC + MTX	> Abatacept IV + MTX	> BSC
TNFi Bundle + MTX	> Abatacept IV + MTX	> BSC
Abatacept SC + MTX	> Tocilizumab IV + MTX	> BSC

BSC=best supportive care; cDMARD=conventional disease modifying anti-rheumatic drug; IV=intravenous; MTX=methotrexate; SC=subcutaneous; TNFi=tumour necrosis factor inhibitor

Table 5.12 Treatment sequence comparisons for population C2 (patients with severe active RA that have not responded adequately to therapy with DMARDs including at least one TNFi (rituximab-tolerant in combination with MTX))

Line 1	Line 2	Line 3
Sarilumab + MTX	> Abatacept IV + MTX	> BSC
Rituximab + MTX	> Abatacept IV + MTX	> BSC

BSC=best supportive care; cDMARD=conventional disease modifying anti-rheumatic drug; IV=intravenous; MTX=methotrexate; SC=subcutaneous; TNFi=tumour necrosis factor inhibitor

Table 5.13 Treatment sequence comparisons for population C3 (patients for whom rituximab therapy cannot be given because MTX is contraindicated or withdrawn (monotherapy))

Line 1	Line 2
Sarilumab	> BSC
TNFi Bundle	> BSC

BSC=best supportive care; cDMARD=conventional disease modifying anti-rheumatic drug; MTX=methotrexate; TNFi=tumour necrosis factor inhibitor

Table 5.14 Treatment sequence comparisons for population C4 (patients with severe, active disease despite treatment with bDMARDs recommended according to NICE guidance (combination with MTX))

Line 1	Line 2
Sarilumab + MTX	> BSC
Tocilizumab IV + MTX	> BSC
Tocilizumab SC + MTX	> BSC
BSC	-

BSC=best supportive care; bDMARD=biologic disease-modifying anti-rheumatic drug; cDMARD=conventional disease modifying anti-rheumatic drug; IV=intravenous; SC=subcutaneous; TCZ=tocilizumab

5.3 Clinical parameters and variables

5.3.1 Baseline characteristics of patients

From previous RA models it appears that the key parameter affecting patient outcomes in the model is baseline HAQ-DI. In terms of the model parameters, the baseline HAQ-DI of the MOBILITY B, MONARCH and TARGET trial populations were comparable to those reported in a recent UK study investigating tocilizumab in patients from the BSRBR; a population highly aligned to the anticipated sarilumab patient population (see Table 5.15)[358]. In first-line, HAQ-DI from MOBILITY B and MONARCH were 1.75 and 1.63 respectively compared with 1.60 from the BSRBR which is well within the minimal clinically important difference of 0.22[1,56,238,358]. In second-line, HAQ-DI from TARGET was 1.88 compared with 2.00 from the BSRBR which is again well within the MCID[57,358].

Age and weight may also impact cost and utility due to total treatment duration and weight-based dosing regimens with intravenous products. Mean age from the trials was slightly lower than from BSRBR which may be reflective of the BSRBR being a historic dataset and therefore include more patients with longer disease durations. Mean weight was not available from the BSRBR sources however comparing the trial populations with the weight used to calculate annual drug costs of intravenous technologies in TA375 and TA195 (70kg), the trial populations show a small increase. The impact of this weight difference is tested in sensitivity analysis. Patient characteristics for MOBILITY B, MONARCH and TARGET are fully described in Section 4.5.

Table 5.15 Baseline covariates[1,9,17,56,57,61,62,358]

Source	Mean age (years)	Mean weight (kg)	Median HAQ-DI
MOBILITY B (first-line)	51	74	1.75
MONARCH (first-line)	52	72	1.63
BSRBR First-line tocilizumab (Kihara)	58[a]	NR	1.60
BSRBR (first-line) (TA375)	56	NR	NR
TARGET (subsequent-line)	53	78	1.88
BSRBR First-line tocilizumab (Kihara)	58[a]	NR	1.60
BSRBR Subsequent-line tocilizumab (Kihara)	58[a]	NR	2.00

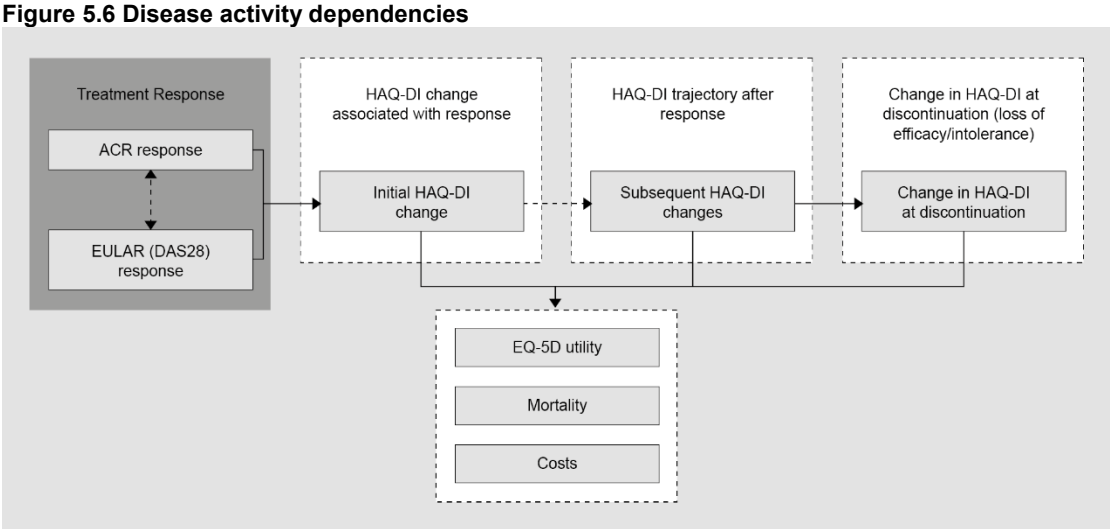
[a] Median (mean not available)

BSRBR =British Society for Rheumatology Biologics Register; bDARD=biologic disease-modifying anti-rheumatic drug; cDMARD=conventional disease-modifying anti-rheumatic drug; IR=irresponsive; NR = not reported;

5.3.2 Treatment response

Disease activity as represented by HAQ-DI affects utilities, costs and mortality. At any time point in the model, HAQ-DI is determined by baseline HAQ-DI, EULAR treatment response, HAQ-DI trajectory after initial response, and discontinuation. The model concept is summarised in Figure 5.6 and described in more detail in the sections below.

Figure 5.6 Disease activity dependencies



ACR=American College Rheumatology; DAS=Disease Activity Score; EULAR=European League Against Rheumatism; EQ-5D=EuroQuol 5-dimension health questionnaire; HAQ-DI=Health Assessment Questionnaire Disability Index;

This model is EULAR-based whereby EULAR categories are used to evaluate response to treatment. This is an advantage over other RA models which use ACR to evaluate treatment response because NICE guidance defines stopping rules for bDMARDs based on DAS28 and EULAR classification (TA375, TA195). The response to treatment for each bDMARD was determined from the NMA. Due to the severe lack of reporting of EULAR outcomes from RCTs identified in the clinical SLR (see Section 4.10), it was not possible to directly identify EULAR reponse for each comparator directly from the NMA. However, ACR outcomes were widely reported in trials enabling robust estimates of these responses to be derived from the NMA.

To obtain the EULAR response rates applied in the model for each comparator, a two-step approach was employed. Firstly, absolute ACR response rates were calculated from the NMA (see Section 4.10) by benchmarking against control (cDMARD for combination therapy and placebo for monotherapy). Control response was deduced from the mean log odds across all control arms and the absolute response for active comparators was calculated by transforming the relative effect versus control to the natural scale. Secondly, the absolute ACR response was

mapped to EULAR response using the matrix developed by the AG in TA375 for all patients from the Veterans Affairs Rheumatoid Arthritis registry (Table 5.16). The model demonstrated stable and good prediction power with root mean squared error <5%. We also tested the impact of alternate assumptions by deriving de novo ACR/EULAR mapping matrices from MOBILITY B at Week 24 and 52, TARGET at Week 12 and 24, and the severe only model from TA375. All models were found to predict well and a description is provided in Appendix 14. The EULAR responses for each bDMARD derived from the mapping exercise are shown in Table 5.17 to Table 5.19. It is important to note that the credible intervals of ACR responses from the NMA, which are used to derive the EULAR responses shown below, of sarilumab vs. all comparators overlap indicating no statistically significant differences. The only exception is with adalimumab in monotherapy where sarilumab showed superior ACR response. The EULAR estimates shown below should therefore be interpreted with caution and are used only to enable reference case analysis mandated by NICE. A cost-minimisation scenario is presented in sensitivity analysis which may be a more appropriate economic evaluation to consider due to the uncertainty in differences of outcomes from the NMA.

Table 5.16 ACR to EULAR mapping

	ACR<20	ACR20–50	ACR50–70	ACR70
EULAR no response	79.6%	7.0%	14.3%	–
EULAR moderate response	14.3%	47.4%	14.3%	50.0%
EULAR good response	6.0%	45.6%	71.4%	50.0%

ACR=American College of Rheumatology; EULAR= European League Against Rheumatism

Table 5.17 cDMARD-IR combination therapy population treatment response based on NMA and TA375 mapping matrix

Comparator	Treatment response with EULAR moderate, % (95%CI)	Treatment response with EULAR good, % (95%CI)
Sarilumab + MTX	[redacted]	[redacted]
TNFi bundle + MTX	[redacted]	[redacted]
Tocilizumab (IV) + MTX	[redacted]	[redacted]
Tocilizumab (SC) + MTX	[redacted]	[redacted]
Abatacept (SC) + MTX	[redacted]	[redacted]

cDMARD=conventional disease modifying anti-rheumatic drug; CI=confidence interval; EULAR= European League Against Rheumatism; IV=intravenous; MTX=methotrexate; SC=subcutaneous;

Table 5.18 cDMARD-IR monotherapy population treatment response based on NMA and TA375 mapping matrix

Comparator	Treatment response with EULAR moderate, % (95%CI)	Treatment response with EULAR good, % (95%CI)
Sarilumab	[redacted]	[redacted]
TNFi bundle	[redacted]	[redacted]
Tocilizumab (IV)	[redacted]	[redacted]
Tocilizumab (SC)	[redacted]	[redacted]

cDMARD=conventional disease modifying anti-rheumatic drug; CI=confidence interval; EULAR= European League Against Rheumatism; IV=intravenous; SC=subcutaneous

Table 5.19 TNF-IR combination therapy population treatment response based on NMA and TA375 mapping matrix

Comparator	Treatment response with EULAR moderate, % (95%CI)	Treatment response with EULAR good, % (95%CI)
Sarilumab + MTX	[redacted]	[redacted]
TNFi bundle + MTX	[redacted]	[redacted]
Tocilizumab (IV) + MTX	[redacted]	[redacted]
Tocilizumab (SC) + MTX	[redacted]	[redacted]
Abatacept (SC) + MTX	[redacted]	[redacted]
Rituximab (IV) + MTX	[redacted]	[redacted]

bDMARD=biological disease-modifying anti-rheumatic drug; CI=confidence interval; EULAR= European League Against Rheumatism; IV=intravenous; MTX=methotrexate; SC=subcutaneous

It is important to note that the credible intervals of ACR responses from the NMA, which are used to derive the EULAR responses shown below, of sarilumab vs. all comparators overlap indicating no statistically significant differences. The only exception is with adalimumab in monotherapy where sarilumab showed superior ACR response. The EULAR estimates shown below should therefore be interpreted with caution as numerical difference in EULAR may not indicate MCID. A cost-minimisation scenario based on the assumption of no MCID between sarilumab and the other bDMARD treatment options is presented in sensitivity analysis justified by the overlapping credible intervals in the NMA. One further significant assumption affects all bDMARDs for population C3 (evaluating second-line bDMARDs in monotherapy). No RCT has been conducted to specifically investigate any bDMARD in monotherapy following failure of a previous bDMARD. As such, response for the comparators in this population can be based on evidence from the cDMARD-IR monotherapy population, or, the TNF-IR combination therapy population. We make the conservative assumption that response for population C3 should be informed by the TNF-IR evidence for the following reasons:

- The EULAR responses in cDMARD-IR combination and monotherapy populations for sarilumab are similar [redacted] and [redacted] respectively) whereas there is a notable difference between the cDMARD-IR and TNF-IR response in combination therapy [redacted] and [redacted] respectively). This is suggestive of prior bDMARD failure having a greater impact on sarilumab response than the presence or absence of concomitant cDMARD therapy

- No advantage is given to sarilumab vs. the TNFi bundle (the only comparator in this population). The sarilumab response in cDMARD-IR monotherapy is slightly higher than it is for the cDMARD-IR combination therapy population whereas the reverse trend is seen for the TNFi bundle. Advantage is therefore given to the TNFi bundle if response for this population is based on the TNF-IR evidence.

BSC, which is applied at the end of every comparator sequence, is assumed to achieve no EULAR response. It should be noted that there is a significant evidence gap in the effectiveness of cDMARDs/non-biologic therapies following bDMARD treatment therefore any assumption on treatment response at this point in the pathway would be associated with considerable uncertainty. The assumption of non-response is also aligned with the AG model in TA375.

5.3.3 Change in HAQ-DI associated with treatment response

The effect of treatment response on disease progression was implemented in the model as a reduction in HAQ-DI. Unlike EULAR response, which is treatment specific, change in HAQ-DI is dependent on the level of response (i.e. EULAR good, EULAR moderate, or non-response). This approach applies an equal benefit to all comparators that achieve a particular level of response. This assumption was considered clinically reasonable and aligns with the approach taken by the AG in TA375. The model applies a relative change from baseline (CFB) in HAQ-DI dependent on the categorical EULAR response. This relationship was determined by analysing Week 24 data from MOBILITY B, as it provided the largest patient population and reflected the model time-cycle. The relationship is shown in Table 5.21 and details of the analysis are provided in Appendix 14. The investigation showed that a EULAR non-response, EULAR moderate response, and EULAR good response was associated with a 7.17%, 22.63% and 47.28% reduction in HAQ-DI from baseline at six months respectively. The observation that an improvement in disease is attained despite failing to achieve a EULAR response is, although

potentially confusing, reasonable since HAQ-DI is measured on a continuous scale and consequently more sensitive to change than categorical EULAR response which is not able to capture smaller improvements. This finding is also clinically reasonable as it suggests that the introduction of any targeted therapy for the disease will have some level of impact even if the response is not clinically meaningful.

Table 5.20 Change in HAQ-DI following EULAR treatment response

Treatment response	Change in HAQ-DI according to EULAR response level	95% CI Lower value	95% CI Upper value
EULAR— No response	−7.17%	−15.98%	1.63%
EULAR—Moderate response	−22.63%	−28.27%	−16.99%
EULAR—Good response	−47.28%	−55.70%	−38.86%

CI=confidence interval; EULAR= European League Against Rheumatism; HAQ-DI=Health Assessment Questionnaire Disability Index

5.3.4 HAQ-DI trajectory following response

Consistent with previous RA models and the literature, patient HAQ-DI following response to bDMARDs was assumed constant in the model[1,9]. This feature was investigated by analysing HAQ-DI scores in sarilumab-treated patients in MOBILITY B and TARGET who were ACR responders at Week 24 and following their HAQ-DI in the open-label extension trial (EXTEND)[59]. Patients with both baseline and post-baseline HAQ-DI scores were assessed and mean and standard deviation (SD) of HAQ-DI values were computed and plotted for each available visit. In both populations, the HAQ-DI score for patients continuing sarilumab treatment in EXTEND remained constant after the initial Week 24 improvement (Figure 5.7 and Figure 5.8).

Figure 5.7 Evolution of HAQ-DI score over time by ACR response at Week 24 among patients in MOBILITY B continuing into EXTEND

ACR20/50/70-American College of Rheumatology 20/50/70% improvement; BL=baseline; HAQ0DI=Health Assessment Questionnaire Disability Index; Wk=week

Figure 5.8 Evolution of HAQ-DI score over time by ACR response at Week 24 among patients in TARGET continuing into EXTEND

ACR20/50/70-American College of Rheumatology 20/50/70% improvement; BL=baseline; HAQ0DI=Health Assessment Questionnaire Disability Index; Wk=week

Similar results were also observed in analysis of the RHUMADATA dataset where average HAQ scores among responding patients was estimated and plotted according to the modified ACR (mACR) response (Appendix 14 and 15) and the same trend is also observed in the BSRBR dataset for EULAR responses as presented in TA375 (Figure 5.9 and Figure 5.10)[17]. RHUMADATA is a large clinical database and registry in Canada set up to evaluate the effectiveness and safety of

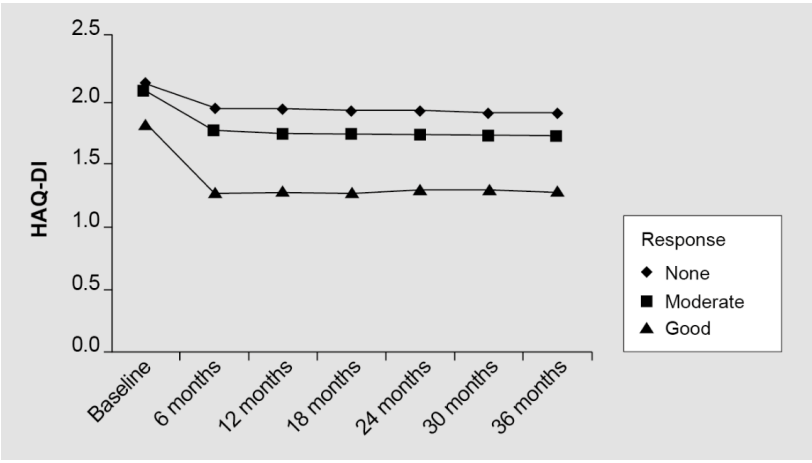
therapies used in rheumatic diseases. We used this registry to supplement our clinical trial data to investigate relationships such as HAQ-DI trajectory and time to treatment discontinuation while on bDMARDs. We considered the BSRBR a suitable supplementary data source however we were unable to obtain access to the full registry data therefore we used RHUMADATA. The advantage of the RHUMADATA dataset is it provides a real-world data source which represents how patients fare in a usual clinical setting rather than under the strict conditions of a RCT. This is of particular significance since RHUMADATA included patients treated with an IL-6 pathway inhibitor which, as a class, have not been available for as long as the older TNFis and therefore any additional data is to be welcomed. RHUMADATA is not a UK registry however recommendations from the Canadian Rheumatology Association suggest that patients are pharmacologically managed in a very similar fashion to the UK as there is much overlap with NICE guidance therefore observations from the registry are expected to be generalisable to the UK[359].

Figure 5.9 HAQ-DI trajectory following response in RHUMADATA

[redacted]

ACR20/50/70=American College of Rheumatology 20/50/70% improvement; HAQ-DI=Health Assessment Questionnaire Disability Index

Figure 5.10 HAQ-DI trajectory following response in the BSRBR[17]



HAQ-DI=Health Assessment Questionnaire Disability Index

In line with previous models, HAQ-DI for patients on BSC with cDMARDs/non-biologic therapy are assumed to increase annually by 0.06 in the base case[17]. This assumption is varied in sensitivity analysis by applying rates of and by 0.012 and 0.045 in sensitivity analyses[67].

5.3.5 HAQ-DI rebound at treatment discontinuation

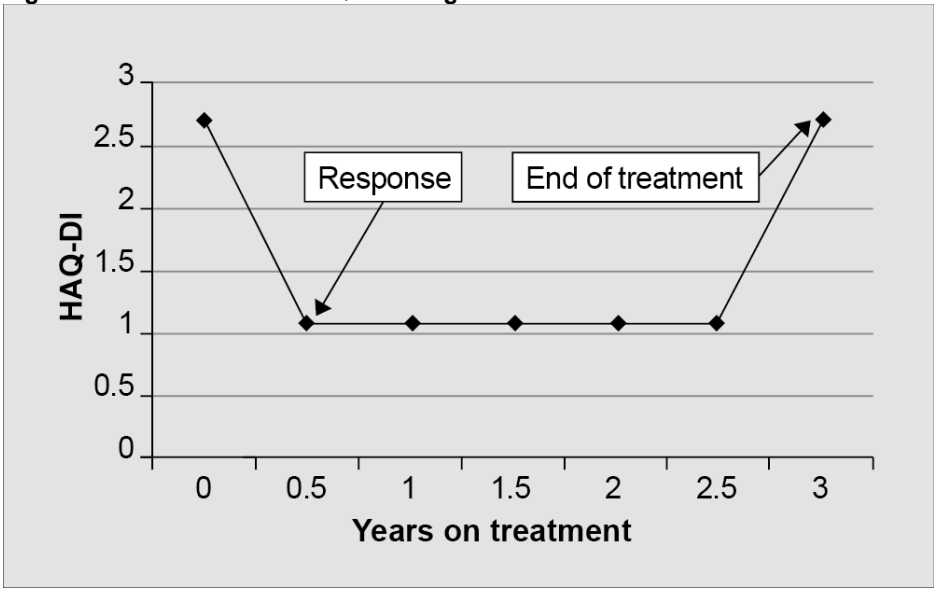
Consistent with the literature, HAQ-DI returns to baseline following withdrawal of treatment[68,290]. When a patient moves to the next treatment in the sequence, the model assumes that:

1. HAQ-DI returns to the baseline value when treatment is discontinued

2. According to clinical experts, when patients switch treatment, there is a small gap of approximately one month between two treatments. However due to the short time period, the gap has a negligible influence on disease progression. In addition, the gap is seen for all biologic treatments and is not specific to one type or class of drug, resulting in minimal incremental differences between the treatment sequences. Thus, this gap is not modelled.

3. The changes in HAQ-DI score at the initiation and discontinuation of a treatment is gradual. To capture this gradual change, a midway HAQ-DI value (midway between baseline and response HAQ-DI value) in the cycle of the treatment switch is modelled.

Figure 5.11 Illustration of HAQ-DI change at the initiation and discontinuation of bDMARD



HAQ-DI=Health Assessment Questionnaire Disability Index

5.3.6 Time to treatment discontinuation

Data on long-term treatment duration is not available from clinical trials and published data is very limited and generally focuses on TNFis. Two approaches for modelling treatment duration were implemented in our model. The base-case used a time-to-event analysis of patients from the RHUMADATA registry. The approach used by the AG in TA375 was implemented in sensitivity analysis. The base-case approach is considered more appropriate because it takes into account differences in retention among different classes of therapy which was established in TA195 and acknowledged in TA375[67,68].

The time-to-event (discontinuation) analysis produced separate Kaplan-Meier curves by drug class: TNFis, IL-6 inhibitors, and other modes of action. Parametric curves were then fitted from six distributions (Weibull, log-normal, log-logistic, exponential, generalised gamma, and Gompertz) to obtain long-term discontinuation curves. Details of the analysis are provided in Appendix 16. The base-case parametrisation is the Gompertz distribution which provided the best fit, the resultant curves for each treatment class are shown in Figure 5.12. The results showed a statistically significant advantage for non-TNFis over TNFis, and a non-significant advantage for IL-6 over TNFis in terms of treatment duration. In sensitivity analysis, we also test the impact of applying the curve associated with the TNFis (worst observed retention) to all comparators.

Figure 5.12 Treatment discontinuation curves by drug class from RHUMADATA fitted with Gompertz distribution

IL6=interleukin 6; TNFi=tumour necrosis factor inhibitor

The second approach applied a probability of discontinuing treatment as a function of the level of EULAR response achieved. Similar to our time-to-event analysis, the TA375 AG applied parametric curves to Kaplan-Meier plots from BSRBR data however this analysis didn't differentiate between class of treatment, only by EULAR responses. Both methods have merit and hence both are presented in our submission.

Treatment discontinuation is implemented in the de novo model as follows. If a patient has no response, treatment is discontinued after the first cycle of treatment. If a patient reaches the minimum response level in the first cycle of treatment, a random treatment discontinuation time is drawn from the selected distribution and treatment discontinues at the end of the model cycle where the simulated discontinuation time falls.

5.3.7 Mortality

While the effect of RA on mortality is well recognised in the literature, no standard approach to incorporating its effects in modelling is evident as several approaches were identified in the economic evaluation SLR. As such, the approach taken by the AG in TA375 was replicated in the analysis where baseline HAQ-DI was assumed to affect mortality and UK life table hazard ratios were adjusted according to Table 5.21. This is considered to be a conservative approach because it does not acknowledge mortality benefits for improvements in disease severity.

Table 5.21 Hazard Ratio for mortality associated with baseline HAQ-DI category[17]

Initial HAQ-DI	HR (95% CI)
0.000	1 referent
0.125–0.375	1.4 (1.1–1.8)
0.500–0.875	1.5 (1.2–1.9)
1.000–1.375	1.8 (1.4–2.2)
1.500–1.875	2.7 (2.2–3.5)
2.000–2.375	4.0 (3.1–5.2)
2.500–3.000	5.5 (3.9–7.7)

CI=confidence interval; HAQ-DI=Health Assessment Disability Index; HR=Hazard Ratio

5.4 Measurement and valuation of health effects

5.4.1 Health-related quality of life data from clinical trials

Utility data from clinical trials are not used to inform the de novo model since EQ-5D utility was not available for all comparators across all patient populations and there is well established practice in estimating utility from patient characteristics in RA. Current modelling methodology makes use of regression-based predictive functions which estimate utility from patient HAQ-DI due to the recognised link between disease severity and quality of life. However, a brief summary of HRQoL from MOBILITY B, TARGET and MONARCH are described below with full results described in Section 4.7. The findings from the RCTs confirm that in line with the model, response to treatment is associated with improvements in quality of life.

5.4.1.1 MOBILITY B

Sarilumab 150 mg and sarilumab 200 mg plus MTX were associated with statistically significant, clinically meaningful and sustained improvements in PROs (including SF-36 PCS and MCS, FACIT-Fatigue, pain, PtGA, and sleep VAS) and HRQoL vs. placebo at Week 24 and Week 52 (Table 4.18 and Figure 4.14)[61,64]. Improvements in PtGA, pain, HAQ-DI, and FACIT-F scores were evident by 2 weeks after the start of treatment Figure 4.13).

5.4.1.2 TARGET

Sarilumab 150 mg and sarilumab 200 mg plus cDMARD were associated with statistically significant and clinically meaningful improvements in PROs including EQ-5D, SF-36 PCS and MCS, FACIT-Fatigue, pain, productivity and participation vs. placebo at Week 24 (Table 4.20)[62,65].

5.4.1.3 MONARCH

Sarilumab 200 mg Q2W was significantly superior to adalimumab 40 mg Q2W in terms of improvements in the SF-36 PCS at Week 24 (Table 4.22). Both groups demonstrated similar improvement in SF-36 MCS at Week 24. An improvement from baseline to Week 24 in EQ-5D and FACIT-F score was observed in both groups, with a trend towards greater improvement in the sarilumab group (Table 4.22)[1,63].

5.4.2 Adverse reactions

Consistent with TA375, the only AE considered to have a meaningful impact HRQoL is serious infection. This AE is often not included within RA models due to the low

frequency of occurrence and lack of differential occurrence rates between comparators. However, to be consistent with the AG approach of TA375, the model includes the impact of serious infection, applied with the rates observed in the trials of the respective populations to all bDMARDs equally (Table 5.22). The equal rate assumption is supported by the NMA. The rates applied in TA375 were tested in sensitivity analysis. Utility loss due to serious infections was taken from TA375, which applied a disutility of 0.156 for 28 days. The model, therefore, included a utility loss of 0.024 for a six-month cycle.

Table 5.22 Per cycle serious infection rates

Drug Class	Source	MOBILITY B	TARGET	MONARCH
bDMARD	Trials	4.0%	1.1%	1.1%
	TA375	3.5%	-	3.5%
BSC	Trials	2.3%	1.1%	2.3%
	TA375	2.6%	-	2.6%

bDMARD=biological Disease-Modifying Anti-Rheumatic Drug; BSC=Best Supportive Care. *Serious infection rate for BSC in monotherapy is assumed the same as in MOBILITY B

5.4.3 Health-related quality of life data used in cost-effectiveness analysis

The SLR described in Section 5.1 was used to identify published predictive functions for estimating utility in RA as mentioned in Section 5.4.1. UK studies were extracted and the methods for incorporating utility were reviewed (Appendix 16 for summary of all identified methods). None of the methods identified in the economic studies offered a methodology that stood out as superior therefore the base-case approach used in the de novo model mirrored the approach taken by the AG in TA195. This was selected because it was considered appropriate, formed the basis for utility estimation in previous appraisals, and has been previously accepted by NICE. The TA195 method utilises a quadratic equation to relate HAQ score to HRQoL in the form of $HRQoL = a - b_1 \times HAQ - b_2 \times HAQ^2$ where the coefficients are shown in Table 5.23. This method differs from the approach taken by the AG in TA375 where pain was first estimated on the VAS scale and utility was then estimated from both HAQ and VAS pain. During early development of the model, the method used in TA375 was considered. However, in the Advisory Board, expert clinical opinion noted that it may double count the effects of pain since the HAQ-DI assessment already includes pain. The TA375 method was however tested in sensitivity analysis along with the method employed in Bansback et al. (2005)[360] because utility is a fundamental determinant of cost-effectiveness and therefore it is critical to understand the uncertainty around the ICER due to utility estimates.

Table 5.23 Coefficients for the Birmingham AG analysis relating HRQoL to HAQ-DI[9]

Coefficient	Point estimate
a	0.804
b_1	−0.203
b_2	−0.045

CI=confidence interval

5.5 Cost and healthcare resource use identification, measurement and valuation

5.5.1 Resource identification, measurement and valuation studies

Relevant costs and resource use were identified from previous UK economic evaluations in the SLR described in Section 5.1. Many appropriate approaches for implementing resource use have been used in UK studies, a summary of these is provided in Appendix 16. Similar to utility estimation methods, no stand out approach was identified therefore resource use and costs of routine management were taken from TA375 which was considered the most appropriate due to being a very recent multiple technology appraisal and considers all the comparators relevant in the decision problem for this appraisal.

5.5.2 Intervention and comparators' costs and resource use

Drug costs were applied in the model using price per pack per product. For products with a subcutaneous administration regimen, price per pack was transformed into a cost per cycle using the dosage and treatment schedule as described in Table 5.5. For IV products, wastage (no vial sharing) was included in the base-case, and no wastage (vial sharing) as scenario analysis. With wastage, if after administering the correct dose to a patient, there was leftover, this was discarded. With vial sharing, the leftover was assumed to be used for another patient or administration, so that no drug is discarded. It should be noted that vial sharing is not a practice supported by the marketing authorisations of the IV products. Sanofi Genzyme do not advocate vial sharing, it is tested in sensitivity analysis to reflect the reality of some UK clinical practice.

Without wastage, drug unit costs were calculated per mg derived from the pack price and divided by the number of vials and the strength of the comparator. With wastage, the required number of vials per administration depends on the vial sizes available and the required dose. First, the dose for each administration was determined for each patient accounting for the patient's weight. Then, the number of vials needed for

the required dose was estimated taking into account the different available vial sizes. For each potential required dose, the optimal combination of vials was determined. The drug cost per administration was then calculated as the sum of the costs of the required vials. The cost per pack for all comparators included in the analysis is shown in Table 5.24.

Table 5.24 Package costs of comparators

Drug	Package	Cost
Sarilumab	200mg syringe x 1	[redacted]
Abatacept[361]	125mg syringe x 4	£1,209.40[a]*
	250mg vial x 1	£302.40[a]*
Golimumab[362]	50mg syringe x 1	£762.97[a]
	100mg syringe x 1	£1,525.94[a]**
Etanercept[363]	50mg syringe x 4	£715.00[a]
	25mg syringe x 4	£357.50[a]
Etanercept (biosimilar)[364]	50mg syringe x 4	£656.00[a]
Adalimumab[365]	40mg syringe x 2	£704.28[a]
Rituximab[366]	500mg vial x 1	£873.15[a]
	100mg vial x 2	£349.25[a]
Certolizumab pegol[367]	200mg syringe x 2	£715.00[a]***
Tocilizumab IV[368]	80mg vial x 1	£102.40[a]*
	200mg vial x 1	£256.00[a]*
	400mg vial x 1	£512.00[a]*
Tocilizumab SC[368]	162mg x 4	£913.12[a]*
Infliximab[369]	100mg vial x 1	£419.62[a]
Infliximab (biosimilar)[370]	100mg vial x 1	£377.66[a]
Methotrexate†[371]	2.5mg tablet x 28	£1.79 [a]
	10mg tablet x 100	£37.89 [a]

[¥]Sanofi Genzyme PASLU Application, [a]http://www.mims.co.uk/, *Exploratory 15% discount applied in base-case due to confidential PAS, **PAS makes 100mg dose available at same price as 50mg dose applied in all analysis, ***12 weeks free PAS applied in all analysis, †Adjuvant therapy added to all bDMARDs in combination analyses.

The cost of the TNFi bundle was calculated using a weighted average of the individual agents informed by market share (Table 5.8).

Cost of infusion and resource requirements for SC administration were applied as in the TA375 AG model. This assumed a fixed cost associated per IV infusion which was inflated to 2015–2016 value using the Personal Social Services Research Unit (PSSRU) unit costs of health and social care inflation index, and 10% of SC administrations would require nurse visits, the unit costs are shown in Table 5.25. This approach may overestimate resource use associated with sarilumab since Sanofi Genzyme provides and funds a homecare service for sarilumab patients at no

cost to the NHS. This is thought to be similar to comparator product manufacturers with SC bDMARDs therefore minimal impact is expected on the results.

Table 5.25 Unit costs of treatment administration

	Mean	SD
Nurse visit[a]	£77	£6
Infusion[b]	£170	£14

a. Source: National schedule of Reference Costs 2015/16 (N29AF)
b. Source: NICE TA375/PSSRU Unit Costs of Health and Social Care 2016
SD = standard deviation

5.5.3 Adverse reaction unit costs and resource use

As described in section 5.4.2, the only AE included in the model was serious infection. The cost associated with this event was taken from TA375 and inflated to 2015–2016 prices using the PSSRU unit costs of health and social care inflation index, this resulted in a per episode cost of £1,588.

5.5.4 Miscellaneous unit costs and resource use

Cost of routine care in RA was based on HAQ ranges as reported in TA375. This method relates the cost of care to HAQ-DI which is assumed to capture any hospitalisations or other costs associated with increased disability and morbidity due to a worsening of the disease. The values are shown in Table 5.26 and were derived from the Norfolk Arthritis Register (NOAR) on inpatient days and joint replacements and multiplied by NHS reference costs. The costs were inflated to 2015–2016 value using the PSSRU unit costs of health and social care inflation index.

Table 5.26 Routine cost of care by HAQ-DI band (TA375, PSSRU Unit Costs of Health and Social Care 2016)

HAQ score	Total costs, 2010 prices, per year	Total cost, inflated to 2015/16 prices, per year
	Mean	Mean
0 < HAQ-DI score ≤ 0.5	£167	£180
0.5 < HAQ-DI score ≤ 1.0	£103	£110
1 < HAQ-DI score ≤ 1.5	£365	£391
1.5 < HAQ-DI score ≤ 2.0	£524	£562
2 < HAQ-DI score ≤ 2.5	£1,246	£1,338
2.5 < HAQ-DI score ≤ 3.0	£2,688	£2,885

HAQ-DI=Health Assessment Questionnaire Disability Index

The SLR described in Section 5.1 identified multiple but similar ways of incorporating routine monitoring testing while receiving treatment. Again, to align with current methodology and ensure consistency, the same practice and costs were applied in the de novo model as in the TA375 AG model. These are described in Table 5.27 –

Table 5.28. The exception to this is the inclusion of monitoring costs for lipid levels with IL-6 pathway inhibitor usage applied to sarilumab and tocilizumab. This was added as lipid monitoring is recommended in the label and draft label for both products, though, at a lower frequency than applied in the model. The frequency of this testing was kept consistent with the other monitoring requirements to align with the accepted assumptions thought to be reflective of clinical practice in England, however it is noted that the frequency of all testing in the TA375 model is higher than the requirements recommended in the label of all the comparators.

Table 5.27. Routine monitoring requirements for bDMARDs

Test	Number of events		
	Before treatment initiation	First 6 months of treatment	After first 6 months of treatment
IL-6			
FBC[a]	1	10	6
ESR[a]	1	0	0
BCP[a]	1	10	6
CXR[a]	1	0	0
Lipid profile[a,b]	1	10	6
Hospital outpatient attendance[a]	1	10	6
Anti-TNF and other biologics			
FBC[a]	1	10	6
ESR[a]	1	0	0
BCP[a]	1	10	6
CXR[a]	1	0	0
Hospital outpatient attendance[a]	1	10	6

BCP, biochemical profile; CXR, chest X-ray; ESR, erythrocyte sedimentation rate; FBC, full blood count; IL-6, interleukin-6; SAR, sarilumab; SmPC, Summary of Product Characteristics; TCZ, tocilizumab; TNF, tumour necrosis factor. [a]Obtained from TA375. [b]Obtained from TCZ SmPC/SAR draft SmPC.

Table 5.28 Costs of routine monitoring

Test	Unit cost
Full blood count (FBC)[a]	£2
Erythrocyte sedimentation rate (ESR)[b]	£3
Biochemical profile (BCP)[b]	£3
Chest X-ray (CXR)[c]	£34
Lipid profile[a]	£2
Hospital outpatient attendance[d]	£143

a. National schedule of Reference Costs 2015/16 (Currency code DAPS03)
b. National schedule of Reference Costs 2015/16 (Currency code DAPS05)
c. TA375/PSSRU Unit Costs of Health and Social Care 2016
d. National schedule of Reference Costs 2015/16 (Service code 410)

5.6 Summary of base-case de novo analysis inputs and assumptions

5.6.1 Summary of base-case de novo analysis inputs

A list of variables included in the base-case with associated distributions is shown in Table 5.29.

Table 5.29 Base-case parameters

Parameter group	Parameter	Base-case value	DSA Lower value	DSA Upper value	PSA distribution	SE
TNFi market shares	ETN	[redacted]	[redacted]	[redacted]	Dirichlet	0.0325
	ETN (biosimilar)	[redacted]	[redacted]	[redacted]	Dirichlet	0.0114
	ADA	[redacted]	[redacted]	[redacted]	Dirichlet	0.0370
	IFX	[redacted]	[redacted]	[redacted]	Dirichlet	0.0005
	IFX (biosimilars)	[redacted]	[redacted]	[redacted]	Dirichlet	0.0049
	GOL	[redacted]	[redacted]	[redacted]	Dirichlet	0.0071
	CTZ	[redacted]	[redacted]	[redacted]	Dirichlet	0.0087
Utility equation coefficients	Intercept	0.804	-	-	-	-
	Current HAQ-DI	−0.203	-	-	-	-
	HAQ-DI^2	−0.045	-	-	-	-
Response rates (cDMARD-IR combination therapy) - EULAR Good	SAR	[redacted]	[redacted]	[redacted]	Beta	[redacted]
	TNFi Bundle	[redacted]	[redacted]	[redacted]	Beta	[redacted]
	TCZ (IV)	[redacted]	[redacted]	[redacted]	Beta	[redacted]
	TCZ (SC)	[redacted]	[redacted]	[redacted]	Beta	[redacted]
	ABT (SC)	[redacted]	[redacted]	[redacted]	Beta	[redacted]
Response rates	SAR	[redacted]	[redacted]	[redacted]	Beta	[redacted]

Parameter group	Parameter	Base-case value	DSA Lower value	DSA Upper value	PSA distribution	SE
(cDMARD-IR combination therapy) - EULAR Moderate	TNFi Bundle	[redacted]	[redacted]	[redacted]	Beta	[redacted]
	TCZ (IV)	[redacted]	[redacted]	[redacted]	Beta	[redacted]
	TCZ (SC)	[redacted]	[redacted]	[redacted]	Beta	[redacted]
	ABT (SC)	[redacted]	[redacted]	[redacted]	Beta	[redacted]
Response rates (cDMARD-IR monotherapy) - EULAR Good	SAR	[redacted]	[redacted]	[redacted]	Beta	[redacted]
	TNFi Bundle	[redacted]	[redacted]	[redacted]	Beta	[redacted]
	TCZ (IV)	[redacted]	[redacted]	[redacted]	Beta	[redacted]
	TCZ (SC)	[redacted]	[redacted]	[redacted]	Beta	[redacted]
Response rates (cDMARD-IR monotherapy) - EULAR Moderate	SAR	[redacted]	[redacted]	[redacted]	Beta	[redacted]
	TNFi Bundle	[redacted]	[redacted]	[redacted]	Beta	[redacted]
	TCZ (IV)	[redacted]	[redacted]	[redacted]	Beta	[redacted]
	TCZ (SC)	[redacted]	[redacted]	[redacted]	Beta	[redacted]
Response rates (TNF-IR) - EULAR Good	SAR	[redacted]	[redacted]	[redacted]	Beta	[redacted]
	TNFi Bundle	[redacted]	[redacted]	[redacted]	Beta	[redacted]
	TCZ (IV)	[redacted]	[redacted]	[redacted]	Beta	[redacted]
	TCZ (SC)	[redacted]	[redacted]	[redacted]	Beta	[redacted]
	ABT (SC)	[redacted]	[redacted]	[redacted]	Beta	[redacted]
	RTX	[redacted]	[redacted]	[redacted]	Beta	[redacted]
Response rates (TNF-IR) - EULAR Moderate	SAR	[redacted]	[redacted]	[redacted]	Beta	[redacted]
	TNFi Bundle	[redacted]	[redacted]	[redacted]	Beta	[redacted]
	TCZ (IV)	[redacted]	[redacted]	[redacted]	Beta	[redacted]
	TCZ (SC)	[redacted]	[redacted]	[redacted]	Beta	[redacted]
	ABT (SC)	[redacted]	[redacted]	[redacted]	Beta	[redacted]
	RTX	[redacted]	[redacted]	[redacted]	Beta	[redacted]
Response based HAQ-DI change	Good	−47.3%	−55.7%	−38.9%	Normal	4.3%
	Moderate	−22.6%	−28.3%	−17.0%	Normal	2.9%
	None	−7.2%	−16.0%	1.6%	Normal	4.5%
HAQ-DI annual increase on BSC	-	0.06	0.048	0.072	Gamma	0.0061
Serious infection rate (cDMARD-IR combination therapy)	bDMARDs	4.0%	3.2%	4.8%	Beta	0.41%
	BSC	2.3%	1.8%	2.8%	Beta	0.23%
Serious infection rate (cDMARD-IR monotherapy)	bDMARDs	1.1%	0.9%	1.3%	Beta	0.1%
	BSC	2.3%	1.8%	2.8%	Beta	0.2%
Serious infection rate (TNF-IR)	bDMARDs	1.1%	0.9%	1.3%	Beta	0.1%
	BSC	1.1%	0.9%	1.3%	Beta	0.1%
Serious infection disutility	-	−0.02	−0.02	−0.03	Beta	0.0024
Serious infection cost	-	£1,587.85	£1,270.28	£1,905.42	Gamma	£162.03
BSC per cycle	-	£360.00	£288	£432	Gamma	36.7354

Parameter group	Parameter	Base-case value	DSA Lower value	DSA Upper value	PSA distribution	SE
cost						
Pack cost of comparators	SAR 200mg syringe x 1	[redacted]	-	-	-	-
	ABT 125mg syringe x 4	£1,027.99	-	-	-	-
	ABT 250mg vial x 1	£257.04	-	-	-	-
	GOL 50mg syringe x 1	£762.97	-	-	-	-
	GOL 100mg syringe x 1	£762.97	-	-	-	-
	ETN 50mg syringe x 4	£715.00	-	-	-	-
	ETN 25mg syringe x 4	£357.50	-	-	-	-
	ETN (biosimilar) 50mg syringe x 4	£656.00	-	-	-	-
	ADA 40mg syringe x 2	£704.28	-	-	-	-
	RTX 500mg vial x 1	£873.15	-	-	-	-
	RTX 100mg vial x 2	£349.25	-	-	-	-
	CTZ 200mg syringe x 2	£715.00	-	-	-	-
	TCZ 80mg vial x 1	£87.04	-	-	-	-
	TCZ 200mg vial x 1	£217.60	-	-	-	-
	TCZ 400mg vial x 1	£435.20	-	-	-	-
	TCZ 162mg syringe x 4	£776.15	-	-	-	-
	IFX 100mg vial x 1	£419.62	-	-	-	-
	IFX (biosimilar) 100mg vial x 1	£377.66	-	-	-	-
	MTX 2.5mg tablet x 28	£1.79	-	-	-	-
	MTX 10mg tablet x 100	£37.89	-	-	-	-
CTZ PAS	# of free administration	9	7	11	Normal	0.9184
Administration unit cost	Nurse visit	£77.24	£61.79	£92.69	Gamma	£6.4367
	Infusion	£170.24	£136.19	£204.28	Gamma	£14.1863
Monitoring unit cost	Full blood count	£1.59	£1.27	£1.91	Gamma	0.1622
	Erythrocyte sedimentation rate	£3.10	£2.48	£3.72	Gamma	0.3163
	Biochemical profile	£3.10	£2.48	£3.72	Gamma	0.3163

Parameter group	Parameter	Base-case value	DSA Lower value	DSA Upper value	PSA distribution	SE
	Chest X-ray	£34.45	£27.56	£41.34	Gamma	3.5154
	Lipid Profile	£1.59	£1.27	£1.91	Gamma	0.1622
	Hospital outpatient attendance	£142.74	£114.19	£171.29	Gamma	14.5656
Routine care cost	0 < HAQ-DI ≤ 0.5	£180	-	-	-	-
	0.5 < HAQ-DI ≤ 1.0	£110	-	-	-	-
	1 < HAQ-DI ≤ 1.5	£391	-	-	-	-
	1.5 < HAQ-DI ≤ 2.0	£562	-	-	-	-
	2 < HAQ-DI ≤ 2.5	£1,338	-	-	-	-
	2.5 < HAQ-DI ≤ 3.0	£2,885	-	-	-	-
	Routine care cost multiplier	1	0.8	1.2	Normal	10%
ACR to EULAR response mapping	ACR < 20 to EULAR non	0.796	-	-	-	-
	ACR 20–50 to EULAR non	0.07	-	-	-	-
	ACR 50−70 to EULAR non	0.143	-	-	-	-
	ACR > 70 to EULAR non	0	-	-	-	-
	ACR < 20 to EULAR Moderate	0.143	-	-	-	-
	ACR 20–50 to EULAR Moderate	0.474	-	-	-	-
	ACR 50–70 to EULAR Moderate	0.143	-	-	-	-
	ACR > 70 to EULAR Moderate	0.5	-	-	-	-
	ACR < 20 to EULAR Good	0.06	-	-	-	-
	ACR 20–50 to EULAR Good	0.456	-	-	-	-
	ACR 50–70 to EULAR Good	0.714	-	-	-	-
	ACR > 70 to EULAR Good	0.5	-	-	-	-
Mortality hazard ratio	Baseline HAQ at 0.000	1	-	-	-	-
	Baseline HAQ at	1.4	-	-	-	-

Parameter group	Parameter	Base-case value	DSA Lower value	DSA Upper value	PSA distribution	SE
	0.125 - 0.375					
	Baseline HAQ at 0.500 - 0.875	1.5	-	-	-	-
	Baseline HAQ at 1.000 - 1.375	1.8	-	-	-	-
	Baseline HAQ at 1.500 - 1.875	2.7	-	-	-	-
	Baseline HAQ at 2.000 - 2.375	4	-	-	-	-
	Baseline HAQ at 2.500 - 3.000	5.5	-	-	-	-

ABT=abatacept; ADA=adalimumab; BSC=best supportive care CTZ=certolizumab pegol; ETN=etanercept; GOL=golimumab; HAQ-DI=Health Assessment Questionnaire Disability Index; IFX=Infliximab; PAS=Patient Access Scheme; PSA= probabilistic sensitivity analysis; RTX=Rituximab; SAR=sarilumab; TCZ=tocilizumab; TNFi=Tumour Necrosis Factor inhibitor; DSA=deterministic sensitivity analysis

5.6.2 Assumptions

A number of assumptions are required in the de novo model. These are described in Table 5.30 with the rationale behind it.

Table 5.30 Assumptions and justifications

Assumption	Rationale
Transient inflammation, long-term consequences of inflammation and systemic manifestations of RA are not required to be explicitly modelled	These basal effects of RA are reflected through patient HAQ-DI score which affects costs and utility therefore they do not require explicit modelling
The six-month cycle length adequately captures the frequency of treatment decisions	NICE guidance mandates stopping rules at six months following initiation of bDMARDs
HAQ-DI, costs and utility are constant within a cycle	The evidence informing these parameters reflect a six-month time period therefore holding parameters constant during a time-cycle is appropriate
Upon treatment discontinuation, HAQ-DI returns to baseline value	Clinical opinion suggests that benefits of treatment (improvement in disease) are rescinded following removal of treatment in line with the majority of RA models
Treatments within a sequence are discontinued/initiated without an interim period	In clinical practice, there is thought to be a gap of approximately one month between treatments. However, this gap has negligible influence on disease progression and therefore is not modelled
The sequences adopted in the model represent standard clinical practice in the UK for the respective populations	To isolate the decision problem of each analysis it is necessary to use consistent sequences among comparator arms wherever possible. This may over-simplify the complexity of treatment decisions however with no formal guidelines on the optimal sequencing of

Assumption	Rationale
	bDMARDs, this is a necessary simplification. The sequences adopted are broadly in line with previous RA models
Population A2 (evaluating sarilumab following cDMARD failure in moderate disease) is adequately captured by modelling patients with 4 < DAS28 ≤5	Clinical opinion suggests that moderate patients with DAS28 >4 are those whose disease may be rapidly progressing and in whom bDMARD treatment is likely to be cost-effective in clinical practice
In population A2 (evaluating sarilumab following cDMARD failure in moderate disease), the BSC comparator is assumed to have no response	This population is representative of patients who have already received, or are currently receiving, intensive cDMARD therapy and failed. BSC is comprised of further cDMARD/non-biologic therapy therefore it is not clinically reasonable to assume a response in these patients who have failed the same treatment immediately prior
In all populations, BSC as a last line of therapy is assumed to have no response	Clinical opinion suggests that following failure of more efficacious bDMARDs (and prior failure of initial cDMARDs), further cDMARD/non-biologic therapy is not likely to achieve any response. This is in line with assumptions from TA375
Biosimilars are assumed to have equal efficacy and positioning to the reference product	The Department of Health has confirmed that a technology appraisal remit referred to NICE enables NICE to decide to apply the same remit, and the resulting guidance, to relevant licensed biosimilar products which subsequently appear on the market. This remit is underpinned by an assumption that the biosimilar product will have the same outcomes as the originator
The TNFis can be modelled as a class	This approach was taken in order to simplify the decision problem. TNFis are often referred to by clinicians as having a class effect which is supported by the undifferentiating results from the NMA. Furthermore, the TNFi class affect the same physiological pathway making it a reasonable assumption that their effects would be similar
The TNFi response in second-line (post bDMARD failure) is informed by the golimumab response from the NMA	As golimumab is the only TNFi to have robust RCT data in this position, it is used as the reference. The same rationale applies for an assumed 'class effect' of TNFis
Where RCT data was not available for SC formulations of ABT and TCZ, the IV response was applied	Clinical opinion suggests it is reasonable to assume the same clinical outcome for different formulations of the same product according to licensed dosing. For SC products, it is recognised that efficacy may be reduced compared to IV so this is considered a conservative assumption
Treatment response for a given therapy in a given population is assumed the same irrespective of the line of treatment	There is limited data to inform how response to treatment may vary in different lines of therapy therefore any assumption adds considerable uncertainty to the sequence effect. Consequently, incorporating such assumptions without robust evidence would detract from the decision point (first comparator in sequence)
Improvement in HAQ-DI is linked only on level of response	Clinical response to treatment is thought to be the only factor influencing improvements in disease in line with TA375 assumptions
HAQ-DI remains constant following initial improvement following response for all comparators	Investigation from the sarilumab long-term extension study (EXTEND), RHUMADATA registry patients, and BSRBR registry patients all indicate that HAQ remains constant while response is maintained
Treatment with IL-6 pathway inhibitors require additional lipid monitoring	The label for sarilumab and tocilizumab recommend monitoring for lipid levels during therapy. This is implemented in the model at the same schedule as other

Assumption	Rationale
	routine monitoring tests (as applied in TA375) though this may be an over-estimation of testing in clinical practice
The weights of patients in MOBILITY B, MONARCH and TARGET are representative of UK patients	To maintain internal validity of the trial data, cohorts unadjusted for weight are applied in the model. This may overestimate the cost of IV treatments due to a higher proportion of heavier patients in the trials than might be expect within the UK RA patient population (based on annual drug cost assumptions in TA375 and TA195). This is tested in the sensitivity analysis

bDMARD=biological Disease-Modifying Anti-Rheumatic Drug; BSC=best standard of care; cDMARD=conventional Disease-Modifying Anti-Rheumatic Drug; DAS28=Disease Activity Score 28; HAQ-DI= Health Assessment Questionnaire Disability index; Il-6=interleukin-6; IV=intravenous; NMA=network meta-analysis; RCT=randomised controlled trial; SC=subcutaneous; TNFi=Tumour Necrosis Alpha inhibitor

5.7 Base-case results

5.7.1 Base-case incremental cost-effectiveness analysis results

For the base-case, fully incremental results are presented in line with the reference case. Comparators are ordered from least to most expensive in terms of total cost. Incremental costs and QALYs are presented with reference to the therapy in the previous row in the table. ICERs are presented for sarilumab vs. each comparator (ICER represents the ICER for sarilumab), and ICERs/domination rules presented for the fully incremental analysis. As per the standard rules of dominance, a result of 'dominant' means the reference comparator is more effective AND less costly, and a result of 'dominated' means the reference comparator is less effective AND more costly. A summary table of ICERs for sarilumab from incremental analysis is shown in Table 5.31.

Whilst interpreting the results, it is important to recognise the marginal QALY differences between some of the comparators and the non-statistically significant differences in response from the NMA that contribute to these.

Table 5.31 Summary of base-case ICERs for sarilumab from incremental analysis (all populations)

Population	Sarilumab ICER
A1	£9,631
A2	£22,275
B	£12,995
C1	£7,583
C2	£104,012
C3	£13,878
C4	£18,394

ICER=incremental cost-effectiveness ratio

The results suggest sarilumab is cost-effective compared with the comparators using a willingness-to-pay threshold of £20K to £30K per QALY gained for all populations

except C2 (where patients are able to tolerate rituximab after TNFi failure) in which the estimated ICER is £104,012 per QALY gained. For populations A1, A2, B, C1, C3 and C4, sarilumab is associated with estimated ICERs ranging from £7,583 per QALY gained in population C1 (where patients are unable to receive rituximab after TNFi failure) to £22,275 per QALY gained in population A2 (moderate patients who have not responded adequately/intolerant to cDMARDs).

Similarly, sarilumab is estimated to attain a positive incremental net monetary benefit compared with all comparators (£29,357 to £10,138) using a £30K threshold for all populations except C2 (-£11,605). Using a 20K threshold, sarilumab is estimated to attain a positive INB against all comparators (£27,911 to £3,185) in all populations except A2 (-£5,461) and C2 (-£13,173).

Compared with tocilizumab, sarilumab is dominant in population A1 and consistently less costly and less effective in the remaining populations where tocilizumab was a comparator. In population A1, sarilumab is estimated to attain marginal QALY gains vs. tocilizumab SC & IV ([redacted] respectively) at significantly lower cost [redacted].

In populations B, C1 and C4, where sarilumab was less costly and less effective, it is less informative to view the result in terms of ICERs. Instead, one might consider the INB framework where incremental costs and QALYs are transformed to an overall cost gain/loss as a function of the willingness-to-pay threshold. If it is considered that the NHS would be willing to forgo QALYs in favour of an alternative therapy due to the cost savings it brings, one might expect a higher value to be placed on the QALY than for therapies which lead to QALY gains (i.e. a higher threshold value). Assuming a doubling of the standard threshold value (to £60,000 per QALY), sarilumab is estimated to result in an INB vs. tocilizumab SC of over £14,500 in population B where the incremental QALY is approximately [redacted] and the incremental cost is approximately [redacted]. The INB of sarilumab is driven by the very marginal QALY difference for the additional cost associated with tocilizumab. The same trend is observed in populations C1 and C4 where the INB of sarilumab over tocilizumab SC is over £3,000 and £500 respectively. Versus the IV formulation of tocilizumab, the INB of sarilumab using a £60,000 per QALY threshold is over £14,000, £6,000, and £3,500 in population B, C1 and C4 respectively.

Table 5.32 Population A1 - Deterministic Base-case results: Patients with severe active RA that has not responded adequately to, or are intolerant of therapy with cDMARDs (combination with MTX)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Sarilumab ICER (£) versus each alternative technology (QALYs)	ICER (£) incremental (QALYs)	Sarilumab INB (£) at a threshold of £20,000	Sarilumab INB (£) at a threshold of £30,000
TNFi Bundle + MTX	[redacted]	15.46	[redacted]	-	-	-	£9,631	-	£6,558	£12,882
SAR + MTX	[redacted]	15.46	[redacted]	[redacted]	0.00	[redacted]	-	£9,631	-	-
TZC (SC) + MTX	[redacted]	15.46	[redacted]	[redacted]	0.00	[redacted]	Dominant	Dominated	£14,259	£15,726
TCZ (IV) + MTX	[redacted]	15.46	[redacted]	[redacted]	0.00	[redacted]	Dominant	Dominated	£15,267	£16,372
ABT (SC) + MTX	[redacted]	15.46	[redacted]	[redacted]	0.00	[redacted]	Dominant	Dominated	£27,911	£29,357

ABT=abatacept; ICER=incremental cost-effectiveness ratio; IV=intravenous; LYG= life years gained; QALYs=quality-adjusted life years; SAR=sarilumab; SC=subcutaneous; TNFi=tumour necrosis factor inhibitor; TCZ=tocilizumab

Table 5.33 Population A2 - Deterministic Base-case results: Patients with moderate active RA that has not responded adequately to, or are intolerant of therapy with cDMARDs (combination with MTX)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Sarilumab ICER (£) versus each alternative technology (QALYs)	ICER (£) incremental (QALYs)	Sarilumab INB (£) at a threshold of £20,000	Sarilumab INB (£) at a threshold of £30,000
BSC + MTX	[redacted]	16.81	[redacted]	-	-	-	£22,275	-	-£5,461	£18,538
SAR + MTX	[redacted]	16.81	[redacted]	[redacted]	0.00	[redacted]	-	£22,275	-	-

BSC=best standard care; ICER=incremental cost-effectiveness ratio; LYG= life years gained; QALYs=quality-adjusted life years; SAR=sarilumab

Table 5.34 Population B - Deterministic Base-case results: Patients with severe active RA that has not responded adequately to, or are intolerant of therapy with cDMARDs (monotherapy)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Sarilumab ICER (£) versus each alternative technology (QALYs)	ICER (£) incremental (QALYs)	Sarilumab INB (£) at a threshold of £20,000	Sarilumab INB (£) at a threshold of £30,000
TNFI Bundle	[redacted]	14.94	[redacted]	-	-	-	£12,995	-	£8,199	£19,903
SAR	[redacted]	14.94	[redacted]	[redacted]	0.00	[redacted]	-	£12,995	-	-
TCZ (IV)	[redacted]	14.94	[redacted]	[redacted]	0.00	[redacted]	Less costly, less effective	£1,013,528	£15,108	£14,956
TCZ (SC)	[redacted]	14.94	[redacted]	[redacted]	0.00	[redacted]	Less costly, less effective	Dominated	£15,651	£15,499

ICER=incremental cost-effectiveness ratio; IV=intravenous; LYG= life years gained; QALYs=quality-adjusted life years; SAR=sarilumab; SC=subcutaneous; TNFi=tumour necrosis factor inhibitor; TCZ=tocilizumab

Table 5.35 Population C1 - Deterministic Base-case results: Patients with severe active RA that have not responded adequately to, or are intolerant of therapy with DMARDs including at least one TNFi (RTX intolerant in combination with MTX)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Sarilumab ICER (£) versus each alternative technology (QALYs)	ICER (£) incremental (QALYs)	Sarilumab INB (£) at a threshold of £20,000	Sarilumab INB (£) at a threshold of £30,000
TNFi Bundle + MTX	[redacted]	14.34	[redacted]	-	-	-	£7,583	-	£9,922	£17,913
SAR + MTX	[redacted]	14.34	[redacted]	[redacted]	0.00	[redacted]	-	£7,583	-	-
TCZ (SC) + MTX	[redacted]	14.34	[redacted]	[redacted]	0.00	[redacted]	Less costly, less effective	£77,024	£12,293	£10,138
TCZ (IV) + MTX	[redacted]	14.34	[redacted]	[redacted]	0.00	[redacted]	Less costly, less effective	Dominated	£15,306	£13,150
ABT (SC) + MTX	[redacted]	14.34	[redacted]	[redacted]	0.00	[redacted]	Less costly, less effective	Dominated	£25,173	£23,265

ABT=abatacept; ICER=incremental cost-effectiveness ratio; IV=intravenous; LYG= life years gained; QALYs=quality-adjusted life years; SAR=sarilumab; SC=subcutaneous; TNFi=tumour necrosis factor inhibitor; TCZ=tocilizumab

Table 5.36 Population C2 - Deterministic Base-case results: Patients with severe active RA that have not responded adequately to, or are intolerant of therapy with DMARDs including at least one TNFi (RTX tolerant in combination with MTX)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Sarilumab ICER (£) versus each alternative technology (QALYs)	ICER (£) incremental (QALYs)	Sarilumab INB (£) at a threshold of £20,000	Sarilumab INB (£) at a threshold of £30,000
RTX + MTX	[redacted]	14.34	[redacted]	-	-	-	£104,012	-	-£13,173	-£11,605
SAR + MTX	[redacted]	14.34	[redacted]	[redacted]	0.00	[redacted]	-	£104,012	-	-

ICER=incremental cost-effectiveness ratio; LYG= life years gained; QALYs=quality-adjusted life years; RTX=rituximab; SAR=sarilumab

Table 5.37 Population C3 - Deterministic Base-case results: Patients with severe active RA that have not responded adequately to, or are intolerant of therapy with DMARDs including at least one TNFi (RTX therapy cannot be given because MTX is contraindicated or withdrawn [monotherapy])

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Sarilumab ICER (£) versus each alternative technology (QALYs)	ICER (£) incremental (QALYs)	Sarilumab INB (£) at a threshold of £20,000	Sarilumab INB (£) at a threshold of £30,000
TNFi	[redacted]	14.34	[redacted]	-	-	-	£13,878	-	£6,882	£18,125
SAR	[redacted]	14.34	[redacted]	[redacted]	0.00	[redacted]	-	£13,878	-	-

ICER=incremental cost-effectiveness ratio; LYG= life years gained; QALYs=quality-adjusted life years; SAR=sarilumab; TNFi=tumour necrosis factor inhibitor

Table 5.38 Population C4 - Deterministic Base-case results: Patients with severe, active disease despite treatment with bDMARDs recommended according to NICE guidance (combination with MTX)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Sarilumab ICER (£) versus each alternative technology (QALYs)	ICER (£) incremental (QALYs)	Sarilumab INB (£) at a threshold of £20,000	Sarilumab INB (£) at a threshold of £30,000
BSC	[redacted]	14.34	[redacted]	-	-	-	£18,394	-	£3,185	£23,015
SAR + MTX	[redacted]	14.34	[redacted]	[redacted]	0.00	[redacted]	-	£18,394	-	-
TCZ (SC) + MTX	[redacted]	14.34	[redacted]	[redacted]	0.00	[redacted]	Less costly, less effective	£63,276	£13,250	£10,189
TCZ (IV) + MTX	[redacted]	14.34	[redacted]	[redacted]	0.00	[redacted]	Less costly, less effective	Dominated	£16,263	£13,201

BSR=best standard care; ICER=incremental cost-effectiveness ratio; IV=intravenous; LYG= life years gained; QALYs=quality-adjusted life years; SAR=sarilumab; SC=subcutaneous; TCZ=tocilizumab

5.8 Sensitivity analyses

5.8.1 Probabilistic sensitivity analysis

As described in Section 5.2.1 probabilistic sensitivity analysis was performed for one set of analyses in each of the three populations on which the response and patient data were drawn from (i.e. one for the MOBILITY B derived population [cDMARD-IR], one for the MONARCH derived population [cDMARD-IR monotherapy], and one for the TARGET derived population [TNF-IR]). All variables subject to parameter uncertainty were included in the PSA and these are described in Table 5.29.Tabulated results are presented along with cost-effectiveness acceptability curves (CEACs), which shows the proportion of simulations for which each comparator is considered cost-effective over a range of thresholds.

The same trend is observed in the PSA as the deterministic analysis. The results suggest sarilumab is cost-effective vs. the comparators at willingness-to-pay thresholds of £20K to £30K per QALY gained in all populations. Sarilumab is associated with estimated probabilistic ICERs of £7,948, £13,586 and £6,222 per QALY gained from incremental analysis in populations A1, B and C1 respectively.

5.8.1.1 RESULTS

Table 5.39 Population A1 - Probabilistic Base-case results: Patients with severe active RA that has not responded adequately to, or are intolerant of therapy with cDMARDs (combination with MTX)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Sarilumab ICER (£) vs. each alternative technology (QALYs)	ICER (£) incremental (QALYs)
TNFi Bundle + MTX	[redacted]	15.56	[redacted]	-	-	-	£7,948	-
SAR + MTX	[redacted]	15.56	[redacted]	[redacted]	0.00	[redacted]	-	£7,948
TZC (SC) + MTX	[redacted]	15.56	[redacted]	[redacted]	0.00	[redacted]	Dominant	Dominated
TCZ (IV) + MTX	[redacted]	15.56	[redacted]	[redacted]	0.00	[redacted]	Dominant	Dominated
ABT (SC) + MTX	[redacted]	15.56	[redacted]	[redacted]	0.00	[redacted]	Dominant	Dominated

ICER=incremental cost-effectiveness ratio; LYG= life years gained; QALYs=quality-adjusted life years

Figure 5.13 Population A1 - CEAC

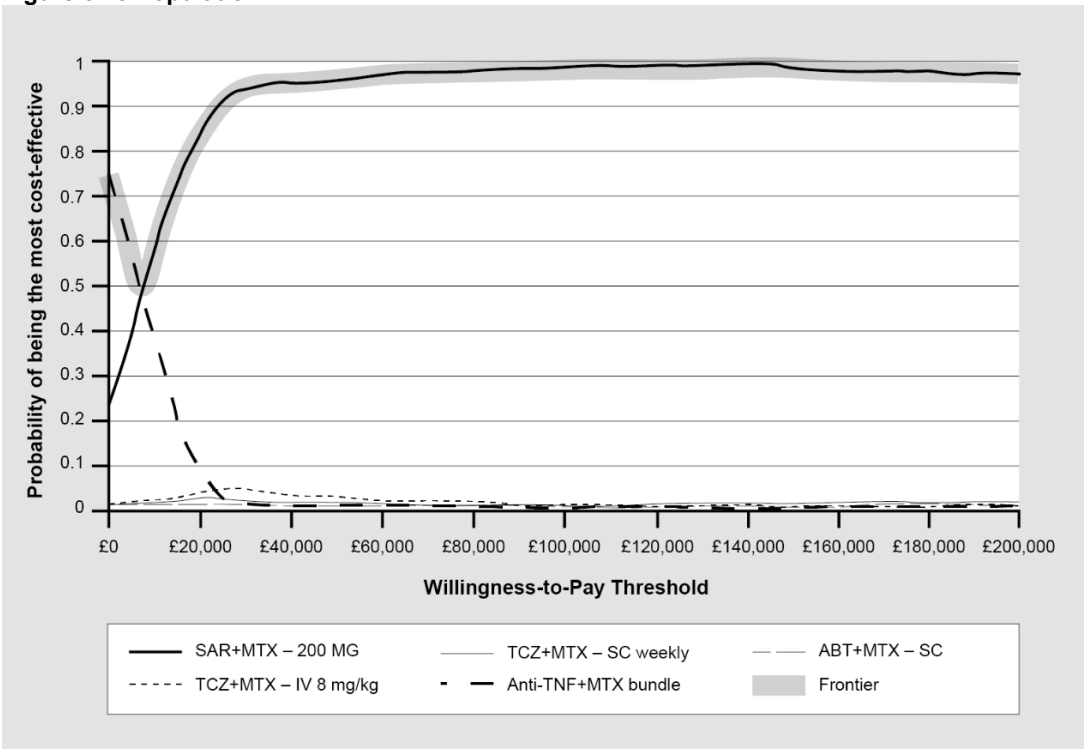


Table 5.40 Population B - Probabilistic Base-case results: Patients with severe active RA that has not responded adequately to, or are intolerant of therapy with cDMARDs (monotherapy)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Sarilumab ICER (£) versus each alternative technology (QALYs)	ICER (£) incremental (QALYs)
TNFi Bundle	[redacted]	15.00	[redacted]	-	-	-	£13,586	-
SAR + MTX	[redacted]	15.00	[redacted]	[redacted]	0.00	[redacted]	-	£13,586
TZC (SC)	[redacted]	15.00	[redacted]	[redacted]	0.00	[redacted]	Less costly, less effective	£2,159,489
TCZ (IV)	[redacted]	15.00	[redacted]	[redacted]	0.00	[redacted]	Less costly, less effective	Dominated

ICER=incremental cost-effectiveness ratio; LYG= life years gained; QALYs=quality-adjusted life years

Figure 5.14 Population B - CEAC

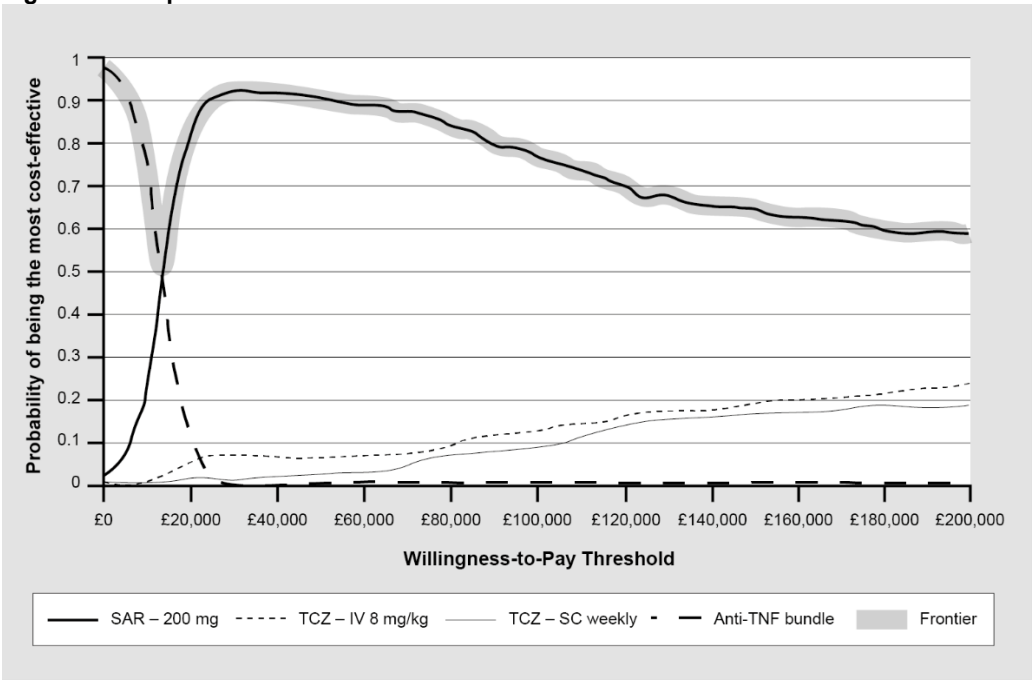
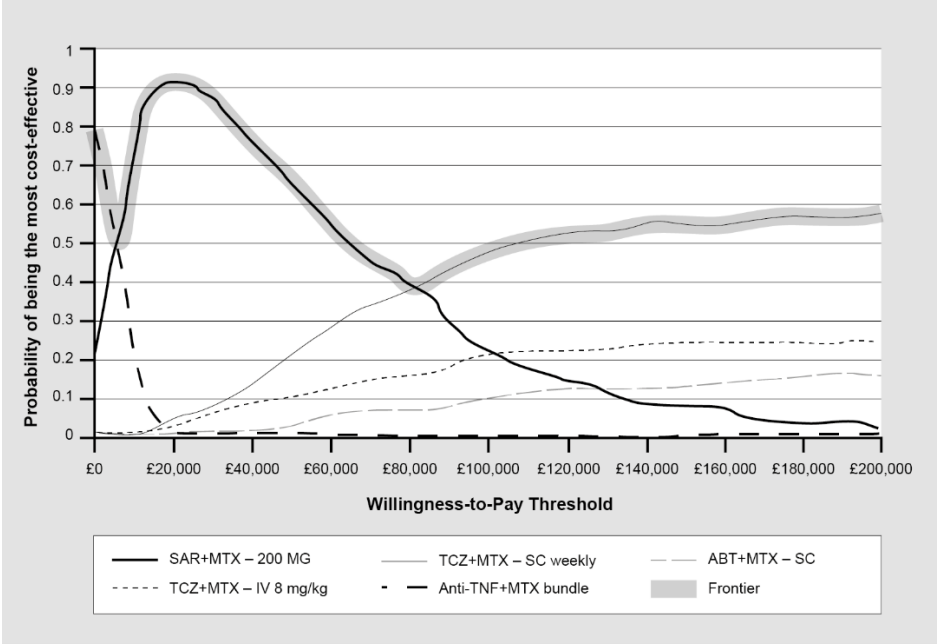


Table 5.41 Population C1 - Probabilistic Base-case results: Patients with severe active RA that have not responded adequately to, or are intolerant of therapy with DMARDs including at least one TNFi (RTX intolerant in combination with MTX)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Sarilumab ICER (£) versus each alternative technology (QALYs)	ICER (£) incremental (QALYs)
TNFi Bundle + MTX	[redacted]	14.35	[redacted]	–	–	–	£6,222	–
SAR + MTX	[redacted]	14.35	[redacted]	[redacted]	0.00	[redacted]	–	£6,222
TZC (SC) + MTX	[redacted]	14.35	[redacted]	[redacted]	0.00	[redacted]	Less costly, less effective	£75,625
TCZ (IV) + MTX	[redacted]	14.35	[redacted]	[redacted]	0.00	[redacted]	Less costly, less effective	Dominated
ABT (SC) + MTX	[redacted]	14.35	[redacted]	[redacted]	0.00	[redacted]	Less costly, less effective	Dominated

ICER=incremental cost-effectiveness ratio; LYG= life years gained; QALYs=quality-adjusted life years

Figure 5.15 Population C1 – CEAC



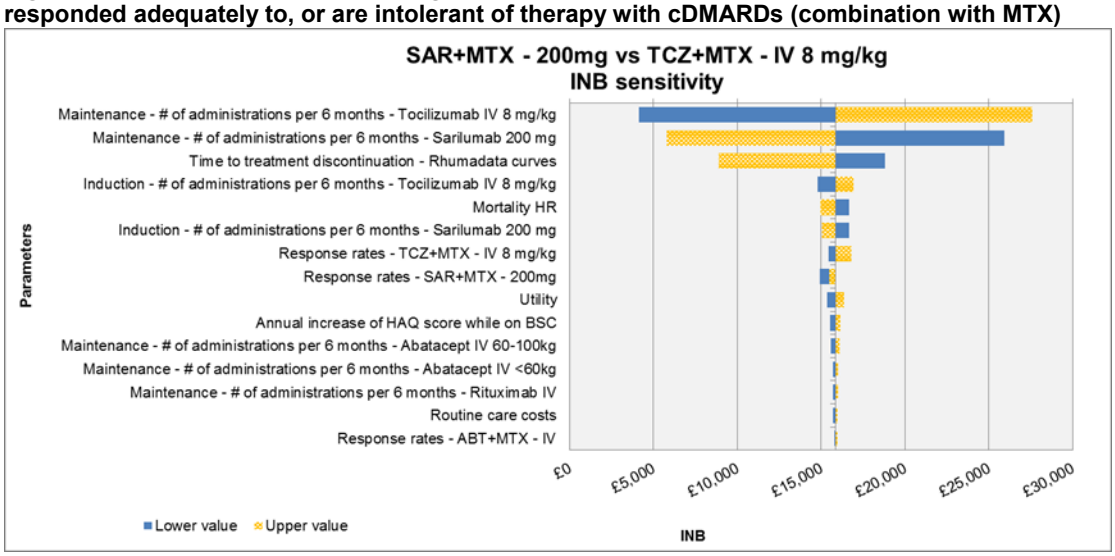
5.8.2 Deterministic sensitivity analysis

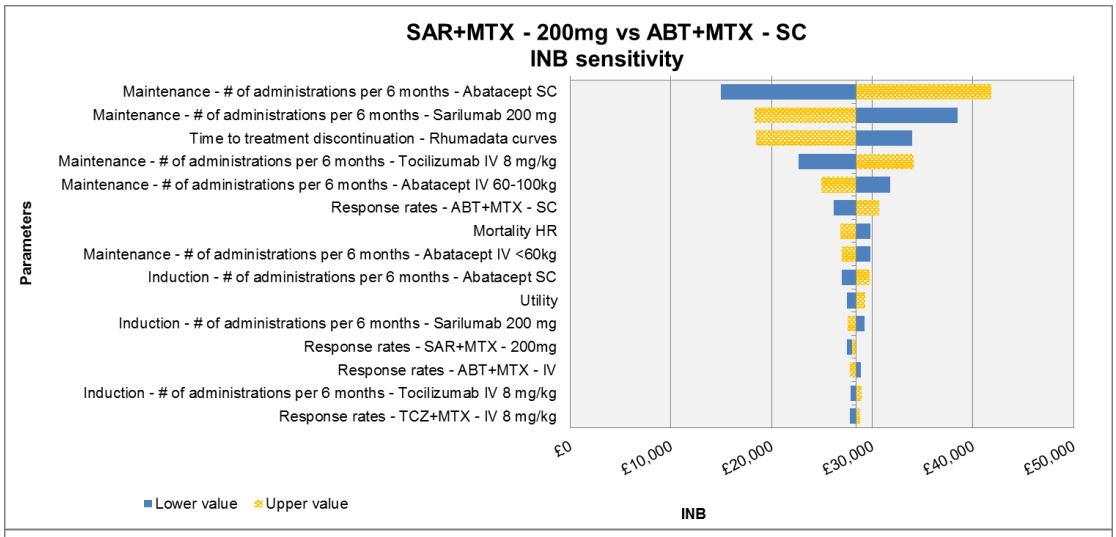
To identify key model drivers and examine key areas of uncertainty within the model, one-way sensitivity analysis was performed for all major model variables. Parameters were set to the boundaries of their two-sided 95% confidence intervals. If standard error or confidence intervals were not available for parameters then ±20% of the base-case values were applied as lower and upper values. For utility and routine care cost, a ±20% range around the estimated values was applied instead of the individual coefficients. The parameters were changed one by one, in order to see their independent effects on the results.

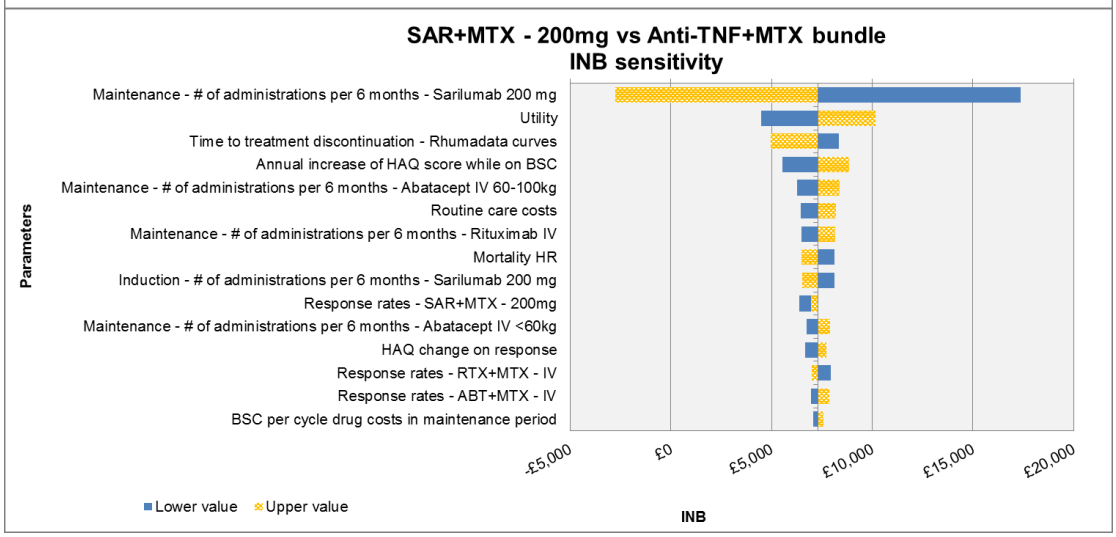
A tornado diagram illustrates the results of the one-way sensitivity analysis by showing the outputs when using both the lower and upper bounds of selected input parameters. The difference between these results shows the effect of the uncertainty of the parameters. By putting the differences in descending order, the diagram depicts the parameters to which the results were most sensitive. Each tornado diagram shows the estimated 15 most influential parameters on the incremental net benefit of sarilumab versus the selected comparator. The yellow (light shaded bar) represents the effect of applying the upper value of the parameter tested and the blue (darker shaded bar) represents the effect of the lower value.

The key drivers of results across all populations were consistently the number of administrations per cycle of the comparators and the time to treatment discontinuation, both of these parameters relate directly to acquisition cost. Other parameters that had a notable effect of the INB were utility and annual increase of HAQ whilst on BSC.

Figure 5.16 Population A1 – Tornado graphs: Patients with severe active RA that has not responded adequately to, or are intolerant of therapy with cDMARDs (combination with MTX)







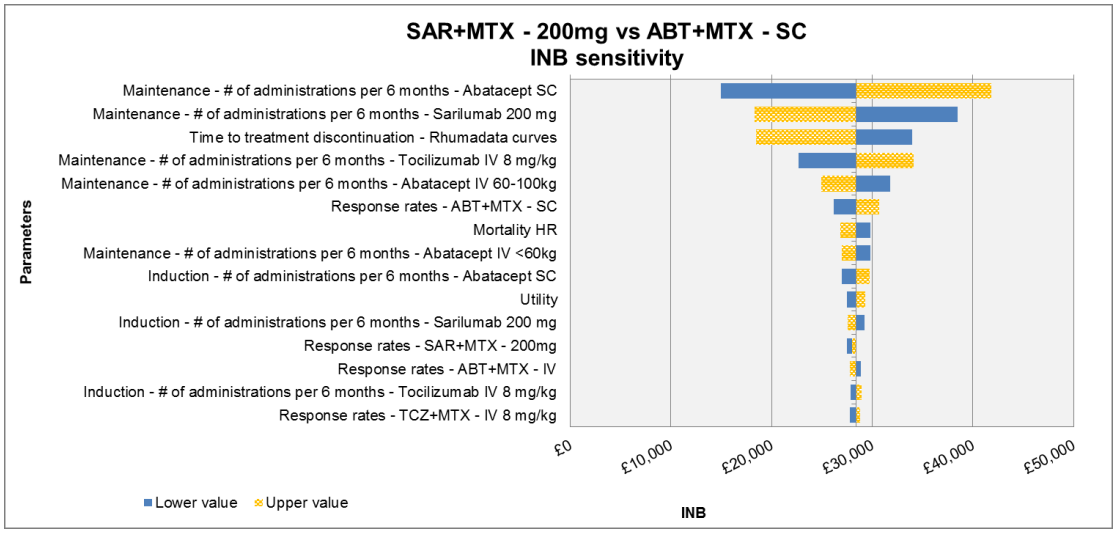
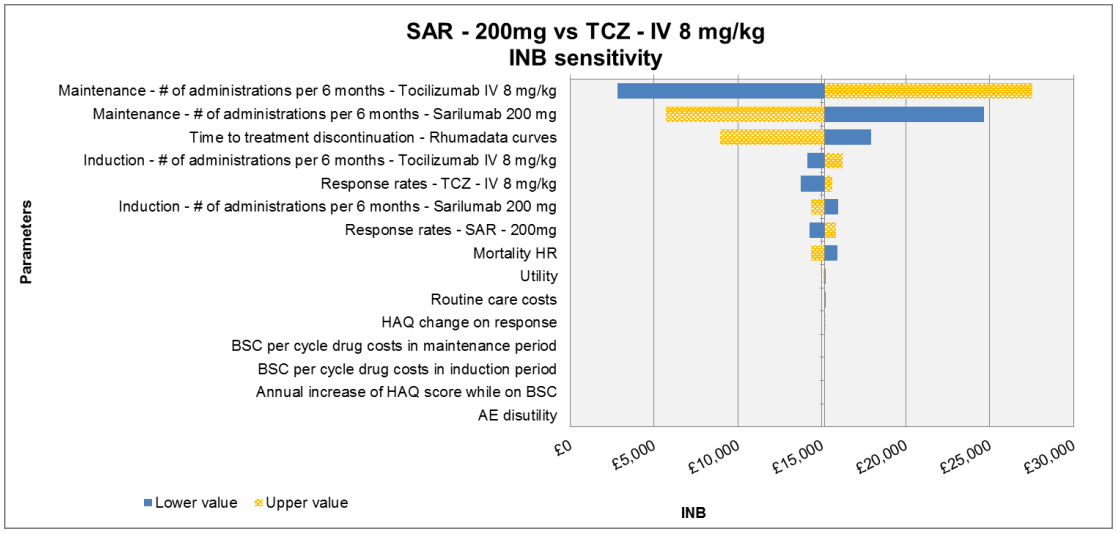
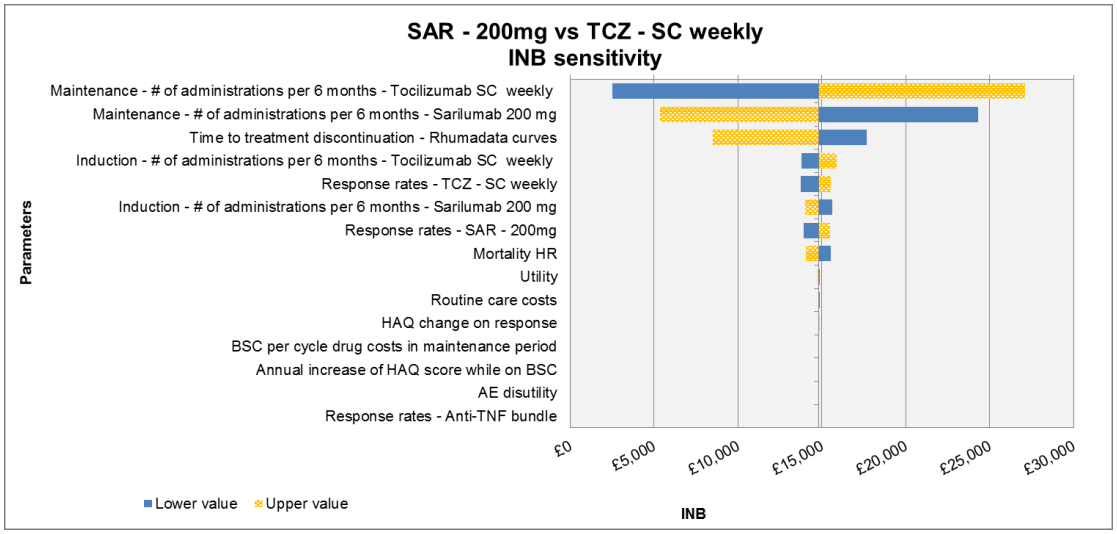


Figure 5.17 Population B – Tornado graphs: Patients with severe active RA that has not responded adequately to, or are intolerant of therapy with cDMARDs (monotherapy)





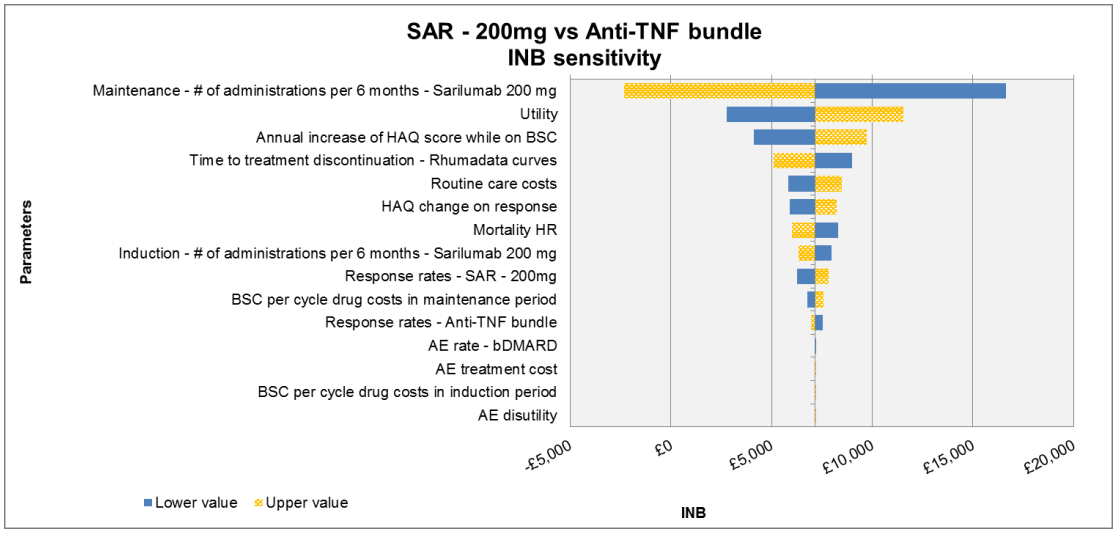
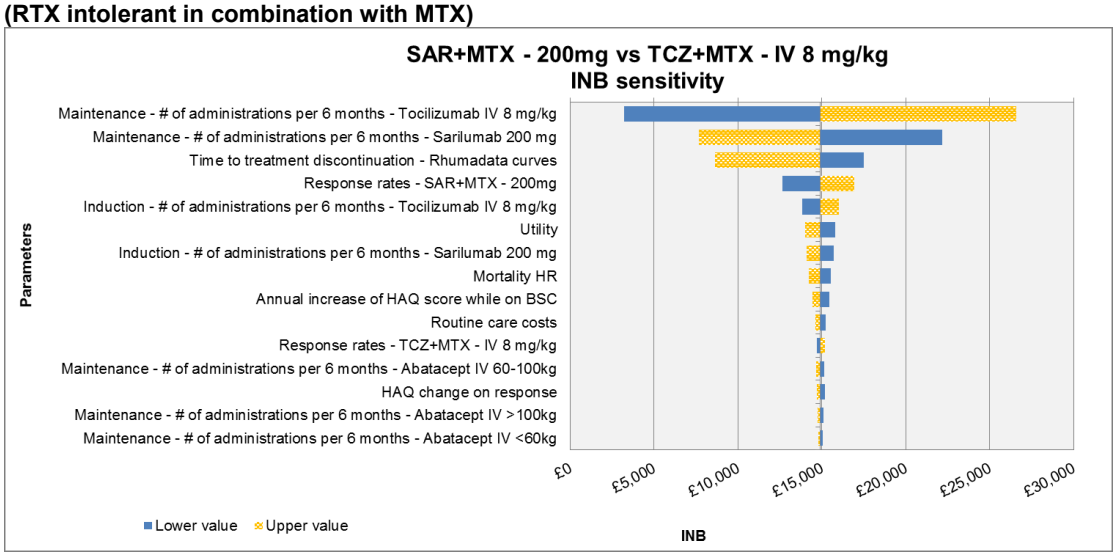
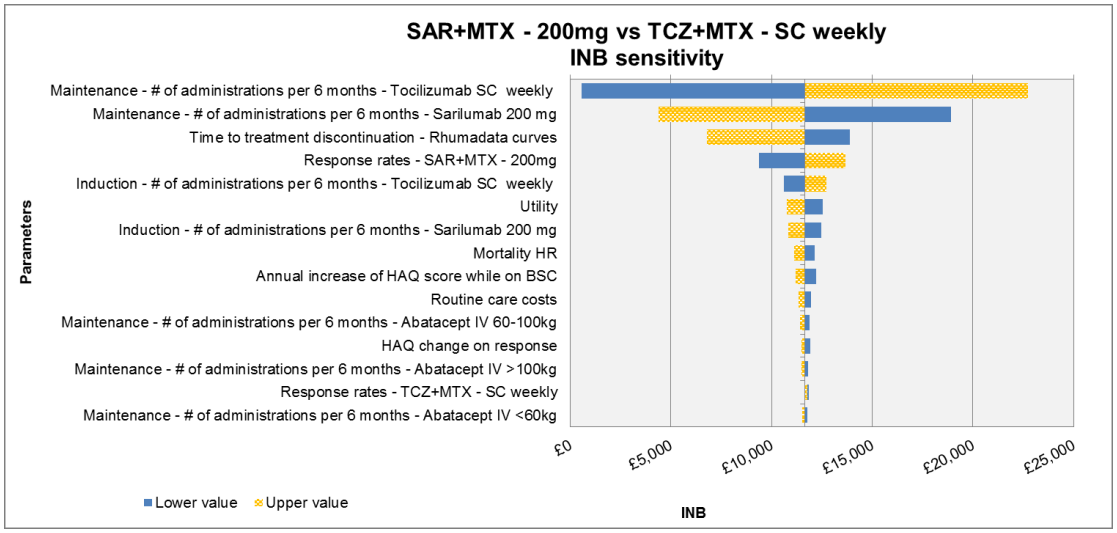
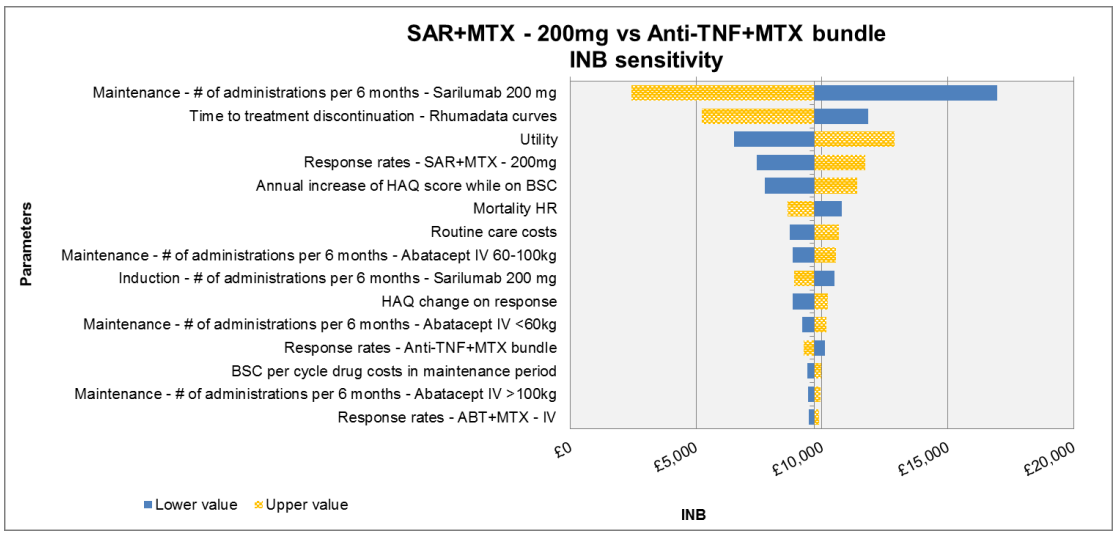
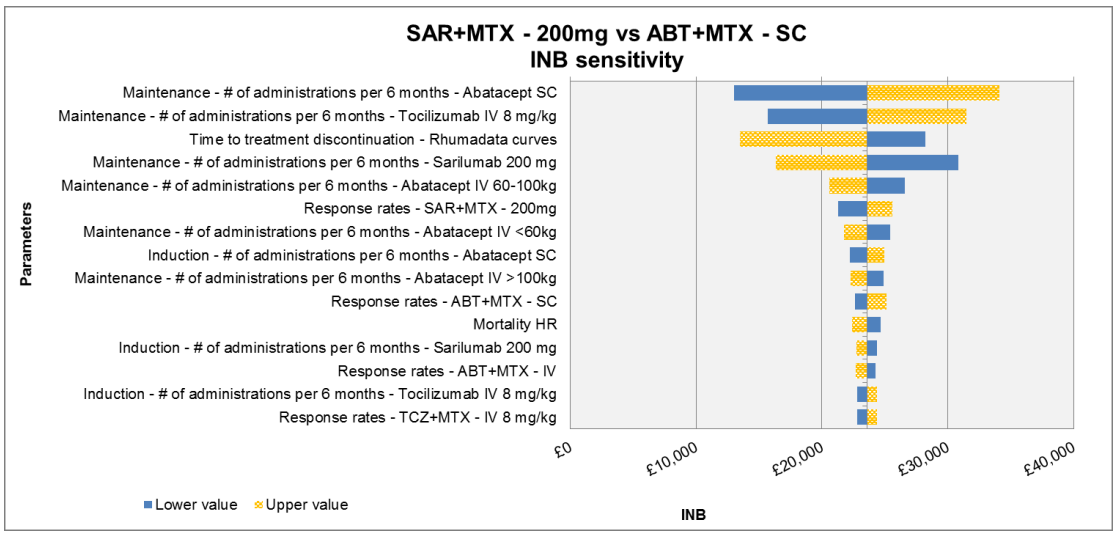


Figure 5.18 Population C1 – Tornado graphs: Patients with severe active RA that have not responded adequately to, or are intolerant of therapy with DMARDs including at least one TNFi (RTX intolerant in combination with MTX)




SAR+MTX - 200mg vs TCZ+MTX - SC weekly
INB sensitivity
Parameters
Maintenance - # of administrations per 6 months - Tocilizumab SC weekly
Maintenance - # of administrations per 6 months - Sarilumab 200 mg
Time to treatment discontinuation - Rhumadata curves
Response rates - SAR+MTX - 200mg
Induction - # of administrations per 6 months - Tocilizumab SC weekly
Utility
Induction - # of administrations per 6 months - Sarilumab 200 mg
Mortality HR
Annual increase of HAQ score while on BSC
Routine care costs
Maintenance - # of administrations per 6 months - Abatacept IV 60-100kg
HAQ change on response
Maintenance - # of administrations per 6 months - Abatacept IV >100kg
Response rates - TCZ+MTX - SC weekly
Maintenance - # of administrations per 6 months - Abatacept IV <60kg
£0
£5,000
£10,000
£15,000
£20,000
£25,000
Lower value
Upper value
INB


SAR+MTX - 200mg vs Anti-TNF+MTX bundle
INB sensitivity
Parameters
Maintenance - # of administrations per 6 months - Sarilumab 200 mg
Time to treatment discontinuation - Rhumadata curves
Utility
Response rates - SAR+MTX - 200mg
Annual increase of HAQ score while on BSC
Mortality HR
Routine care costs
Maintenance - # of administrations per 6 months - Abatacept IV 60-100kg
Induction - # of administrations per 6 months - Sarilumab 200 mg
HAQ change on response
Maintenance - # of administrations per 6 months - Abatacept IV <60kg
Response rates - Anti-TNF+MTX bundle
BSC per cycle drug costs in maintenance period
Maintenance - # of administrations per 6 months - Abatacept IV >100kg
Response rates - ABT+MTX - IV
£0
£5,000
£10,000
£15,000
£20,000
Lower value
Upper value
INB


SAR+MTX - 200mg vs ABT+MTX - SC
INB sensitivity
Parameters
Maintenance - # of administrations per 6 months - Abatacept SC
Maintenance - # of administrations per 6 months - Tocilizumab IV 8 mg/kg
Time to treatment discontinuation - Rhumadata curves
Maintenance - # of administrations per 6 months - Sarilumab 200 mg
Maintenance - # of administrations per 6 months - Abatacept IV 60-100kg
Response rates - SAR+MTX - 200mg
Maintenance - # of administrations per 6 months - Abatacept IV <60kg
Induction - # of administrations per 6 months - Abatacept SC
Maintenance - # of administrations per 6 months - Abatacept IV >100kg
Response rates - ABT+MTX - SC
Mortality HR
Induction - # of administrations per 6 months - Sarilumab 200 mg
Response rates - ABT+MTX - IV
Induction - # of administrations per 6 months - Tocilizumab IV 8 mg/kg
Response rates - TCZ+MTX - IV 8 mg/kg
£0
£10,000
£20,000
£30,000
£40,000
Lower value
Upper value
INB

5.8.3 Scenario analysis

Several scenarios were considered which aimed to test the sensitivity of the results to alternative plausible assumptions in the model structure. The most significant of these is a cost-minimisation approach. The NMA showed that there were very few statistical differences in all efficacy and safety outcomes between the bDMARDs therefore a cost-minimisation approach was considered appropriate and is presented for a one year horizon. In the cost-minimisation analysis, all clinical outcomes with product specific values in the base-case are assumed identical among all bDMARDs (i.e. treatment response, utility, mortality, safety, and time to treatment discontinuation) therefore no effectiveness outcomes are evaluated. All costs specific to each comparator were included. The results of the analysis are presented as bar diagrams showing the incremental cost of sarilumab vs. each comparator over the one year horizon in the three populations.

Similar to the cost-minimisation approach, another key scenario sets the level of response (only) for each comparator to that achieved by sarilumab. The final key scenario to highlight is the analysis presented for sarilumab vs. each TNFi as an individual agent including biosimilar products. Other scenarios were also tested to assess the structural uncertainty on the results and a list of these is shown in Table 5.42.

Table 5.42 Assumptions tested in scenario analysis

Assumption	Base-case	Scenario analyses
Minimum response	EULAR Moderate	ACR 20
Discount rates	Costs: 3.5% Benefit: 3.5%	Costs: 1.5% Benefit: 1.5%
TNFi comparators	TNFi bundle	TNFis separately
Patient cohort weight	As per MOBILITY B, MONARCH & TARGET trials	Mean weight = 70kg
ACR to EULAR mapping source	TA375 (all patients)	MOBILITY trial data analysis
EULAR Responses for comparators	Based on individual ACR point estimates from NMA	Sarilumab response rate for all
Annual increase of HAQ score while on BSC	0.06	0.045
		0.012
Utilities	Malottki et al. 2011[68]	Bansbank et al. 2005[360], TA375 method[17]
Time to treatment discontinuation	By treatment class according to RHUMADATA results	TNFi curve for all classes from RHUMADATA analyses, TA375 method
Serious infection rate	Trial data	TA375 rate

Assumption	Base-case	Scenario analyses
Wastage	No vial sharing	Vial sharing
Drug costs	Visible prices (15% discount for all TCZ & ABT pack price)	ABT & TCZ at list price and 25% discount simultaneously

ABT = abatacept; ACR = American College of Rheumatology; BSC=Best Supportive Care; EULAR = European League against Rheumatism; TCZ = tocilizumab; TNFi = tumour necrosis factor inhibitor;

Results of the cost-minimisation suggest that treatment with sarilumab achieves cost savings vs. all comparators except certolizumab pegol driven by its 12 weeks free PAS. Over one year, the cost-saving is estimated to range from approximately [redacted] from abatacept (SC), to [redacted] from etanercept biosimilar.

The scenario setting all comparators' response levels to the same as sarilumab resulted in sarilumab dominance vs. tocilizumab (IV & SC) and similar results to the base-case vs. TNFis and abatacept in all populations.

The analysis vs. each individual TNFi supports the base-case in that the ICER for sarilumab remains cost-effective over all populations using a threshold of £20K to £30K per QALY gained. Over all TNFi comparisons and populations, sarilumab ICERs are estimated to range from £3,520 to £14,804 per QALY gained.

The results are presented as the sarilumab ICER vs. each comparator and suggest that the structural uncertainty in the model is low with the results remaining constant across all populations. The only factors to notably affect the results were decreasing the annual HAQ-DI increase on BSC which increased the ICER for sarilumab, and using alternate treatment discontinuation assumptions which lowered the ICER for sarilumab.

5.8.3.1 Results

Figure 5.19 Population A1 – Incremental cost of sarilumab vs. comparators over 12 months in the cost-minimisation: Patients with severe active RA that has not responded adequately to, or are intolerant of therapy with cDMARDs (combination with MTX)

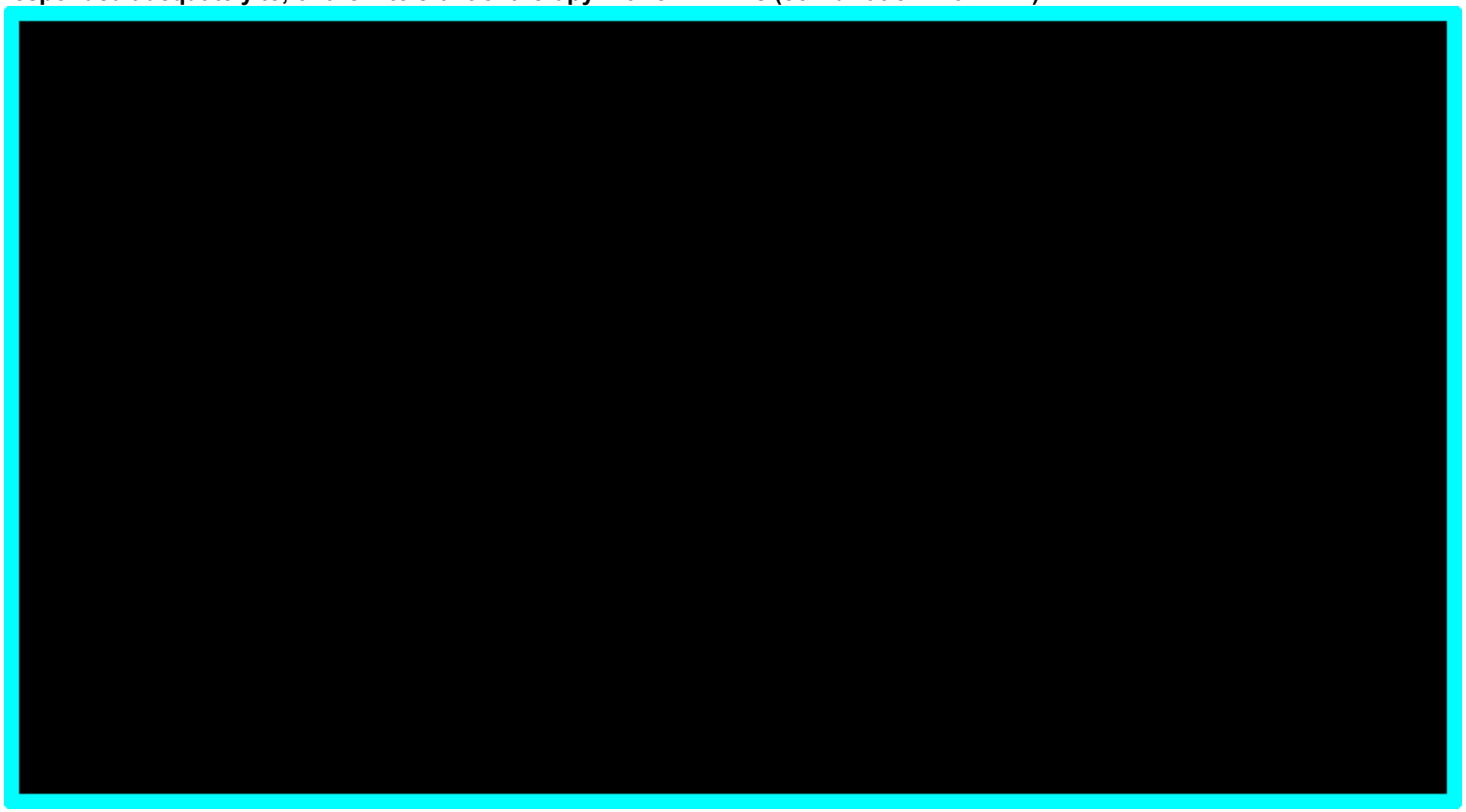


Table 5.43 Population A1 - Scenarios results: Patients with severe active RA that has not responded adequately to, or are intolerant of therapy with cDMARDs (combination with MTX)

Sarilumab Scenario	vs. TCZ (IV) + MTX ICER (£ / QALY)	vs. TCZ (SC) + MTX ICER (£ / QALY)	vs. TNFi Bundle + MTX ICER (£ / QALY)	Vs. ABT (SC) + MTX ICER (£ / QALY)
Base-case	**Dominant**	**Dominant**	**£9,589**	**Dominant**
Scenarios				
Sarilumab response for all	Dominant	Dominant	£9,393	Dominant
Average weight 70kg	Dominant	Dominant	£9,974	Dominant
ACR to EULAR mapping method: MOBILITY B	Dominant	Dominant	£9,271	Dominant
Minimum response ACR20	Dominant	Dominant	£6,260	Dominant
Discount rate at 1.5%	Dominant	Dominant	£9,411	Dominant
Annual HAQ increase at 0.045	Dominant	Dominant	£11,883	Dominant
Annual HAQ increase at 0.012	Dominant	Dominant	£21,928	Dominant
Utility: TA375	Dominant	Dominant	£12,835	Dominant
Utility: Bansback (2005)	Dominant	Dominant	£12,107	Dominant
TTD: TNFi curve for all drug classes	Dominant	Dominant	Dominant	Dominant
TTD source - TA375	Dominant	Dominant	Dominant	Dominant
Serious Infection: ScHARR report	Dominant	Dominant	£9,523	Dominant
No wastage	Dominant	Dominant	£9,904	Dominant
ABT & TCZ at list price	Dominant	Dominant	£7,686	Dominant
ABT & TCZ discount of 25%	Dominant	Dominant	£10,857	Dominant

Sarilumab Scenario	vs. ETN + MTX ICER (£ / QALY)	vs. ETN + MTX (biosimilar) ICER (£ / QALY)	vs. ADA + MTX ICER (£ / QALY)	vs. INF + MTX (branded) ICER (£ / QALY)	vs. INF + MTX (biosimilar) ICER (£ / QALY)	vs. GOL + MTX ICER (£ / QALY)	vs. CTZ + MTX ICER (£ / QALY)	vs. ABT (IV) + MTX ICER (£ / QALY)
TNFis separately	£3,520	£10,960	£10,110	£11,237	£14,804	£10,451	£12,537	£-
ABT IV	-	-	-	-	-	-	-	Dominant

ABT=abatacept; ADA=adalimumab; CTZ=certolizumab; ETN=etanercept; HAQ=health assessment questionnaire; ICER=incremental cost-effectiveness ratio; LY= life years gained; MTX=methotrexate; QALYs=quality-adjusted life years; TCZ=tocilizumab; TNFi=tumour necrosis factor inhibitor

Figure 5.20 Population B – Incremental cost of sarilumab vs comparators over 12 months in the cost-minimisation: Patients with severe active RA that has not responded adequately to, or are intolerant of therapy with cDMARDs (monotherapy)

Table 5.44 Population B - Scenarios results: Patients with severe active RA that has not responded adequately to, or are intolerant of therapy with cDMARDs (monotherapy)

Sarilumab scenario	vs. TCZ (IV) + MTX ICER (£ / QALY)	vs. TCZ (SC) + MTX ICER (£ / QALY)	vs. TNFi bundle + MTX ICER (£ / QALY)
Base-case	**Less costly, less effective**	**Less costly, less effective**	**£13,479**
Scenarios			
Sarilumab response for all	Dominant	Dominant	£12,262
Average weight 70kg	Less costly, less effective	Less costly, less effective	£12,978
ACR to EULAR mapping method: MOBILITY	Less costly, less effective	Less costly, less effective	£12,480
Minimum response ACR20	Dominant	Dominant	£8,927
Discount rate at 1.5%	Less costly, less effective	Less costly, less effective	£12,394
Annual HAQ increase at 0.045	Less costly, less effective	Less costly, less effective	£16,593
Annual HAQ increase at 0.012	Less costly, less effective	Less costly, less effective	£30,549
Utility: TA375	Less costly, less effective	Less costly, less effective	£17,920
Utility: Bansback (2005)	Less costly, less effective	Less costly, less effective	£17,142
TTD: TNFi curve for all drug classes	Less costly, less effective	Less costly, less effective	Dominant
TTD source - TA375	Less costly, less effective	Less costly, less effective	Dominant
Serious Infection: ScHARR report	Less costly, less effective	Less costly, less effective	£13,650
No wastage	Less costly, less effective	Less costly, less effective	£13,691
ABT & TCZ at list price	Less costly, less effective	Less costly, less effective	£13,479
ABT & TCZ discount of 25%	Less costly, less effective	Less costly, less effective	£13,479

Sarilumab Scenario	vs. ETN + MTX ICER (£ / QALY)	vs. ETN + MTX (biosimilar) ICER (£ / QALY)	vs. ADA + MTX ICER (£ / QALY)	vs. CTZ + MTX ICER (£ / QALY)
TNFis separately	£9,150	£13,640	£9,734	£14,189

ABT=abatacept; ADA=adalimumab; CTZ=certolizumab; ETN=etanercept; HAQ=health assessment questionnaire; ICER=incremental cost-effectiveness ratio; LY= life years gained; MTX=methotrexate; QALYs=quality-adjusted life years; TCZ=tocilizumab; TNFi=tumour necrosis factor inhibitor; TTD=time to treatment discontinuation

Figure 5.21 Population C1 – Incremental cost of sarilumab vs. comparators over 12 months in the cost-minimisation: Patients with severe active RA that have not responded adequately to, or are intolerant of therapy with DMARDs including at least one TNFi (RTX intolerant in combination with MTX)

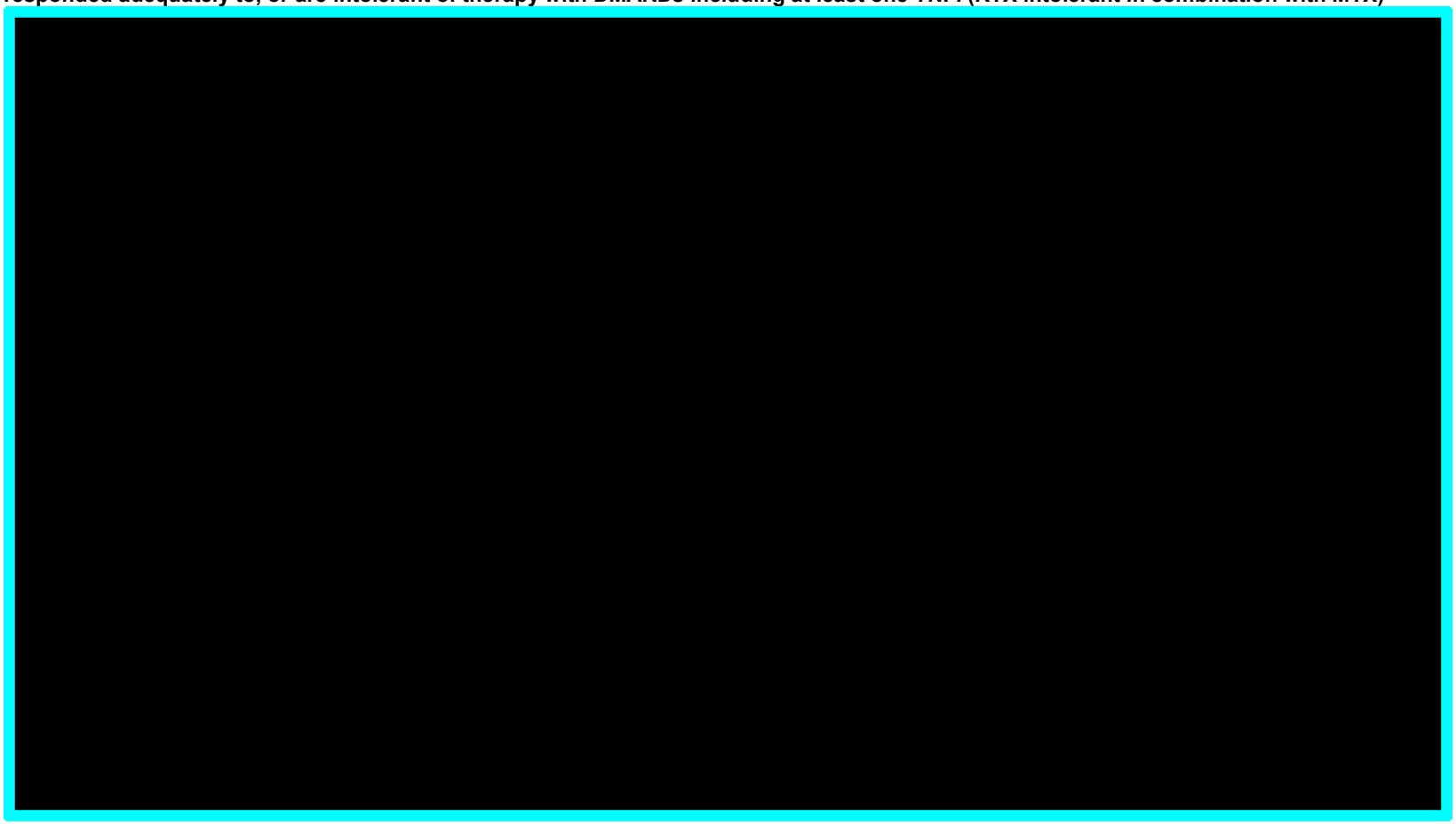


Table 5.45 Population C1 - Scenarios results: Patients with severe active RA that have not responded adequately to, or are intolerant of therapy with DMARDs including at least one TNFi (RTX intolerant in combination with MTX)

Sarilumab scenario	vs. TCZ (IV) + MTX ICER (£ / QALY)	vs. TCZ (SC) + MTX ICER (£ / QALY)	vs. TNFi Bundle + MTX ICER (£ / QALY)	vs. ABT (SC) + MTX ICER (£ / QALY)
Base-case	**Less costly, less effective**	**Less costly, less effective**	**£7,842**	**Less costly, less effective**
Scenarios				
Sarilumab response for all	Dominant	Dominant	£7,433	Less costly, less effective
Average weight 70kg	Less costly, less effective	Less costly, less effective	£8,659	Less costly, less effective
ACR to EULAR mapping method: MOBILITY B	Less costly, less effective	Less costly, less effective	£7,661	Less costly, less effective
Minimum response ACR20	Less costly, less effective	Less costly, less effective	£5,892	Less costly, less effective
Discount rate at 1.5%	Less costly, less effective	Less costly, less effective	£7,666	Less costly, less effective
Annual HAQ increase at 0.045	Less costly, less effective	Less costly, less effective	£9,853	Less costly, less effective
Annual HAQ increase at 0.012	Less costly, less effective	Less costly, less effective	£18,298	Less costly, less effective
Utility: TA375	Less costly, less effective	Less costly, less effective	£10,435	Less costly, less effective
Utility: Bansback (2005)	Less costly, less effective	Less costly, less effective	£9,944	Less costly, less effective
TTD: TNFi curve for all drug classes	Less costly, less effective	Less costly, less effective	Dominant	Less costly, less effective
TTD source - TA375	Less costly, less effective	Less costly, less effective	Dominant	Less costly, less effective
Serious Infection: ScHARR report	Less costly, less effective	Less costly, less effective	£7,914	Less costly, less effective
No wastage	Less costly, less effective	Less costly, less effective	£8,045	Less costly, less effective
ABT & TCZ at list price	Less costly, less effective	Less costly, less effective	£6,141	Less costly, less effective
ABT & TCZ discount of 25%	Less costly, less effective	Less costly, less effective	£8,976	Less costly, less effective

Sarilumab Scenario	vs. ETN + MTX ICER (£ / QALY)	vs. ETN + MTX (biosimilar) ICER (£ / QALY)	vs. ADA + MTX ICER (£ / QALY)	vs. INF + MTX (branded) ICER (£ / QALY)	vs. INF + MTX (biosimilar) ICER (£ / QALY)	vs. GOL + MTX ICER (£ / QALY)	vs. CTZ + MTX ICER (£ / QALY)	vs. ABT (IV) + MTX ICER (£ / QALY)
TNFis separately	**£5,960**	**£9,334**	£8,102	£7,083	£9,540	£8,506	£10,359	-
ABT IV	**-**	**-**	-	-	-	-	-	Less costly, less effective

ABT=abatacept; ADA=adalimumab; CTZ=certolizumab; ETN=etanercept; HAQ=health assessment questionnaire; ICER=incremental cost-effectiveness ratio; IV=intravenous; LY= life years gained; MTX=methotrexate; QALYs=quality-adjusted life years; TCZ=tocilizumab; TNFi=tumour necrosis factor inhibitor

5.8.3.2 Summary of sensitivity analyses results

Results from the PSA, DSA and scenario analysis all support the base-case results. The PSA suggests that sarilumab is the cost-effective option across all populations vs. bDMARD therapies if the willingness-to-pay threshold is above £13,586 and below £75,625 per QALY gained which is well inclusive of the £20K to £30K threshold range.

The DSA supports the stability of the results since very few parameters have a significant impact on the results. The parameters with such an impact relate to the number of administrations and length of treatment which are directly associated with the acquisition cost of the comparators. The inference from this finding is that the most influential differentiator between all bDMARD comparators is cost. This in turn supports the findings from the NMA which found very few statistical differences in efficacy or safety between comparators with superiority of sarilumab vs. adalimumab in efficacy endpoints standing out as one of the exceptions.

The DSA supported the approach of the cost-minimisation analysis which assumed no MCID between the comparators. Over a 12 month horizon, this demonstrated that sarilumab would incur less cost to the health service than all comparators bar certolizumab pegol which, over this short time horizon, was less costly due to its PAS which provides the first 12 weeks of therapy for free. This saving would be reversed following on from the initial 12 week period if treatment were maintained. The other scenario analyses demonstrated the robustness of our cost-effectiveness model where changing many of the key model assumptions did not significantly affect the base-case results.

5.9 Subgroup analysis

Several subgroups were considered in the submission however these were all specified in the scope as primary analysis and are therefore described and reported in the previous sections of Section 5.

5.10 Validation

5.10.1 Validation of de novo cost-effectiveness analysis

Face validity was assessed in a three-stage process. Internal peer review consisting of senior scientists with extensive modelling and RA experience reviewing the model

structure, major assumptions, approaches and sources of inputs (HAQ change, mortality, response, discontinuation, AEs, utilities and costs).

In the second stage, a one day Rheumatology Health Economics Advisory Board was held in April, 2015 in Montreal, Canada. The objective of the Advisory Board was to validate the methods and data sources used and the assumptions made in developing the health economic model to assess the cost-effectiveness of sarilumab in treating patients with RA. Participants included clinical and health economics experts from Canada and the UK and the model framework, model inputs, outputs and assumptions were discussed. Modifications, additions recommended were documented in a summary report (Appendix 13) and subsequently implemented. After changes were implemented, an additional round of review was conducted with the participating health economists (UK and Canada).

In addition, the NMA informing clinical responses in the model was reviewed by an independent expert in health economics and evidence synthesis. The analysis was not found to have any critical flaws and the review provided recommendations for potential further investigations and alternate scenarios to consider.

Further validation can be drawn from an exploratory analysis developed to compare estimated ICERs from an adapted version of our model with ICERs from the AG model from TA375. This analysis is based on the severe cDMARD-IR population over a lifetime time horizon and includes a cDMARD comparator using the response estimate from our NMA. Our model uses our base-case settings and sequences with a £378.31 cycle cost of cDMARDs, 0.045 annual HAQ-DI increase whilst on cDMARDs, and a sequence of cDMARDs → BSC. This roughly correlates to Table 204 in Stevenson et al 2016 where the analysis is based on ACR mapped to EULAR data, Malottki et al utility algorithm, linear cDMARD HAQ progression and a severe MTX-experienced population. Our model estimates similar and consistently lower ICERs to the AG model (Table 5.46). Small differences in results should be expected between different models informed by different NMAs. Further confidence can be placed in the results presented in Section 5.8 and Section 5.9 from this verification.

Table 5.46 Comparison of ICERs by intervention in submission model and ScHARR model in RA.

Comparator	Stevenson et al. ICER vs. MTX	Sanofi Genzyme ICER vs. cDMARD
MTX/cDMARD	-	-
TCZ (IV) + MTX	£29,087	£26,825
ABT (IV) +MTX	£29,472	£27,690
IFX + MTX	£29,940	£25,161
CTZ + MTX	£30,948	£24,841
GOL + MTX	£31,900	£25,327
ABT (SC) +MTX	£31,970	£30,365
ADA + MTX	£32,190	£25,372
ETN + MTX	£33,104	£26,163

ABT=abatacept; ADA=adalimumab; cDMARD=conventional disease-modifying anti-rheumatic drug; CTZ=certolizumab pegol; ETN=etanercept; GOL=golimumab; ICER=incremental cost-effectiveness ratio; IFX=infliximab; IV=intravenous; MTX=methotrexate; SC=subcutaneous; TCZ=tocilizumab

5.10.2 Technical validation

Internal technical verification was carried out first by performing extreme-value sensitivity analyses to study the behaviour of the model. Unexpected model behaviour, redundant variables, programming errors, and typing errors can be identified by performing such extreme-value sensitivity analyses. After the completion of model programming, a comprehensive and rigorous quality check was performed. This included validating the logical structure of the model, mathematical formulas and sequences of calculations. The model was reviewed by a peer reviewer not involved with the original programming. In addition, another reviewer confirmed the source of the data and verified all input data against the source.

5.10.3 External verification

The de novo model underwent rigorous validation and verification by an external expert involved in the development of the AG model in TA375. The process investigated the model validity in terms of: alignment with the final scope, appropriate methodology employed, and consistency with the Sheffield RA model. The verification process consisted of logic checks and a sheet by sheet examination of the model. The model was found to be valid and robust with many similarities to the Sheffield RA model used in TA375.

5.10.4 Patient sample size

Patient-level data was available for 1,197 patients (204 for the moderate population and 980 for the severe population, dubbed ‘filtered cohort size’) in the MOBILITY data source, 369 patients (317 for the severe population) in the MONARCH data source, and 546 (486 for the severe population) in the TARGET data source.

Patient numbers however might not be sufficient in some populations and sources to produce stable results. In order to create stable results, two methods were explored – replication and bootstrapping. In the replication method, each patient in the cohort is replicated the same number of times to obtain a sufficient sample size. This way, the average patient characteristics, assumed to reflect patients in the UK, does not change as the sample size increases. The second method, bootstrapping (sample with replacement), includes randomly selecting patients to run through the model and place them back to the cohort. Run sufficient number of times, this would also keep the average patient characteristics of the cohort however it is likely to require higher number of runs therefore the replication method was used in our analysis.

To determine the sufficient sample size the convergence patterns of the sample means of incremental net benefit of sarilumab versus tocilizumab was analysed in three populations. The stabilization of the mean outcome was compared with increasing sample sizes both with the replication method and the alternative bootstrapping (sample with replacement) method.

Figure 5.22, Figure 5.23 and Figure 5.24 below show the results of convergence. Based on the convergence graphs, a sample size of approximately 5000 patients ensures sufficiently stable results in all populations. Therefore, for the base-case deterministic analyses, the number of replications were chosen for each population such that the full sample size (the population size times the number of replications) exceeded 5000.

For sensitivity and scenario analyses that require a large number of simulations the same sample size was not feasible due to the extended run times of the simulations. Based on the convergence graphs samples of approximately 1000 patients in individual simulations ensures a level of stability of results that ensures changes in model parameters can be properly examined. The random draws for each patient in the individual simulations are fixed across the sensitivity analyses, so no extra noise is introduced. Hence, in sensitivity analyses (one-way deterministic sensitivity analysis, probabilistic sensitivity analysis, and scenario analyses) replication numbers in each cohort was selected to approximate a sample size of 1000.

Figure 5.22 Convergence of mean results - MOBILITY B population

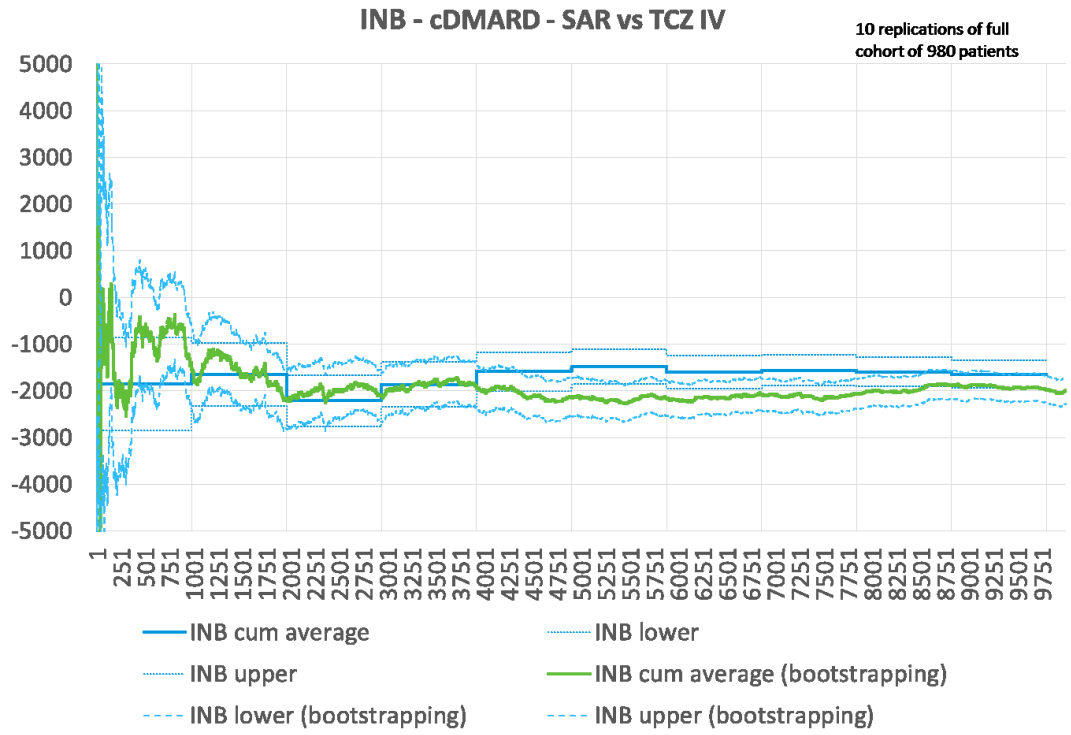


Figure 5.23 Convergence of mean results - MONARCH population

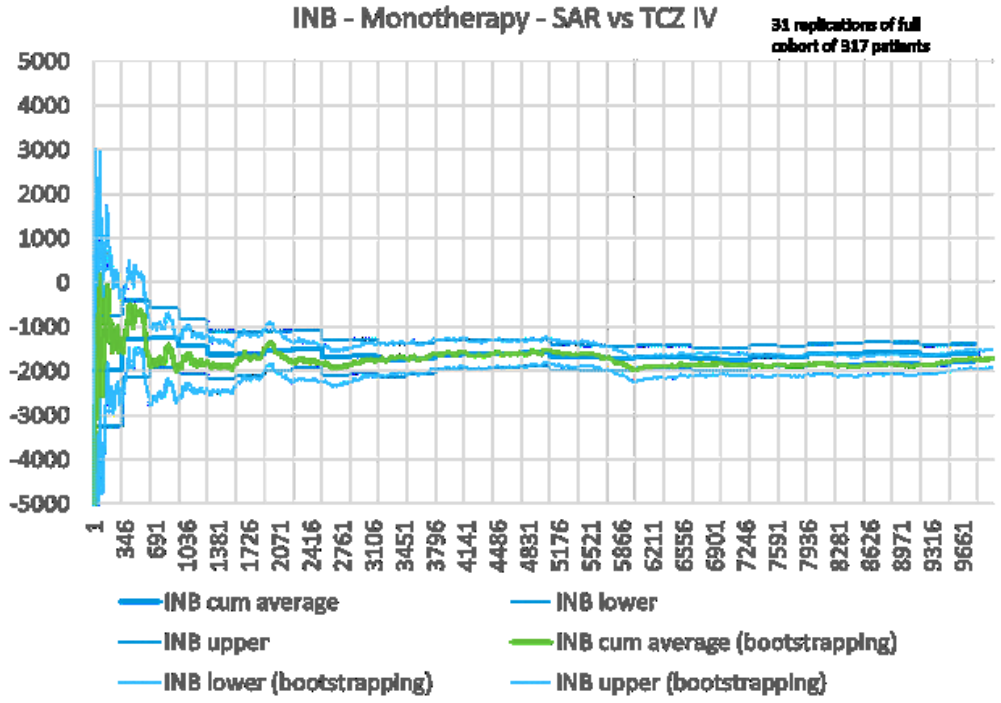
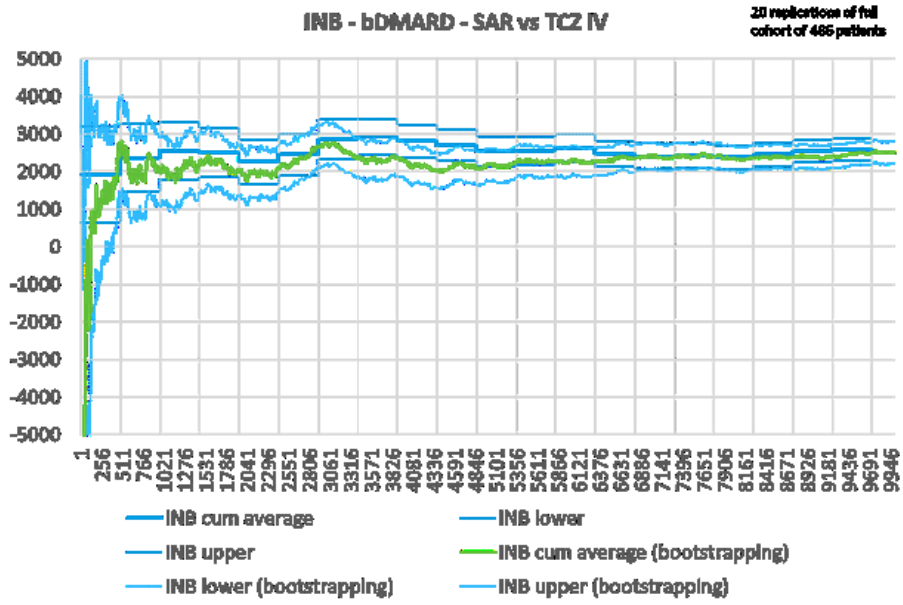


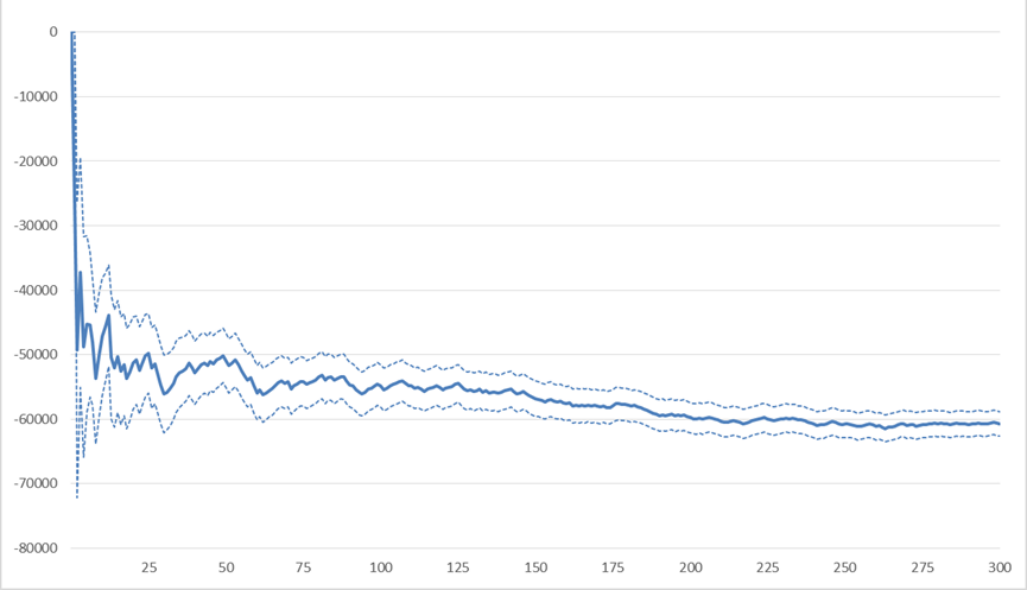
Figure 5.24 Convergence of mean results - TARGET population



5.10.5 Number of PSA simulations

To determine the number of PSA simulations required to obtain stable outputs, the convergence of mean INB of sarilumab vs. tocilizumab in the TARGET population was assessed over an increasing number of simulations (Figure 5.25). The exercise showed that convergence occurs after approximately 200 runs therefore we used 300 simulations in our analysis. This number of runs is large enough to allow the stable estimation of CEACs, and assessment of individual simulation results across the four quadrants of the cost-effectiveness plane (though these are not presented due to the high overlap of total costs and QALYs of the multiple comparator arms and are therefore difficult to interpret).

Figure 5.25 Convergence of INB from PSA simulations



5.11 Interpretation and conclusions of economic evidence

It is seen from the base-case and sensitivity analysis results that sarilumab is likely to be cost-effective in the UK compared with currently available therapies in the treatment of moderate-to-severe RA. The main driver of this is cost. Though some QALY differences are noted between sarilumab and the bDMARD comparators, these are largely driven by non-statistically significant differences in efficacy outcomes from the NMA suggesting there may not be many clinically important differences between sarilumab and the comparators with the exception of adalimumab in monotherapy. The differences in lifetime accumulated QALYs between the different treatments were small. There are uncertainties, particularly regarding the efficacy and safety results from the NMA. On the basis of small differences in lifetime QoL and such uncertainties, it is difficult to make a comparison between the cost-effectiveness of different types of treatments over another on considerations of cost-effectiveness alone. The choice of treatments should be determined by the total cost saving to the NHS and the preferences of both the clinician and the patient. The evidence presented here strongly suggests that the addition of sarilumab as a treatment option in the RA populations investigated would lead to efficiencies in NHS spending in this disease due to similar patient outcomes at reduced cost.

The economic evidence compliments the value of sarilumab as an alternative option for patients not achieving satisfactory responses to current therapies. Sarilumab may offer an effective and cost-efficient additional choice to clinicians and patients at several points in the RA treatment pathway whilst reducing economic burden to the health service.

6 Assessment of factors relevant to the NHS and other parties

6.1 Eligible patient population

The number of patients with RA eligible for biologics in England is estimated based on 2014 Office for Nation Statistics (ONS) population projections for 2017 to 2021, published literature on RA prevalence and incidence, and a NICE commissioning guide on biologic drugs[8,130,372]. The estimated eligible population is presented in Table 6.1. An important point to note in this section is that the analysis relates only to currently eligible patients to receive bDMARDs, i.e. severe patients with DAS28 >5.1. The reason for this is that there are no credible estimates on the number of moderate patients in the UK with DAS >4 ≤5.1. The uncertainty surrounding an uninformed estimate used in that population would render the results obsolete since no robust conclusion could be drawn.

Table 6.1 Number of patients with RA eligible for treatment with biologics in England

	2017	2018	2019	2020	2021
Population	55,640,400	56,061,500	56,466,300	56,862,300	57,248,400
Prevalence of RA	0.67%	0.67%	0.67%	0.67%	0.67%
Prevalent population, n	372,791	393,990	415,349	436,863	458,527
Incidence of RA	0.0381%	0.0381%	0.0381%	0.0381%	0.0381%
Incident cases of RA, n	21,199	21,359	21,514	21,665	21,812
Net population with RA	393,990	415,349	436,863	458,527	480,339
Percentage of RA patients eligible for biologic treatment	10%	10%	10%	10%	10%
Patients with RA eligible for biologic treatment, n	39,399	41,535	43,686	45,853	48,034

RA=rheumatoid arthritis.

6.2 Current treatment options and uptake of technologies

All biologic treatment options with a NICE recommendation for use in RA were included in the budget impact analysis. We do not include baricitinib or tofacitinib which are currently undergoing NICE appraisals since they do not have any published recommendation from NICE and their costs are unknown. Based on market share projections, the uptake of sarilumab among patients eligible for biologic

treatment is expected to be [redacted] and [redacted] for 2017, 2018, 2019, 2020 and 2021, respectively.

For the base-case analysis, it was assumed that [redacted] of the uptake for sarilumab would displace [redacted], since [redacted]. An equal proportion [redacted] was assumed to displace the [redacted]. The remaining [redacted] of the uptake for sarilumab was assumed to [redacted]

A number of alternative scenarios are also presented:

1) [redacted]

2) [redacted]

3) [redacted].

Market share data were sourced from a FOI request as described in Section 5.2.3. As separate market share data were not available for those therapies with both an intravenous and subcutaneous formulation, the market shares for these products were split equally across the two formulation types. The estimated market shares for the current and proposed scenarios are presented in Table 6.2. Results for scenario analyses in which [redacted] is assumed has also been presented (Table 6.10).

Table 6.2 Market share data for current and proposed scenarios in the base-case analysis

Comparator	Current scenario					Proposed scenario				
	2017	2018	2019	2020	2021	2017	2018	2019	2020	2021
Sarilumab	[redacted]									
Abatacept IV	[redacted]									
Abatacept SC	[redacted]									
Golimumab	[redacted]									
Etanercept	[redacted]									
Etanercept (biosimilar)	[redacted]									
Adalimumab	[redacted]									
Rituximab	[redacted]									
Certolizumab pegol	[redacted]									
Tocilizumab IV	[redacted]									
Tocilizumab SC	[redacted]									
Infliximab	[redacted]									
Infliximab (biosimilar)	[redacted]									

IV, intravenous; RA, rheumatoid arthritis; SC, subcutaneous.

6.3 Other costs

Administration and monitoring costs for all of the biologic treatment options were taken into account in the budget impact model as these represent significant costs associated with these treatments, and are described in Section 6.5 and Section 6.6. The costs of managing adverse drug reactions were not considered in the model, due to the low incidence of serious adverse events with biologic treatment and the relatively small differences in adverse event occurrence across biologics.

6.4 Drug acquisition costs

Drug acquisition costs were calculated as shown in Table 6.3.

Unit drug costs were sourced from MIMS with a discount of 15% applied to abatacept and tocilizumab formulations in line with Section 5. For sarilumab, the dosing schedule was taken from the draft SmPC. The dosing schedule for rituximab was based on NICE TA375. For all other therapies, the dosing schedules were sourced from their respective SmPCs.

To account for loading doses for certain therapies, dosing calculations were separated into 'induction' and 'maintenance' years. Induction year costs were applied to incident patients, whereas maintenance year costs were applied to prevalent patients.

For drugs with more irregular dosing schedules (rituximab and infliximab), the dosing schedule was averaged over their recurring annual dosing cycles. Patients taking rituximab receive a treatment course every 9 months, and would therefore typically experience two treatment courses every 3 years and one treatment course for every intermediary 2 years, meaning that they would receive 2.67 doses on average annually. For patients on infliximab, which has an 8-weekly dosing schedule, patients would interchange between six and seven doses per year, with an average of 6.5 doses per year.

For the weight-based therapies administered intravenously (abatacept IV, tocilizumab IV and infliximab), a mean patient weight of 74.3 kg was assumed, based on the average weight of patients in the MOBILITY B trial. The effect of using a 70kg mean patient weight is tested in Section 5 and shown not to have a notable impact on the results.

The following patient access schemes were also applied:

- For golimumab, the costs of the 50 mg and 100 mg dosing regimens were equal[17].

- For certolizumab pegol, doses within the first 12 weeks of treatment (i.e. the first nine doses) incurred no cost[17].

Table 6.3 Drug acquisition costs

Comparator	Dose(s)	Dose frequency	Unit/vial cost	Units/vials per dose	Induction year doses[a]	Induction year cost	Maintenance year doses[a]	Maintenance year cost
Sarilumab	200 mg	Every other week	[redacted]	1.00	26	[redacted]	26	[redacted]
Abatacept IV	500 mg if <60 kg, 750 mg if 60–100 kg, 1000 mg if >100 kg	Week 0, 2, 4, then every 4 weeks	£257.04¥	3.00	15	£11,566.80	13	£10,024.56
Abatacept SC	125 mg	Once per week	£257.04¥	1.00	52	£13,366.08	52	£13,366.08
Golimumab	50 mg and 100 mg (2 x 50 mg)	Once per month	£762.97‡	1.00	12	£9,155.64	12	£9,155.64
Etanercept	25 mg	Twice weekly	£89.38	1.00	104	£9,295.00	104	£9,295.00
Etanercept (biosimilar)	50 mg	Every week	£164.00	1.00	52	£8,528.00	52	£8,528.00
Adalimumab	40 mg	Every other week	£352.14	1.00	26	£9,155.64	26	£9,155.64
Rituximab	2,000 mg (2 x 1,000 mg)	Two 1000 mg IV infusions separated by 2 weeks (one course) every 9 months	£873.15	2.00§	4	£6,985.20	2.67	£4,656.80
Certolizumab pegol	400 mg (2 x 200 mg) induction dose, 200 mg maintenance dose	400 mg dose at week 0, 2, and 4, followed by maintenance dose every other week (12 weeks free PAS)	£357.50	1.00	29	£6,792.50††	26	£9,295.00
Tocilizumab IV	8 mg/kg	Every 4 weeks	£87.04¥	7.43¶	13	£8,407.19	13	£8,407.19
Tocilizumab SC	162 mg	Every week	£194.04¥	1.00	52	£10,089.98	52	£10,089.98
Infliximab	3 mg/kg	Week 0, 2 and 6, then every 8 weeks	£419.62	2.23	8	£7,482.66	6.5	£6,079.66

Comparator	Dose(s)	Dose frequency	Unit/vial cost	Units/vials per dose	Induction year doses[a]	Induction year cost	Maintenance year doses[a]	Maintenance year cost
Infliximab (biosimilar)	3 mg/kg	Week 0, 2 and 6, then every 8 weeks	£377.66	2.23	8	£6,734.43	6.5	£5,471.73

IV, intravenous; SC, subcutaneous. †Assumes 52 weeks in a year. ‡The same unit cost was applied for both the 50mg and 100mg doses for golimumab (Simponi), as per its patient access scheme. §The number of vials per dose for MabThera was calculated on the basis of the 50ml vial size. ¶The number of vials per dose for RoActemra IV was calculated on the basis of the 80 mg/4ml vial size. ¥Representative 15% discount applied due to unknown confidential PAS ††The induction year cost for certlizumab pegol (Cimzia) takes into account its patient access scheme, which states that the first 12 weeks of treatment incur no cost.

6.5 Administration costs

Administration costs were included for both types of administration (subcutaneous and intravenous). For treatments administered intravenously, an infusion administration cost of £170.28[17] was applied for each dose and for therapies self-administered subcutaneously, it was assumed that 10% of administrations would require a nurse visit, at a cost of £77.24 per visit[17] as described in Section 5.5.4. As discussed in Section 5.5.2, Sanofi Genzyme provide a homecare service for sarilumab and patients will self-administer at home therefore this approach, used to keep in line with the cost-effectiveness analysis and methods of the AG in TA375, is likely to overestimate costs associated with sarilumab. Annual administration costs are presented in Table 6.4.

Table 6.4 Administration costs

Generic name (brand name)	Administration method	Induction year doses	Maintenance year doses	Induction year administration cost	Maintenance year administration cost
Sarilumab	SC	26	26	£200.82	£200.82
Abatacept IV	IV	15	13	£2,554.20	£2,213.64
Abatacept SC	SC	52	52	£401.65	£401.65
Golimumab	SC	12	12	£92.69	£92.69
Etanercept	SC	104	104	£803.30	£803.30
Etanercept (biosimilar)	SC	52	52	£401.65	£401.65
Adalimumab	SC	26	26	£200.82	£200.82
Rituximab	IV	4	2.67	£681.12	£454.08
Certolizumab pegol	SC	29	26	£224.00	£200.82
Tocilizumab IV	IV	13	13	£2,213.64	£2,213.64
Tocilizumab SC	SC	52	52	£401.65	£401.65
Infliximab	IV	8	6.5	£1,362.24	£1,106.82
Infliximab (biosimilar)	IV	8	6.5	£1,362.24	£1,106.82

IV, intravenous; SC, subcutaneous.

6.6 Monitoring costs

The number of monitoring events for each therapy are presented in Table 6.5. Lipid profiling events were based on the SmPC for tocilizumab and draft SmPC for sarilumab. All other monitoring requirements and frequency of monitoring events were obtained from NICE TA375[17].

Table 6.5 Number of monitoring events

Test	Number of events		
	Before treatment initiation	First 6 months of treatment	After first 6 months of treatment
IL-6			
FBC[a]	1	10	6
ESR[a]	1	0	0
BCP[a]	1	10	6
CXR[a]	1	0	0
Lipid profile[a,b]	1	10	6
Hospital outpatient attendance[a]	1	10	6
Anti-TNF and other biologics			
FBC[a]	1	10	6
ESR[a]	1	0	0
BCP[a]	1	10	6
CXR[a]	1	0	0
Hospital outpatient attendance[a]	1	10	6

BCP, biochemical profile; CXR, chest X-ray; ESR, erythrocyte sedimentation rate; FBC, full blood count; IL-6, interleukin-6; SAR, sarilumab; SmPC, Summary of Product Characteristics; TCZ, tocilizumab; TNF, tumour necrosis factor. [a]Obtained from TA375. [b]Obtained from TCZ SmPC/SAR draft SmPC.

The unit costs applied for each monitoring event, sourced from NHS reference costs and Stevenson et al (2016)[67], are presented in Table 6.6.

Table 6.6 Unit costs of each monitoring event

Test	Unit cost	Reference
Full blood count	£1.59	National schedule of reference costs 2015/16 (currency code DAPS03)
Erythrocyte sedimentation rate	£3.10	National schedule of reference costs 2015/16 (currency code DAPS05)
Biochemical profile	£3.10	National schedule of reference costs 2015/16 (currency code DAPS05)
Chest X-ray	£34.45	Stevenson et al (2016), inflated to 2015/16 value using PSSRU Unit Costs of Health & Social Care 2016
Lipid profile	£1.59	National schedule of reference costs 2015/16 (currency code DAPS03)
Hospital outpatient attendance	£142.74	National schedule of reference costs 2015/16 (service code 410)

PSSRU, Personal Social Services Research Unit.

This resulted in the following annual monitoring costs for each therapy (Table 6.7).

Table 6.7 Annual monitoring costs

Generic name	Induction year monitoring cost	Maintenance year monitoring cost
Sarilumab	£2,570.89	£1,788.24
Abatacept IV	£2,543.86	£1,769.16
Abatacept SC	£2,543.86	£1,769.16
Golimumab	£2,543.86	£1,769.16
Etanercept	£2,543.86	£1,769.16
Etanercept (biosimilar)	£2,543.86	£1,769.16
Adalimumab	£2,543.86	£1,769.16
Rituximab	£2,543.86	£1,769.16
Certolizumab pegol	£2,543.86	£1,769.16
Tocilizumab IV	£2,570.89	£1,788.24
Tocilizumab SC	£2,570.89	£1,788.24
Infliximab	£2,543.86	£1,769.16
Infliximab (biosimilar)	£2,543.86	£1,769.16

IV, intravenous; SC, subcutaneous.

6.7 NHS resource savings

The resource impact of the proposed scenario versus the current scenario, in terms of the incremental number of events, is shown in Table 6.8 for the base-case analysis and Table 6.9 for the scenario analysis.

Table 6.8 Incremental number of events for the proposed scenario versus the current scenario – base-case analysis

Resource element	2017	2018	2019	2020	2021	Total[a]
Outpatient visits	–730	–4,103	–7,012	–9,907	–12,453	–34,204
Nurse visits	1	8	14	20	25	70
Lipid profile tests	145	815	1,391	1,964	2,467	6,781

[a]The numbers presented for each individual year may not sum to the total number of events due to rounding.

Table 6.9 Incremental number of events for the proposed scenario versus the current scenario – scenario analysis [redacted]

Resource element	2017	2018	2019	2020	2021	Total[a]
Outpatient visits	–768	–4,320	–7,383	–10,431	–13,113	–36,016
Nurse visits	0	0	0	0	0	0
Lipid profile tests	0	0	0	0	0	0

[a]The numbers presented for each individual year may not sum to the total number of events due to rounding.

In the base-case analysis, there was a large reduction in outpatient visits and a minor increase in nurse visits, due to sarilumab displacing therapies administered intravenously. There was also an increase in the number of lipid profile tests, with

sarilumab (an IL-6 inhibitor) displacing therapies with other mechanisms of action that do not require lipid profile tests.

In the scenario analysis, [redacted], there was a further reduction in the number of outpatient visits due to an increased displacement of treatment administered intravenously. The difference in the number of nurse visits was negligible, due to a reduction in the difference between the two scenarios of overall subcutaneous administrations, and an increase in overall IV administered treatment. The difference in the number of lipid profile tests was zero across all years due to sarilumab and tocilizumab both being IL-6 inhibitors.

Since the frequency of other tests and monitoring-based outpatient visits did not differ between biologic therapies, there were no differences in resource use for those elements across both sets of analyses.

6.8 Annual NHS budget impact

The estimated budget impact for the base-case analysis and scenario analysis are presented in Table 6.10.

In the base-case analysis, sarilumab is associated with significant net savings from year one [redacted] in year 5) with a majority of its market share displacing tocilizumab.

In scenario analysis, where the sarilumab market share [redacted], the further displacement of [redacted] leads to increased savings to the base-case driven by the higher cost of [redacted] vs. the majority of comparators.

6.8.1 Conclusion

In line with other biologics recently recommended by NICE, sarilumab is not likely have to have significant budget impact for the NHS. However, it is offered to the NHS in England and Wales with a simple PAS that is likely to lead to moderate savings based on acquisition cost differences between the [redacted] alone and, if potential [redacted] patients are instead initiated on sarilumab SC, there are both savings due to lower acquisition costs and due to reduced cost of administration. Sarilumab therefore presents an opportunity to increase efficiencies in resource allocation whilst offering patients and clinicians who have not achieved adequate response with current therapies an effective alternative option in the treatment of RA.

Table 6.10 Budget impact

	2017	2018	2019	2020	2021	Total†
Number of patients eligible for biologic treatment	39,399	41,535	43,686	45,853	48,034	218,507
Number of patients treated with sarilumab	118	665	1,136	1,605	2,017	5,541
Prevalent & incident cases						
Net total budget impact – base−case [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net total budget impact – scenario analysis [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net total budget impact – scenario analysis [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net total budget impact – scenario analysis [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net total budget impact – scenario analysis [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net total budget impact – scenario analysis [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incident cases only						
Net total budget impact – base−case [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net total budget impact – scenario analysis [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net total budget impact – scenario analysis [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net total budget impact – scenario analysis [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net total budget impact – scenario analysis [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net total budget impact – scenario analysis [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

† Patient numbers and costs for each year may not sum to total due to rounding

6.9 Limitations within the budget impact analysis.

Limitations identified with the budget impact analysis are as follows:

- The cost of concomitant treatment with cDMARDs was not included in the model. However, since the cost of cDMARD treatment is low relative to biologic treatment costs, and it is expected that there would be only small (if any) differences between biologic treatments in terms of concomitant medication use, the budget impact was assumed to be negligible.

- The cost of managing adverse drug reactions was not considered in the model, due to the low incidence of serious adverse events with biologic treatment and the relatively small differences in adverse event occurrence across biologics.

- It is assumed that no vial wastage occurs for infliximab, abatacept, rituximab and tocilizumab IV. This means that the acquisition costs for these therapies may be underestimated.

- While the ONS population projections account for general mortality, the increased mortality risk associated with moderate-to-severe RA was not considered in the budget impact. However, it is not expected that there would be significant differences in mortality between individual biologic therapy options and therefore no significant impact on the analysis.

- The model does not consider discontinuation of patients from biologic therapy. This is considered a conservative simplifying assumption as the RHUMADATA analysis showed higher retention rates with IL-6 compared with other modes of action. This is expected to have a positive budgetary impact due to fewer patient attendances and fewer costs associated with worsening disease.

- The model does not consider the impact of prevalent patients switching therapies, which may result in some patients incurring increased costs in the first 6 months after switching therapies due to higher induction costs. However, it is not anticipated that the introduction of sarilumab will have a large impact on overall drug discontinuation events between biologic therapies and therefore the associated cost impact is assumed to be negligible.

- The analysis does not include an estimate for the moderate population. The reason for this is that there are no credible estimates on the number of moderate patients in the UK with DAS >4 ≤5.1.

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365. MIMS. Adalimumab (Humira). 2016. http://www.mims.co.uk/drugs/musculoskeletal-disorders/rheumatoid-arthritis-other-autoimmune-disorders/humira (accessed December 2016).

366. MIMS. Rituximab (MabThera). 2016. http://www.mims.co.uk/drugs/musculoskeletal-disorders/rheumatoid-arthritis-other-autoimmune-disorders/mabthera (accessed December 2016).

367. MIMS. Certolizumab pegol (Cimzia). 2016. http://www.mims.co.uk/drugs/musculoskeletal-disorders/rheumatoid-arthritis-other-autoimmune-disorders/cimzia (accessed December 2016).

368. MIMS. Tocilizumab (RoActemra). 2016. http://www.mims.co.uk/drugs/musculoskeletal-disorders/rheumatoid-arthritis-other-autoimmune-disorders/roactemra (accessed December 2016).

369. MIMS. Infliximab (Remicade). 2016. http://www.mims.co.uk/drugs/musculoskeletal-disorders/rheumatoid-arthritis-other-autoimmune-disorders/remicade (accessed December 2016).

370. MIMS. Infliximab (Remsima). 2016. http://www.mims.co.uk/drugs/musculoskeletal-disorders/rheumatoid-arthritis-other-autoimmune-disorders/remsima (accessed December 2016).

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8 Appendices

12 Expert clinical opinion
13 Advisory board recommendations for cost-effectiveness model
14 Sanofi Genzyme trial data analysis
  14.1 HAQ change by ACR or EULAR response at 6 months
  14.2 Analysis of HAQ-DI trajectory by initial ACR category
  14.3 Mapping ACR to EULAR response categories at 6 months
15 Rhumadata® inputs
  15.1 Rationale
  15.2 Objective
  15.3 Method
  15.4 Results
16 Cost and healthcare resource identification, measurement and validation
17 References (for appendix)

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

Single Technology Appraisal (STA)

Sarilumab for treating moderate-to-severe rheumatoid arthritis [ID994]

Dear [redacted]

The Evidence Review Group, School of health and related research (ScHARR) and the technical team at NICE have now had an opportunity to take a look at the submission received on the 15th May by Sanofi. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **5pm** on **21st June**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

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

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be emailed to us separately as attachments or sent on a CD.

If you have any further queries on the technical issues raised in this letter then please contact Victoria Kelly, Technical Lead (victoria.kelly@nice.org.uk). Any procedural questions should be addressed to Stephanie Yates, Project Manager (stephanie.yates@nice.org.uk) in the first instance.

Yours sincerely

Frances Sutcliffe
Associate Director – Appraisals
Centre for Health Technology Evaluation

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

Literature searching

Clinical effectiveness search:

1. There can be a delay of some months between online publication and appearance in print, and further delays before appearing fully indexed in Medline. It is conventional therefore for systematic searches to include the "In Process" and "Epub ahead of print" sections of Medline. What steps, if any, were taken to ensure the company submission contains the latest evidence?

Cost effectiveness search:

2. Appendix 9 reproduces the Medline and EMBASE update searches from December 2016 but the NHS EED search (to 2015) is missing, as are the first round searches from 2014. Please provide these (if available) and indicate whether any additional steps were undertaken in 2016 to identify economic studies beyond Medline and EMBASE.

3. It is noted that the MEDLINE search (Appendix, Table 9.1) includes the use of limits (language, humans, abstracts). While these are in accordance with the stated inclusion criteria, database limits can lead to the accidental exclusion of records where fields are blank. Please comment on your reasons for deciding upon this approach.

Section A: Clarification on effectiveness data

A1. Appendix 1 (page 12). Please provide Appendix 1.1 EPAR

A2. Please clarify why studies NCT01217814 and NCT01764997 were terminated. Were any data collected prior to termination? If so, please supply the relevant data.

A3. Page 66 (Table 4.4). Please elaborate on the reasons for exclusions of the studies shown in Table 1 below. Further, please clarify why these trials did not contribute to the synthesis of safety data.

Table 1: Excluded studies

Study	Reason for exclusion
ONE NCT02121210	Dose study

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EASY NCT02057250	All arms sarilumab (comparing types of injection)
KAKEHASI NCT02293902	Dose-response profile of Japanese patients?
HARUKA NCT02373202	Compares sarilumab monotherapy with sarilumab +cDMARDs (non-MTX)

A4. Please clarify how many patients from the UK were included in the MONARCH and ASCERTAIN studies.

A5. Please confirm if the only difference between selection criteria for the initial and update searches (page 53, Table 4.1 and page 58, Table 4.2) was that investigational drugs were limited to baricitinib and sirukumab in the update search.

A6. Page 121 (Table 4.21). Please provide comparative statistics for ASCERTAIN effectiveness results

Network Meta-Analysis

A7. **Priority question:** Please provide the NMA results for ACR and EULAR response in the cDMARD-IR and TNFi-IR population with the following settings:

- Using a random effects probit model with an informative prior for the between-study variance (log normal with mean -2.56 and variance of 1.74*1.74, which is proposed by Turner et al 2012. The log normal is truncated so that the odds ratio in one study would not be ≥50 times than in another, and re-scaled to match the probit scale). The BUGS code for this prior is:
  var~dlnorm(-2.56,0.33)I(,1)

  sd<-sqrt(var)/1.81

  tau <- pow(sd,-2)

  Turner RM, Davey J, Clarke MJ, Thompson SG, Higgins JP; Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. Int J Epidemiol 2012;41:818–27. doi:10.1093/ije/dys041
- Keeping all treatment separate.
- Including combination therapy and monotherapy in one network in order that trials comparing both regimens can provide evidence (including the studies in Appendix 8, Table 8.7 and HARUKA).
- Including the studies which were excluded due to small sample size (Appendix 8 Table 8.1 and Table 8.9)

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- Please check the studies in Table 8.2 of the appendix and include them if they were included in TA375.
- Include the studies in Table 8.3 of the appendix assuming that etanercept 50mg once weekly is equivalent to etanercept 25mg twice weekly.
- Please incorporate the KAKEHASI for consistency with the main network, which includes studies in Asian patients.

  Please present the results using both relative and absolute measures. Please also present the point estimate and 95% credible interval for the between-study standard deviation, and the goodness of model fitting. In the results, please also provide how the baseline absolute probabilities were estimated. Please supply sensitivity analyses amending parts of this proposed NMA where you feel this is appropriate.

A8. **Priority question:** Please provide a sensitivity analysis for the NMA requested in question A7 pooling TNFis together (TNFi-bundle).

A9. **Priority question:** Please clarify how the baseline absolute effect was modelled for each outcome in the cDMARD-IR and TNFi-IR population in the submission.

A10. **Priority question:** For the analysis where standard logit model was used (for example, for safety outcomes), please re-run the model using prior d[k]~dnorm(0,0.001) for k bigger than 1. If data were sparse, please use the prior var~dlnorm(-2.56,0.33)I(,1) for the between-study variance. Please present the point estimate and 95% credible interval for the between-study standard deviation, and the goodness of model fitting.

A11. **Priority question:** Probabilities are constrained between 0 and 1. Please clarify what approach was used to achieve this in the model where risk difference was used as the measurement of effect.

A12. **Priority question:** Appendix (page 201, section 8.8.1.5). Please clarify which less vague priors were used in the TNFi-IR population.

A13. Please provide the point estimate and 95% credible interval for the between-study standard deviation when a random effects model was used.

A14. Please clarify what method was used for convergence checking when performing the NMAs. Please provide the number of iterations for burn-in and the number of iterations for estimating the parameters in each NMA.

A15. Please provide comments on goodness of model fitting for all NMAs.

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Manchester
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A16. **Priority question:** Please clarify why in the WinBUGS code where a fixed effect model was stated as the model of choice, a random effects model was used.

A17. Please clarify why Relative risks (RR) vs. treatment 1 (control) are calculated in the winBUGS code (company submission, winBUGS excel sheet) but are not mentioned anywhere else the company submission. We would like to know if the RRs were used and if so how.

Section B: Clarification on cost-effectiveness data

B1. **Priority question:** Please provide analyses for all the populations with the following assumptions if possible (if not possible please clarify why):

a. Using the results of the NMA described in question A8.
b. Using Hernandez et al. 2013 (see TA375 section 4.65) to map HAQ to EQ-5D.
c. Using change in HAQ upon response based on TA375 (-0.317 for moderate EULAR responders, -0.672 for good EULAR responders).
d. Rounding HAQ scores after every change to a valid HAQ score (a multiple of 0.125 between 0 and 3). Please use the following method: with the probabilities of being at the higher or lower valid HAQ score proportional to the distances from each HAQ score. For example: round a score of 0.400 to 0.375 with a probability of 0.8 and to 0.500 with a probability of 0.2.
e. Using a non-linear HAQ progression for patients on cDMARDs, ideally the one used in TA375 (HTA monograph for TA375, "Stevenson Health technology assessments 2016" from the company's reference pack, page 254).
f. Using the probability of EULAR response calculated for cDMARDs in the NMA for the MTX and SSZ treatments.
g. Use generalised gamma distributions for time to treatment discontinuation (see question B3 for further details). If it is not possible to implement the generalised gamma then use the lognormal distribution. Time permitting provide scenario analyses using different distributions for good and moderate EULAR responses.
h. Using correlated samples from the CODA of the NMA in the PSA for the probabilities of ACR responses instead of using independent samples from beta distributions.
i. Using 10 free doses of certolizumab pegol (as established in NICE guidance TA375 and TA415) instead of 9.
j. Removing the half cycle correction for the first cycle: patients only are assessed for response at six months and therefore cannot progress earlier. Add in drug, AE and administration costs at cycle 0.
k. Removing the speculative PAS of 15% applied to tocilizumab and abatacept.
l. Using the following sequences as shown in Tables 2 to 8:

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Manchester
M1 4BT
United Kingdom

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Table 2: Sequences for the severe cDMARD-iR population (MTX-tolerant)

1	Sarilumab + MTX	Tocilizumab IV + MTX	Tocilizumab SC + MTX	TNFi bundle + MTX	Abatacept SC + MTX
2	Rituximab + MTX	Rituximab + MTX	Rituximab + MTX	Rituximab + MTX	Rituximab + MTX
3	MTX	MTX	MTX	Tocilizumab IV + MTX	Tocilizumab IV + MTX
4	BSC	BSC	BSC	MTX	MTX
5				BSC	BSC

B2. Please provide an incremental analysis for moderate cDMARD-IR patients with a DAS28 score between 4.0 and 5.1 with the sequences described in Table 2 so that patients receive the moderate treatment sequences until they progress to severe RA and then receive treatment for severe patients (severe sequences in Table 2). In order to do this a relationship between HAQ and DAS28 score would need to be estimated. If you do not have the data from your trials, assume a 1:1 mapping.

Table 3: Sequences for the moderate cDMARD-IR population

	Moderate sequences	
1	Sarilumab + MTX	MTX
2	MTX	BSC
3	BSC	
	Severe sequences	
1	TNFi bundle + MTX	
2	Rituximab + MTX	
3	Tocilizumab IV + MTX	
4	SSZ	
5	BSC	

SSZ: sulfasalazine

Table 4: Sequences for the severe cDMARD-IR MTX-intolerant population

1	Sarilumab	Tocilizumab IV	Tocilizumab SC	TNFi bundle
2	TNFi bundle	TNFi bundle	TNFi bundle	TNFi bundle
3	SSZ	SSZ	SSZ	SSZ
4	BSC	BSC	BSC	BSC

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Manchester
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SSZ: sulfasalazine

Table 5: Sequences for the severe TNFi-IR RTX-ineligible population

1	Sarilumab + MTX	Tocilizumab IV + MTX	Tocilizumab SC + MTX	TNFi bundle + MTX	Abatacept SC + MTX
2	MTX	MTX	Abatacept IV + MTX	Tocilizumab IV + MTX	Tocilizumab IV + MTX
3	BSC	BSC	MTX	MTX	MTX
4			BSC	BSC	BSC

Table 6: Sequences for the severe TNFi-IR RTX-eligible population

1	Sarilumab + MTX	Rituximab + MTX	Sarilumab + MTX	Rituximab + MTX
2	Tocilizumab IV + MTX	Tocilizumab IV + MTX	MTX	MTX
3	MTX	MTX	BSC	BSC
4	BSC	BSC		

Table 7: Sequences for the severe TNFi-IR MTX-intolerant population

1	Sarilumab	TNFi bundle
2	SSZ	SSZ
3	BSC	BSC

Table 8: Sequences for patients with severe active disease despite treatment with bDMARDs recommended according to NICE guidance

1	Sarilumab + MTX	Tocilizumab IV + MTX	Tocilizumab SC + MTX
2	MTX	MTX	MTX
3	BSC	BSC	BSC

B3. **Priority question:** Please perform an analysis where the lowest acquisition and administration price is used for the TNFi bundle based on the analysis in question B1.

B4. Please clarify why the Gompertz distribution was chosen to extrapolate time to treatment discontinuation when the generalised gamma resulted in better statistical fits (using AIC) for all comparisons and the lognormal has a better fit (using AIC) in the combined model.

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B5. Please provide a scenario analysis where the ETN and IFX biosimilars have taken over the market share of their branded formulations.

B6. Please clarify why the number of free doses of certolizumab pegol was varied within the PSA.

Section C: Textual clarifications and additional points

C1. Page 39. Please clarify whether the sentence "Certolizumab pegol and tocilizumab are approved for use only in combination with MTX" is wrong. It contradicts NICE recommendations following TA375 and figure 3.1 on page 40.

C2. Page 48. Please clarify whether the following sentence is wrong "TA375 the moderate RA patients assessed were those are able to respond adequately to and are tolerant of cDMARDs, conversely this appraisal considers only those patients who do not respond adequately to, or are intolerant to cDMARDs". Within TA375, people with moderate RA (Population 2) had already failed on intensive cDMARDs.

C3. Page 128. Please confirm if the data for HAQ score contained in Table 4.25 are missing a minus sign for the midpoint value.

C4. Page 206. Please amend figure 5.5 to state biologic rather than biometric.

C5. Pages 215-216. Please confirm if EULAR moderate refers to at least a moderate EULAR response in Tables 5.17, 5.18 and 5.19.

C6. Page 222. Please clarify whether the legend in figure 5.12 is wrong and confirm whether it should read from top to bottom: IL6, Other biologics and TNFi.

C7. Page 36. Please clarify why percentages do not add up to 100 in Table 3.1.

C8. Page 216. Please clarify whether the first row in Table 5.19 should say "Sarilumab + MTX" instead of "Sarilumab" alone.

Single Technology Appraisal (STA)

Sarilumab for treating moderate-to-severe rheumatoid arthritis [ID994]

Dear Frances,

Thank you for your letter of 7th June requesting further clarification relating to the clinical and cost effectiveness data in our submission. Please find our responses addressing the issues below. As agreed from the communication with NICE on 13th June, the additional analysis requested by the ERG will follow on 26th June. We have also revised the company submission document to reflect the amendments mentioned in this response letter. We will provide the revised company submission document alongside the remaining analysis on 26th June.

Yours sincerely

[redacted]
Head of Health Outcomes UK & Ireland

Literature searching

Clinical effectiveness search:

1. *There can be a delay of some months between online publication and appearance in print, and further delays before appearing fully indexed in Medline. It is conventional therefore for systematic searches to include the "In Process" and "Epub ahead of print" sections of Medline. What steps, if any, were taken to ensure the company submission contains the latest evidence?*

   We confirm that MEDLINE and MEDLINE In-Process were searched using the PubMed interface to ensure that any articles falling into this period and ahead of print citations were retrieved.

Cost effectiveness search:

2. *Appendix 9 reproduces the Medline and EMBASE update searches from December 2016 but the NHS EED search (to 2015) is missing, as are the first round searches from 2014. Please provide these (if available) and indicate whether any additional steps were undertaken in 2016 to identify economic studies beyond Medline and EMBASE.*

   The hits obtained from searching NHS EED are provided in Appendix A and B. These were obtained using the search term "Rheumatoid arthritis". Whilst reviewing our records we identified a typographical error in our submission which has now been corrected. In the original search, 118 records were obtained from NHS EED and 386 from HEED however this was mistakenly reported as 118 from HEED and 386 from NHS EED in our company submission document.

   As indicated above, NHS EED was searched in addition to MEDLINE and EMBASE. Furthermore, the references of any systematic literature review identified in the searches were reviewed for studies matching the inclusion criteria. No further steps were taken to identify economic studies.

3. *It is noted that the MEDLINE search (Appendix, Table 9.1) includes the use of limits (language, humans, abstracts). While these are in accordance with the stated inclusion criteria, database limits can lead to the accidental exclusion of records where fields are blank. Please comment on your reasons for deciding upon this approach.*

   The decision to use limits in the MEDLINE search was pragmatic and was made in order to keep the number of hits in this therapy area manageable. Whilst we recognise the limitations of this, we are also aware of the previous NICE assessments in RA and so expected a low risk of not identifying any pivotal economic

evaluations which are notably different from TA375, TA195, TA415, TA247 and TA225 as a result of the application of these limits.

Section A: Clarification on effectiveness data

A1. *Appendix 1 (page 12). Please provide Appendix 1.1 EPAR*

Apologies for this oversight, the EPAR is provided in Appendix C.

A2. *Please clarify why studies NCT01217814 and NCT01764997 were terminated. Were any data collected prior to termination? If so, please supply the relevant data.*

Termination of NCT01764997

This study was terminated prematurely on 07 August 2014 due to the inability to provide timely results versus the original study plan. This decision was not related to any safety issue, but was a result of study delays caused by a smaller than expected number of patients entering the randomized phase of the study. Approximately 10% of subjects who entered the adalimumab run-in qualified for the randomized study, compared with the 30-40% anticipated.

Termination of NCT01217814

This study was discontinued as a result of the delays incurred in the study and impact to timelines for study completion. At time of study discontinuation, 16 patients had been randomized, [redacted] No efficacy analyses were performed due to insufficient data as a result of the low enrolment relative to the initially planned study sample size. Safety analyses were performed as planned in the statistical analysis plan. Due to the premature termination and small number of patients, no conclusions could be drawn on the safety, efficacy or pharmacokinetic profile of sarilumab from this study.

A3. *Page 66 (Table 4.4). Please elaborate on the reasons for exclusions of the studies shown in Table 1 below. Further, please clarify why these trials did not contribute to the synthesis of safety data*.

Table 1: Excluded studies

Study	***Reason for exclusion***
ONE *NCT02121210*	*Dose study*

EASY *NCT02057250*	*All arms sarilumab (comparing types of injection)*
KAKEHASI *NCT02293902*	*Dose-response profile of Japanese patients?*
HARUKA NCT02373202	*Compares sarilumab monotherapy with sarilumab +cDMARDs (non-MTX)*

Exclusion of ONE and EASY

These studies were excluded form detailed reporting in our submission as they are uncontrolled studies and therefore less informative for estimating treatment effects. It should be noted however that safety outcomes from these studies were included in the EMA licence application as part of the pooled safety analysis of sarilumab. Details of the analysis are provided in the EPAR.

Exclusion of KAKEHASI and HARUKA

These studies were excluded from detailed reporting in our submission as they were conducted in Japanese patients only. The Japanese population are known to have physiological differences to the UK population, particularly in body weight, and therefore the clinical effects observed in clinical trials in these patients may not be generalisable to the UK population. [redacted]

A4. Please clarify how many patients from the UK were included in the MONARCH and ASCERTAIN studies.

In the ASCERTAIN study, 14 patients were treated in the UK. In the MONARCH study, UK sites were selected for patient participation however no UK patients were treated due to the study reaching capacity very quickly from other countries before any UK patients could be recruited.

A5. Please confirm if the only difference between selection criteria for the initial and update searches (page 53, Table 4.1 and page 58, Table 4.2) was that investigational drugs were limited to baricitinib and sirukumab in the update search.

The key difference between the initial and the update searches was the limitation of investigational drugs to baricitinib and sirukumab. Additionally, in the update review, only studies with greater than 12 weeks study duration were selected. This was adopted because in the initial review, studies with less than 12 weeks duration did not provide data related to outcomes of interest.

A6. *Page 121 (Table 4.21). Please provide comparative statistics for ASCERTAIN effectiveness results*

The ASCERTAIN trial was designed as a safety study and was not powered to provide any comparative effectiveness data. Consequently, no comparative analyses were performed as the efficacy endpoints were exploratory only. Furthermore, due to the power limitations of the study it would be misleading to conduct comparative statistical analysis. The study report was however made available in our original submission.

Network Meta-Analysis

A7. ***Priority question:*** *Please provide the NMA results for ACR and EULAR response in the cDMARD-IR and TNFi-IR population with the following settings:*

- *Using a random effects probit model with an informative prior for the between-study variance (log normal with mean -2.56 and variance of 1.74*1.74, which is proposed by Turner et al 2012. The log normal is truncated so that the odds ratio in one study would not be ≥50 times than in another, and re-scaled to match the probit scale). The BUGS code for this prior is:*
  var~dlnorm(-2.56,0.33)I(,1)

  sd<-sqrt(var)/1.81

  tau <- pow(sd,-2)

  Turner RM, Davey J, Clarke MJ, Thompson SG, Higgins JP; Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. Int J Epidemiol 2012;41:818–27. doi:10.1093/ije/dys041
- *Keeping all treatment separate.*
- *Including combination therapy and monotherapy in one network in order that trials comparing both regimens can provide evidence (including the studies in Appendix 8, Table 8.7 and HARUKA).*
- *Including the studies which were excluded due to small sample size (Appendix 8 Table 8.1 and Table 8.9)*
- *Please check the studies in Table 8.2 of the appendix and include them if they were included in TA375.*

- *Include the studies in Table 8.3 of the appendix assuming that etanercept 50mg once weekly is equivalent to etanercept 25mg twice weekly.*
- *Please incorporate the KAKEHASI for consistency with the main network, which includes studies in Asian patients.*

  Please present the results using both relative and absolute measures. Please also present the point estimate and 95% credible interval for the between-study standard deviation, and the goodness of model fitting. In the results, please also provide how the baseline absolute probabilities were estimated. Please supply sensitivity analyses amending parts of this proposed NMA where you feel this is appropriate.

As agreed, we will provide a response by Monday 26th June.

A8. ***Priority question:*** *Please provide a sensitivity analysis for the NMA requested in question A7 pooling TNFis together (TNFi-bundle).*

As agreed, we will provide a response by Monday 26th June.

A9. ***Priority question:*** *Please clarify how the baseline absolute effect was modelled for each outcome in the cDMARD-IR and TNFi-IR population in the submission.*

For both the cDMARD-IR and TNF-IR networks, the baseline absolute effect was calculated by averaging all study effects with baseline arm (cDMARD or MTX, expressed as mu1) plus additional baseline/treatment effect, fixed to a constant value of 0 by default for baseline treatment arm -(d[1]=0). Furthermore, this approach follows NICE DSU technical support document guidance.

The model for baseline effect can be expressed as:

```
{
        mu1[s] <- mu[s] * equals(trt[s,1],1)
        count1[s] <- equals(trt[s,1],1)
        }
for (i in 1:NT)

# Case of log scale model
{
        logit(T[i])<- sum(mu1[])/sum(count1[]) +d[i]
# Case of natural scale model
# T[k] <- sum(mu1[])/sum(count1[])  + d[k]
}
where mu1[s] = study effect with baseline arm
trt = treatment code
count1 = study with baseline arm equal 1
```

A10. ***Priority question:*** *For the analysis where standard logit model was used (for example, for safety outcomes), please re-run the model using prior d[k]~dnorm(0,0.001) for k bigger than 1. If data were sparse, please use the prior var~dlnorm(-2.56,0.33)I(,1) for the between-study variance. Please present the point estimate and 95% credible interval for the between-study standard deviation, and the goodness of model fitting.*

As described in the appendix section 8.11 of the submission, NICE recommended priors were used in all base-case models [mu[i] ~ dnorm(0,0.0001) and d[k] ~ dnorm(0,0.001) for k bigger than 1).

For ACR response and DAS28 remission outcomes in the monotherapy population, a random effects model with informative priors as suggested by NICE was used for the between-study variance. The results are presented in Appendix D and E and demonstrate that the informative priors had minimal impact on the results.

A11. ***Priority question:*** *Probabilities are constrained between 0 and 1. Please clarify what approach was used to achieve this in the model where risk difference was used as the measurement of effect.*

The approach set forth by NICE DSU in technical support documents was used to prevent the fitted probabilities in a risk difference model from being outside the natural zero-to-one range for probabilities. The following WINBUGS code was used:

T[k] <- step((A + d[k]))* (A+d[k])

Where T = absolute probability

A= Effect for treatment 1,

A~ dnorm(meanA, precA) with mean effect meanA and precision precA for treatment 1.

d = treatment effect and A

A12. ***Priority question:*** *Appendix (page 201, section 8.8.1.5). Please clarify which less vague priors were used in the TNFi-IR population.*

Synthesis of sparse event data presents unique challenges for the TNF-IR population and therefore attaining convergence of the model was difficult. As a result, less vague priors for regression coefficient (B), d and mu were used for relative treatment effect using logodds (under the belief of OR=[0,500], d~Normal (0,10)); and study effect (under the belief of p=(0.005, 0.995)), mu~Normal (0,10) based on the work of Spiegelhalter and colleagues.

A13. Please provide the point estimate and 95% credible interval for the between-stud standard deviation when a random effects model was used.

Table A below reports the standard deviation with 95% credible intervals for the random effects models.

Table A. Between-study standard deviation estimates

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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A14. *Please clarify what method was used for convergence checking when performing the NMAs. Please provide the number of iterations for burn-in and the number of iterations for estimating the parameters in each NMA.*

Convergence and lack of autocorrelation was tested using BGR plots and autocorrelation plots respectively. No significant challenges with model convergence and autocorrelation were observed in the chosen models. Hence, the thin parameter was set to 1. All results for conventional OR and RD models were based on 100,000 iterations on three chains, with a burn-in of 20,000 iterations. All results for baseline risk regression models were based on 70,000 iterations on three chains, with a burn-in of 15,000 iterations.

A15. *Please provide comments on goodness of model fitting for all NMAs.*

The goodness-of-fit was estimated by calculating the mean residual deviance of the model (mean residual deviance close to 1 was considered to be a good model fit). For example, DIC and average residual deviance were compared in selecting between REM and FEM. Models with DIC at least 3 points lower than another model was deemed to have a better fit. Mean total residual deviance (compared against the number of fitted data points) was also taken into consideration in selecting the preferred model. Additionally, consistency of the model was checked by comparing the closeness of the model results with direct trial level results and meta-analysis.

A16. ***Priority question:*** *Please clarify why in the WinBUGS code where a fixed effect model was stated as the model of choice, a random effects model was used.*

The reference to a fixed effect model in the WinBUGS code is a typographical error and has been corrected to state random effects model.

A17. *Please clarify why Relative risks (RR) vs. treatment 1 (control) are calculated in the winBUGS code (company submission, winBUGS excel sheet) but are not mentioned anywhere else the company submission. We would like to know if the RRs were used and if so how.*

The primary outputs of the Bayesian NMA were odds ratios and risk difference between all interventions in the network for each outcome. In addition, the expected absolute effect for each of these outcomes by treatment was modelled from the NMA. The relative risks were also calculated from the NMA as a default however these were not used in any subsequent analyses.

SANOFI GENZYME

Section B: Clarification on cost-effectiveness data

B1. ***Priority question:*** *Please provide analyses for all the populations with the following assumptions if possible (if not possible please clarify why):*

a. *Using the results of the NMA described in question A8.*
b. *Using Hernandez et al. 2013 (see TA375 section 4.65) to map HAQ to EQ-5D.*
c. *Using change in HAQ upon response based on TA375 (-0.317 for moderate EULAR responders, -0.672 for good EULAR responders).*
d. *Rounding HAQ scores after every change to a valid HAQ score (a multiple of 0.125 between 0 and 3). Please use the following method: with the probabilities of being at the higher or lower valid HAQ score proportional to the distances from each HAQ score. For example: round a score of 0.400 to 0.375 with a probability of 0.8 and to 0.500 with a probability of 0.2.*
e. *Using a non-linear HAQ progression for patients on cDMARDs, ideally the one used in TA375 (HTA monograph for TA375, "Stevenson Health technology assessments 2016" from the company's reference pack, page 254).*
f. *Using the probability of EULAR response calculated for cDMARDs in the NMA for the MTX and SSZ treatments.*
g. *Use generalised gamma distributions for time to treatment discontinuation (see question B3 for further details). If it is not possible to implement the generalised gamma then use the lognormal distribution. Time permitting provide scenario analyses using different distributions for good and moderate EULAR responses.*
h. *Using correlated samples from the CODA of the NMA in the PSA for the probabilities of ACR responses instead of using independent samples from beta distributions.*
i. *Using 10 free doses of certolizumab pegol (as established in NICE guidance TA375 and TA415) instead of 9.*
j. *Removing the half cycle correction for the first cycle: patients only are assessed for response at six months and therefore cannot progress earlier. Add in drug, AE and administration costs at cycle 0.*
k. *Removing the speculative PAS of 15% applied to tocilizumab and abatacept.*
l. *Using the following sequences as shown in Tables 2 to 8:*

As agreed, we will provide a response by Monday 26th June.

Table 2: Sequences for the severe cDMARD-iR population (MTX-tolerant)

1	*Sarilumab + MTX*	*Tocilizumab IV + MTX*	*Tocilizumab SC + MTX*	*TNFi bundle + MTX*	*Abatacept SC + MTX*
2	*Rituximab + MTX*	*Rituximab + MTX*	*Rituximab + MTX*	*Rituximab + MTX*	*Rituximab + MTX*

3	*MTX*	*MTX*	*MTX*	*Tocilizumab IV + MTX*	*Tocilizumab IV + MTX*
4	*BSC*	*BSC*	*BSC*	*MTX*	*MTX*
5				*BSC*	*BSC*

B2. Please provide an incremental analysis for moderate cDMARD-IR patients with a DAS28 score between 4.0 and 5.1 with the sequences described in Table 2 so that patients receive the moderate treatment sequences until they progress to severe RA and then receive treatment for severe patients (severe sequences in Table 2). In order to do this a relationship between HAQ and DAS28 score would need to be estimated. If you do not have the data from your trials, assume a 1:1 mapping.

Table 3: Sequences for the moderate cDMARD-IR population

	Moderate sequences	
1	*Sarilumab + MTX*	*MTX*
2	*MTX*	*BSC*
3	*BSC*	
	Severe sequences	
1	*TNFi bundle + MTX*	
2	*Rituximab + MTX*	
3	*Tocilizumab IV + MTX*	
4	*SSZ*	
5	*BSC*	

SSZ: sulfasalazine

Table 4: Sequences for the severe cDMARD-IR MTX-intolerant population

1	*Sarilumab*	*Tocilizumab IV*	*Tocilizumab SC*	*TNFi bundle*
2	*TNFi bundle*	*TNFi bundle*	*TNFi bundle*	*TNFi bundle*
3	*SSZ*	*SSZ*	*SSZ*	*SSZ*
4	*BSC*	*BSC*	*BSC*	*BSC*

SSZ: sulfasalazine

Table 5: Sequences for the severe TNFi-IR RTX-ineligible population

1	*Sarilumab + MTX*	*Tocilizumab IV + MTX*	*Tocilizumab SC + MTX*	*TNFi bundle + MTX*	*Abatacept SC + MTX*
2	*MTX*	*MTX*	*Abatacept IV + MTX*	*Tocilizumab IV + MTX*	*Tocilizumab IV + MTX*
3	*BSC*	*BSC*	*MTX*	*MTX*	*MTX*
4			*BSC*	*BSC*	*BSC*

Table 6: Sequences for the severe TNFi-IR RTX-eligible population

1	*Sarilumab + MTX*	*Rituximab + MTX*	*Sarilumab + MTX*	*Rituximab + MTX*
2	*Tocilizumab IV + MTX*	*Tocilizumab IV + MTX*	*MTX*	*MTX*
3	*MTX*	*MTX*	*BSC*	*BSC*
4	*BSC*	*BSC*		

Table 7: Sequences for the severe TNFi-IR MTX-intolerant population

1	*Sarilumab*	*TNFi bundle*
2	*SSZ*	*SSZ*
3	*BSC*	*BSC*

Table 8: Sequences for patients with severe active disease despite treatment with bDMARDs recommended according to NICE guidance

1	*Sarilumab + MTX*	*Tocilizumab IV + MTX*	*Tocilizumab SC + MTX*
2	*MTX*	*MTX*	*MTX*
3	*BSC*	*BSC*	*BSC*

As agreed, we will provide a response by Monday 26th June.

B3. ***Priority question:*** *Please perform an analysis where the lowest acquisition and administration price is used for the TNFi bundle based on the analysis in question B1*

As agreed, we will provide a response by Monday 26th June.

B4. *Please clarify why the Gompertz distribution was chosen to extrapolate time to treatment discontinuation when the generalised gamma resulted in better statistical fits (using AIC) for all comparisons and the lognormal has a better fit (using AIC) in the combined model.*

The selection of the Gompertz distribution was based both on the best fit statistics (AIC and BIC) and visual review of the curve fitting. In terms of best fit statistics, Gompertz is the second best fit of the six functions tested. In terms of visual fit, both generalised gamma and Gompertz fit well at the beginning of the curve. However, towards the end of the curve generalised gamma under predicted for the IL6 class and other mechanisms of action whilst Gompertz provided a good visual fit for all treatment classes, see Fig A (Fig 15.2 in company submission appendix).

Fig A. Predicted drug retention for all classes

Drug Class = TNF	Drug Class = OMA	Drug Class = IL-6

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B5. Please provide a scenario analysis where the ETN and IFX biosimilars have taken over the market share of their branded formulations.

Below we provide results for population A1 in our submission where the biosimilar products have completely displaced their respective originator products. Sarilumab remains cost-effective compared with tocilizumab and abatacept with the TNFi bundle as the reference product and a small increase in ICER was observed from £9,631 in the base case to £11,450 in the scenario.

Table B. Incremental analysis for Population A1 where ETN and IFX biosimilars completely displace their originator products

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Sarilumab ICER (£) versus each alternative technology (QALYs)	ICER (£) incremental (QALYs)	Sarilumab INB (£) at a threshold of £20,000	Sarilumab INB (£) at a threshold of £30,000
TNFi Bundle + MTX	[redacted]	15.46	[redacted]	-	-	-	£11,450	-	£5,407	£11,731
SAR + MTX	[redacted]	15.46	[redacted]	[redacted]	0.00	[redacted]	-	£11,450	-	-
TZC (SC) + MTX	[redacted]	15.46	[redacted]	[redacted]	0.00	[redacted]	Dominant	Dominated	£14,259	£15,726
TCZ (IV) + MTX	[redacted]	15.46	[redacted]	[redacted]	0.00	[redacted]	Dominant	Dominated	£15,267	£16,372
ABT (SC) + MTX	[redacted]	15.46	[redacted]	[redacted]	0.00	[redacted]	Dominant	Dominated	£27,911	£29,357

B6. *Please clarify why the number of free doses of certolizumab pegol was varied within the PSA.*

Based on an assumption that there may be some variation in the initial loading phase in clinical practice we considered there could be some uncertainty in how the CTZ PAS was operationalised. However, we believe this parameter could be removed from the PSA.

Section C: Textual clarifications and additional points

C1. *Page 39. Please clarify whether the sentence "Certolizumab pegol and tocilizumab are approved for use only in combination with MTX" is wrong. It contradicts NICE recommendations following TA375 and figure 3.1 on page 40.*

This is a typographical error which has been amended.

C2. *Page 48. Please clarify whether the following sentence is wrong "TA375 the moderate RA patients assessed were those are able to respond adequately to and are tolerant of cDMARDs, conversely this appraisal considers only those patients who do not respond adequately to, or are intolerant to cDMARDs". Within TA375, people with moderate RA (Population 2) had already failed on intensive cDMARDs.*

Our interpretation of TA375 Population 2, based on the Final Guidance document as opposed to the technical report, led us to understand that these patients had received treatment with MTX but not necessarily failures of cDMARD therapy. In our submission, we specifically focus on moderate patients at the worse end of the scale with >4 DAS28 ≤5.1 who from a clinical perspective, are those most likely to be fast approaching severe disease activity (Population A2 in the company submission document). Assuming NICE guidance is followed in the treatment of these patients, in order to reach DAS28 of 4, we assume a categorical failure of cDMARD therapy since this is initiated in early disease. We had considered that patients towards the lesser end of the moderate disease state, as are included in the moderate population in TA375, as not having had categorical failure of cDMARD therapy and therefore these patients may still achieve adequate response.
Given the statement in question C2, we may have misinterpreted slightly the moderate population in TA375. However, the point we are trying to convey is that the moderate patients in this submission are a small subgroup of moderate patients who have categorically failed treatment, are close to being severe, and currently have no active treatment options.

C3. *Page 128. Please confirm if the data for HAQ score contained in Table 4.25 are missing a minus sign for the midpoint value.*

This is a typographical error which has been amended.

C4. *Page 206. Please amend figure 5.5 to state biologic rather than biometric.*

This is a typographical error which has been amended. We also noted another error in this diagram in which the arrow heads were misplaced, this has also been amended.

C5. *Pages 215-216. Please confirm if EULAR moderate refers to at least a moderate EULAR response in Tables 5.17, 5.18 and 5.19.*

Yes, "EULAR moderate" in Tables 5.17 to 5.19 refer to achieving at least a EULAR moderate.

C6. *Page 222. Please clarify whether the legend in figure 5.12 is wrong and confirm whether it should read from top to bottom: IL6, Other biologics and TNFi.*

This is a typographical error which has been amended.

C7. *Page 36. Please clarify why percentages do not add up to 100 in Table 3.1.*

The percentages of disease severity by gender in Table 3.1 are referenced from *"Cross M, Smith E, Hoy D, Carmona L. The global burden of rheumatoid arthritis: estimates from the global burden of disease 2010 study. Annals of the rheumatic diseases 2014; 73(7): 1316-22"*. The paper describes that the proportions of patients within each severity level are pooled across eight studies. Pooling proportions in this manner is likely to result in the totals not summing to 100.

C8. *Page 216. Please clarify whether the first row in Table 5.19 should say "Sarilumab + MTX" instead of "Sarilumab" alone.*

This is a typographical error which has been amended.

Single Technology Appraisal (STA)

Sarilumab for treating moderate-to-severe rheumatoid arthritis [ID994]

Dear Frances,

Further to our responses of 21st June, please find the remainder of our responses to your questions of 7th June. We also include an updated company submission document and any pages which have been updated are marked with a "superseded" watermark. The following pages have been amended: 39, 128, 195, 206, 216 and 222.

Yours sincerely

[redacted]
Head of Health Outcomes UK & Ireland

SANOFI GENZYME

Network Meta-Analysis

A7. ***Priority question:*** *Please provide the NMA results for ACR and EULAR response in the cDMARD-IR and TNFi-IR population with the following settings:*

- *Using a random effects probit model with an informative prior for the between-study variance (log normal with mean -2.56 and variance of 1.74*1.74, which is proposed by Turner et al 2012. The log normal is truncated so that the odds ratio in one study would not be ≥50 times than in another, and re-scaled to match the probit scale). The BUGS code for this prior is:*
  var~dlnorm(-2.56,0.33)I(,1)

  sd<-sqrt(var)/1.81

  tau <- pow(sd,-2)

  Turner RM, Davey J, Clarke MJ, Thompson SG, Higgins JP; Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. Int J Epidemiol 2012;41:818–27. doi:10.1093/ije/dys041
- *Keeping all treatment separate.*
- *Including combination therapy and monotherapy in one network in order that trials comparing both regimens can provide evidence (including the studies in Appendix 8, Table 8.7 and HARUKA).*
- *Including the studies which were excluded due to small sample size (Appendix 8 Table 8.1 and Table 8.9)*
- *Please check the studies in Table 8.2 of the appendix and include them if they were included in TA375.*
- *Include the studies in Table 8.3 of the appendix assuming that etanercept 50mg once weekly is equivalent to etanercept 25mg twice weekly.*
- *Please incorporate the KAKEHASI for consistency with the main network, which includes studies in Asian patients.*

Please present the results using both relative and absolute measures. Please also present the point estimate and 95% credible interval for the between-study standard deviation, and the goodness of model fitting. In the results, please also provide how the baseline absolute probabilities were estimated.
Please supply sensitivity analyses amending parts of this proposed NMA where you feel this is appropriate.

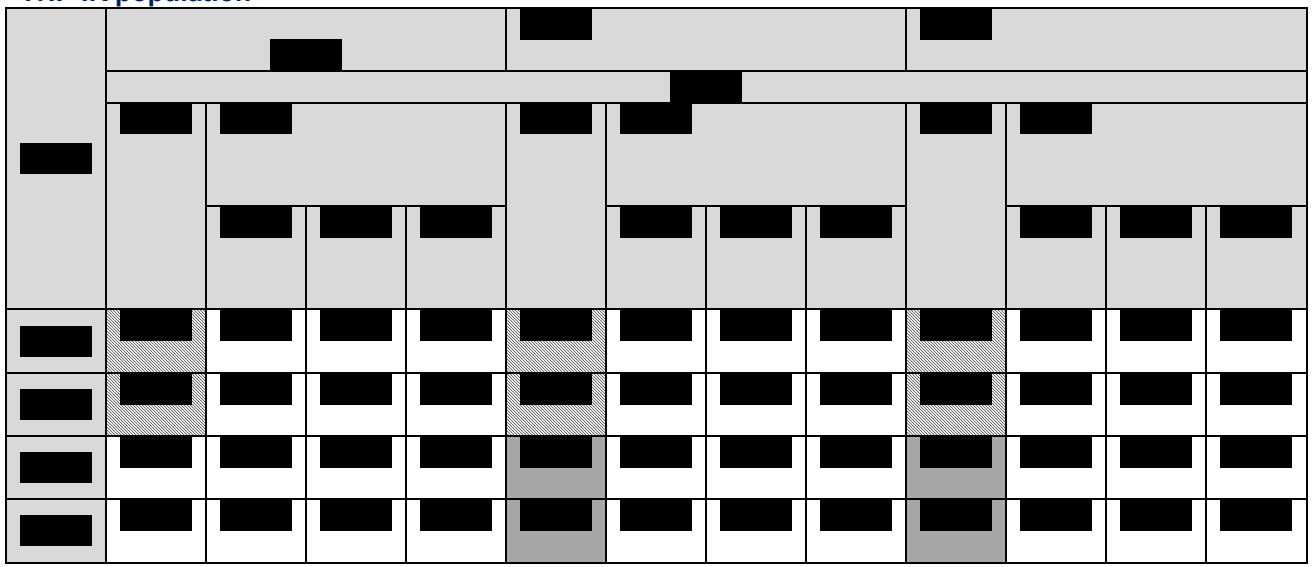
Using the inclusion criteria specified above, studies in the cDMARD-IR combination therapy and monotherapy network were combined within a single model.

Regarding the studies excluded due to sample size: of the ten studies excluded, seven were also excluded as they did not report outcomes of interest. Of the remaining three studies, one study (Smolen et al 2014) was excluded as it failed to connect to the rest of the network; leaving two studies (Weinblatt 1999 and Taylor 2004) that were added to the combined network. In addition to these studies, KAKEHASI and etanercept studies (reported in table 8.3) were included in the network. MTC analyses employed an informative prior as suggested by NICE.

Below is a table reporting the results using the combined network for ACR 20, 50 and 70 response.

As suggested, a random effects probit model was used in the TNF-IR population, however, this analysis produces results that are inconsistent with the observed head-to-head data from both the RADIATE and TARGET studies. The results from the random effects probit model both significantly under- and over-estimate relative treatment effect compared to trial data (see table A1).

Table A1: Comparison ACR20/50/70 responder rate as observed (direct results) and estimated from NMA using probit link approach at Week 24 in TNF-IR population



White cells mean NMA predicts well, hatched cells that the NMA over predicts, grey cells that the NMA under predicts

As described in the NMA section 4.2.2 of the company submission, OR was seemed to correlate with the control arm response, but not the active arm response; and the risk difference was not significantly correlated with the baseline values. Therefore, based on the above factors, the risk difference model was deemed to be an appropriate model to inform the economic evaluation and no further amends were considered for the TNF-IR network.

The data for EULAR outcomes were only available for two categories (i.e. EULAR no response and EULAR moderate –good), hence we were unable to convert EULAR data into three categories for analysis using a probit model, as proposed by NICE DSU technical document.

Results for ACR outcomes from the NMA after incorporating the remaining changes requested in question A7 are shown in Table A2 – A5. These results are in line with the results in the original manufacturer's submission and therefore the conclusion that sarilumab in combination with cDMARDs/MTX shows comparable efficacy to other biologic combination therapies still stands.

Table A2. ACR responses for the cDMARD-IR population using updated NMA

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White cells mean comparable and hatched cells mean that sarilumab 200mg combi was found better

Table A3. Absolute effects with the corresponding 95% CrI for ACR20 response at 24 weeks for the cDMARD-IR population using updated NMA

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Table A4. Absolute effects with the corresponding 95% CrI for ACR50 response at 24 weeks for the cDMARD-IR population using updated NMA

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Table A5. Absolute effects with the corresponding 95% CrI for ACR70 response at 24 weeks for the cDMARD-IR population using updated NMA

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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The baseline absolute probabilities for ACR response in the cDMARD-IR population using a random effects probit model was estimated using the code -

```
for (s in 1:ns)
{
mu1[s] <- mu[s] * equals(t[s,1],1)  # baseline arm (csDMARD or MTX)
count1[s] <- equals(t[s,1],1)
}
for (k in 1:nt) {
# calculate prob of achieving ACR20, ACR50, ACR70 on treat k
   for (j in 1:3) {  T[j,k] <- 1 - phi((sum(mu1[])/sum(count1[]) ) + d[k] + z[j])
odds[j,k]<-T[j,k]/(1-T[j,k])
}
  }
```

A8. ***Priority question:*** *Please provide a sensitivity analysis for the NMA requested in question A7 pooling TNFis together (TNFi-bundle).*

ACR results from the updated NMA using the pooled TNFi comparator in the cDMARD-IR population are shown in Table A6 – A9.

Table A6. ACR responses for the cDMARD-IR population with pooled TNFis using updated NMA

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

White cells mean comparable and hatched cells mean that sarilumab 200mg combi was found better

Table A7. Absolute effects with the corresponding 95% CrI for ACR20 response at 24 weeks for the cDMARD-IR population with pooled TNFis using updated NMA

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Table A8. Absolute effects with the corresponding 95% CrI for ACR50 response at 24 weeks for the cDMARD-IR population with pooled TNFis using updated NMA

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table A9. Absolute effects with the corresponding 95% CrI for ACR70 response at 24 weeks for the cDMARD-IR population with pooled TNFis using updated NMA

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Section B: Clarification on cost-effectiveness data

B1. ***Priority question:*** *Please provide analyses for all the populations with the following assumptions if possible (if not possible please clarify why):*

The impact of making the changes requested in this question are described in more detail after point l. below.

a. *Using the results of the NMA described in question A8.*

   This has been implemented and used in the requested analysis.

b. *Using Hernandez et al. 2013 (see TA375 section 4.65) to map HAQ to EQ-5D.*

   This was implemented in our original model as a scenario analyses (please see section 5.4.3 of the company submission document) and we have used it in the requested analysis.

c. *Using change in HAQ upon response based on TA375 (-0.317 for moderate EULAR responders, -0.672 for good EULAR responders).*

   This has been implemented as an option in the model (HAQ sheet cell G7) and has been used in the requested analysis.

d. *Rounding HAQ scores after every change to a valid HAQ score (a multiple of 0.125 between 0 and 3). Please use the following method: with the probabilities of being at the higher or lower valid HAQ score proportional to the distances from each HAQ score. For example: round a score of 0.400 to 0.375 with a probability of 0.8 and to 0.500 with a probability of 0.2.*

   This has been implemented. The changes can be seen in the model on the Model sheet, cells N27:P228. As requested, the probabilities of the higher and lower rounding have been calculated proportional to the distance from the estimated HAQ score. From the rounding we select randomly according to the calculated probabilities and use as the basis to calculate the HAQ score for the next cycle.

e. *Using a non-linear HAQ progression for patients on cDMARDs, ideally the one used in TA375 (HTA monograph for TA375, "Stevenson Health technology assessments 2016" from the company's reference pack, page 254).*

We could not implement the non-linear HAQ progressions because we could not reproduce the HAQ time trajectories of each group as described in the referenced paper. The paper reported coefficients for cubic equations in time, however we could not reproduce curves similar to those plotted in the paper.

f. *Using the probability of EULAR response calculated for cDMARDs in the NMA for the MTX and SSZ treatments.*

This has been implemented as requested.

g. *Use generalised gamma distributions for time to treatment discontinuation (see question B3 for further details). If it is not possible to implement the generalised gamma then use the lognormal distribution. Time permitting provide scenario analyses using different distributions for good and moderate EULAR responses.*

This has been implemented as requested. The scenario analyses with different distribution for good and moderate EULAR responses described could not be assessed. The treatment discontinuation estimated from the RHUMADATA registry was based on treatment class rather than EULAR response level, and while the treatment discontinuation from the previous MTA was determined according to EULAR response, alternative distributions were not available.

h. *Using correlated samples from the CODA of the NMA in the PSA for the probabilities of ACR responses instead of using independent samples from beta distributions.*

This has been implemented as requested. The CODA has been added on a separate sheet called CODA, and is used on the Parameter sheet where the parameter samples for the PSA are generated (cells V88:X107).

i. *Using 10 free doses of certolizumab pegol (as established in NICE guidance TA375 and TA415) instead of 9.*

This has been implemented as requested (Model, DMARD Costs sheet, cell G123).

j. *Removing the half cycle correction for the first cycle: patients only are assessed for response at six months and therefore cannot progress earlier. Add in drug, AE and administration costs at cycle 0.*

For disease management and AE costs, currently, the half cycle correction, is applied by averaging the values of the given and the previous cycle. In the first cycle, it means averaging with the value of a virtual cycle 0. However, we assign the same cost to cycle 0 and cycle 1. Therefore in practice there is no half-cycle correction in the first cycle.

For drug and drug administration costs we do not apply half cycle correction in the model. These costs occur if the patient is on treatment at the beginning of the cycle (i.e. at the end of the previous cycle). Therefore, these costs always occur in the first cycle, with a value worth of a full cycle and for the proportion of patients on treatment in the previous cycle (cycle 0 for the first cycle drug and administration costs, i.e. 100% of patients). Adding them to cycle 0 would double count the costs of the first cycle.

AE costs are assumed to occur at an even rate during each cycle therefore we apply half-cycle correction on them, which is equivalent to an assumption that they occur at the mid-point of each cycle. The occurrence of AEs is accounted for according to their probabilities in each real cycle. In cycle 0, there is no treatment and thus no AEs occur. Adding AE cost to cycle 0 would double count AE costs of the first half cycle.

For these reasons, we believe the approach we have taken achieves what is requested in this question.

k. *Removing the speculative PAS of 15% applied to tocilizumab and abatacept.*

This has been implemented as requested.

l. *Using the following sequences as shown in Tables 2 to 8 (now Table 1, :*

The above have been implemented as requested using the sequences specified.

Population A1: severe cDMARD-iR population (MTX-tolerant)

Methods

The above changes were implemented as described. To help explain any changes in the results, two additional sets of results are presented to highlight the effect of the most influential changes: the changes in treatment sequences, the change in the utility equation, and the rest of the changes to our base case analyses. In the revised treatment sequence, the changes are the use of methotrexate prior to BSC instead of the abatacept combination, and the addition of an additional line only for the TNFi bundle and the abatacept combination sequences (to Table B1 from Table B2). The utility equation has been changed from the Malottki et al., 2011 equation to the Hernandez et al., 2013 equation, with great impact on QALYs. From the remaining implemented changes, the HAQ change upon EULAR response mapping and the shorter time to treatment discontinuation due to the use of the generalized gamma distribution influenced the results the most.

The model was run with six replications of the full cohort for the deterministic analyses and one full cohort with 300 simulations for the probabilistic analyses.

Results

With the sequence change and the revised model, the total costs associated with the sarilumab and tocilizumab combination sequences decreased (Table B3 and Table B4). This was mainly due to the sequence change, where instead of the more costly abatacept combination only methotrexate was used (Table B4 and Table B5). At the same time the costs increased for the TNFi and the abatacept combination sequences as an additional line of treatment was added. Although the per cycle cost of methotrexate is negligible, and the per cycle cost of the newly added tocilizumab IV is slightly lower than that of the original abatacept IV, the time to treatment discontinuation is longer with tocilizumab and as a result the drug costs may have increased.

With use of the generalised gamma distribution instead of the Gompertz, time to treatment discontinuation became shorter for each treatment. This has two way effects on costs, as a shorter treatment imply lower drug costs, but also increased HAQ scores and thus increased disease management costs. In addition, for an average patient with the new mapping, the HAQ score became lower resulting in lower disease management costs. Overall, the effect of the revised analysis is an increase in HAQ, and increased total costs (compare Table B3 and Table B6).

With the sequence change and the revised model, the LYs were slightly lower. Although none of the changes affected mortality, a different set of random numbers were used which leads to slightly different results.

At the same time, there was a larger increase in QALYs (Table B3 and Table B4). This increase was due mainly to the use of different utility equations as requested in B1.b. The isolated effect of the utility equation change is highlighted by the comparison of results in Table B5 and Table B6).

For the sarilumab and tocilizumab combination sequences, the use of fewer bDMARDs in the sequence reduced the time on biologics thereby increasing HAQ scores and reducing utilities (Table B4 and Table B5). Comparing tables B5 with B4 demonstrates the impact of changing sequences while keeping all other inputs the same. The overall effect of the revised model without the utility equation change was increased HAQ and decreased utility (Table B3 vs Table B6).

The sarilumab combination continued to dominate the tocilizumab combination and with the shorter sequence, became less costly and less effective than the TNFi bundle and the abatacept combination. The ICERs were £79,199 and £206,188 per QALY for the TNFi-bundle and the abatacept combinations compared to the sarilumab combinations, i.e. the additional line of therapy did not make the TNFi-bundle and the abatacept combinations cost-effective.

Using CODA samples, the probabilistic results show the same trend as the deterministic analysis - the sarilumab combination dominates the tocilizumab combination, while compared to the longer sequences (TNFi-bundle and the abatacept combination sequences) it was less costly and less effective in the severe cDMARD-iR population (Table B7). The cost-effectiveness acceptability curves remained similar also (Figure 1 and Figure 2). Using the original independent variations method, the PSA results are almost the same, which suggests that the results are robust (Table B8).

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Table B1: New sequences for the severe cDMARD-iR population (MTX-tolerant)

1	*Sarilumab + MTX*	*Tocilizumab IV + MTX*	*Tocilizumab SC + MTX*	*TNFi bundle + MTX*	*Abatacept SC + MTX*
2	*Rituximab + MTX*	*Rituximab + MTX*	*Rituximab + MTX*	*Rituximab + MTX*	*Rituximab + MTX*
3	*MTX*	*MTX*	*MTX*	*Tocilizumab IV + MTX*	*Tocilizumab IV + MTX*
4	*BSC*	*BSC*	*BSC*	*MTX*	*MTX*
5				*BSC*	*BSC*

Table B2: Original sequence as in the submission for the severe cDMARD-IR population (MTX-tolerant)

1	Sarilumab + MTX	Tocilizumab IV + MTX	Tocilizumab SC + MTX	TNFi bundle + MTX	Abatacept SC + MTX
2	Rituximab + MTX	Rituximab + MTX	Rituximab + MTX	Rituximab + MTX	Rituximab + MTX
3	Abatacept IV + MTX	Abatacept IV + MTX	Abatacept IV + MTX	Abatacept IV + MTX	Tocilizumab IV + MTX
4	BSC	BSC	BSC	BSC	BSC
5	-	-	-	-	-

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Table B3: Original deterministic results for the severe cDMARD-IR population (MTX-tolerant)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Sarilumab ICER (£) versus each alternative technology (QALYs)	ICER (£) incremental (QALYs)	Sarilumab INB (£) at a threshold of £20,000	Sarilumab INB (£) at a threshold of £30,000
TNFi Bundle + MTX	[redacted]	15.56	[redacted]	-	-	-	£9,513	-	£6,928	£13,534
SAR + MTX	[redacted]	15.56	[redacted]	[redacted]	0.00	[redacted]	-	£9,513	-	-
TCZ (SC) + MTX	[redacted]	15.56	[redacted]	[redacted]	0.00	[redacted]	Dominant	Dominated	£14,410	£15,829
TCZ (IV) + MTX	[redacted]	15.56	[redacted]	[redacted]	0.00	[redacted]	Dominant	Dominated	£15,407	£16,604
ABT (SC) + MTX	[redacted]	15.56	[redacted]	[redacted]	0.00	[redacted]	Dominant	Dominated	£27,981	£29,642

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Table B4: Deterministic results with new ERG recommended sequences and revised model for the severe cDMARD-IR population (MTX-tolerant)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Sarilumab ICER (£) versus each alternative technology (QALYs)	ICER (£) incremental (QALYs)	Sarilumab INB (£) at a threshold of £20,000	Sarilumab INB (£) at a threshold of £30,000
SAR + MTX	[redacted]	15.38	[redacted]	-	-	-	-	-	-	-
TCZ (SC) + MTX	[redacted]	15.38	[redacted]	[redacted]	0.00	[redacted]	Dominant	Dominated	£24,664	£25,388
TCZ (IV) + MTX	[redacted]	15.38	[redacted]	[redacted]	0.00	[redacted]	Dominant	Dominated	£24,414	£24,794
TNFi Bundle + MTX	[redacted]	15.38	[redacted]	[redacted]	0.00	[redacted]	Less costly, less effective	£79,199	£18,289	£15,200
ABT (SC) + MTX	[redacted]	15.38	[redacted]	[redacted]	0.00	[redacted]	Less costly, less effective	£206,188	£51,986	£47,087

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Table B5: Results with the revised model and original sequences for the severe cDMARD-IR population (MTX-tolerant)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Sarilumab ICER (£) versus each alternative technology (QALYs)	ICER (£) incremental (QALYs)	Sarilumab INB (£) at a threshold of £20,000	Sarilumab INB (£) at a threshold of £30,000
TNFi Bundle + MTX	[redacted]	15.38	[redacted]	-	-	-	£10,102	-	£4,858	£9,766
SAR + MTX	[redacted]	15.38	[redacted]	[redacted]	0.01	[redacted]	-	£10,102		
TCZ (SC) + MTX	[redacted]	15.38	[redacted]	[redacted]	-0.01	[redacted]	Dominant	Dominated	£25,184	£25,814
TCZ (IV) + MTX	[redacted]	15.38	[redacted]	[redacted]	0.00	[redacted]	Dominant	Dominated	£24,709	£25,051
ABT (SC) + MTX	[redacted]	15.38	[redacted]	[redacted]	0.00	[redacted]	Dominant	Dominated	£37,317	£37,762

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Table B6: Results with the revised model except the utility equation change (B1.b) and original sequence for the severe cDMARD-IR population (MTX-tolerant)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Sarilumab ICER (£) versus each alternative technology (QALYs)	ICER (£) incremental (QALYs)	Sarilumab INB (£) at a threshold of £20,000	Sarilumab INB (£) at a threshold of £30,000
TNFi Bundle + MTX	[redacted]	15.38	[redacted]	-	-	-	£7,973	-	£7,395	£13,545
SAR + MTX	[redacted]	15.38	[redacted]	[redacted]	0.00	[redacted]	-	£7,973		
TCZ (SC) + MTX	[redacted]	15.38	[redacted]	[redacted]	0.00	[redacted]	Dominant	Dominated	£25,453	£26,186
TCZ (IV) + MTX	[redacted]	15.38	[redacted]	[redacted]	0.00	[redacted]	Dominant	Dominated	£24,860	£25,231
ABT (SC) + MTX	[redacted]	15.38	[redacted]	[redacted]	0.00	[redacted]	Dominant	Dominated	£37,748	£38,341

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Table B7: Probabilistic results using CODA samples with new ERG recommended sequences and revised model for the severe cDMARD-IR population (MTX-tolerant)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Sarilumab ICER (£) versus each alternative technology (QALYs)	ICER (£) incremental (QALYs)
SAR+MTX - 200mg	[redacted]	15.24	[redacted]	-	-	-	-	-
TCZ+MTX - SC weekly	[redacted]	15.24	[redacted]	[redacted]	0.00	[redacted]	Dominant	Dominated
TCZ+MTX - IV 8 mg/kg	[redacted]	15.24	[redacted]	[redacted]	0.00	[redacted]	Dominant	Dominated
Anti-TNF+MTX bundle	[redacted]	15.24	[redacted]	[redacted]	0.00	[redacted]	Less costly, less effective	£69,884
ABT+MTX - SC	[redacted]	15.24	[redacted]	[redacted]	0.00	[redacted]	Less costly, less effective	£203,809

Figure 1: Cost-effectiveness acceptability curves using the CODA samples with new ERG recommended sequences and revised base case for the severe cDMARD-iR population (MTX-tolerant)

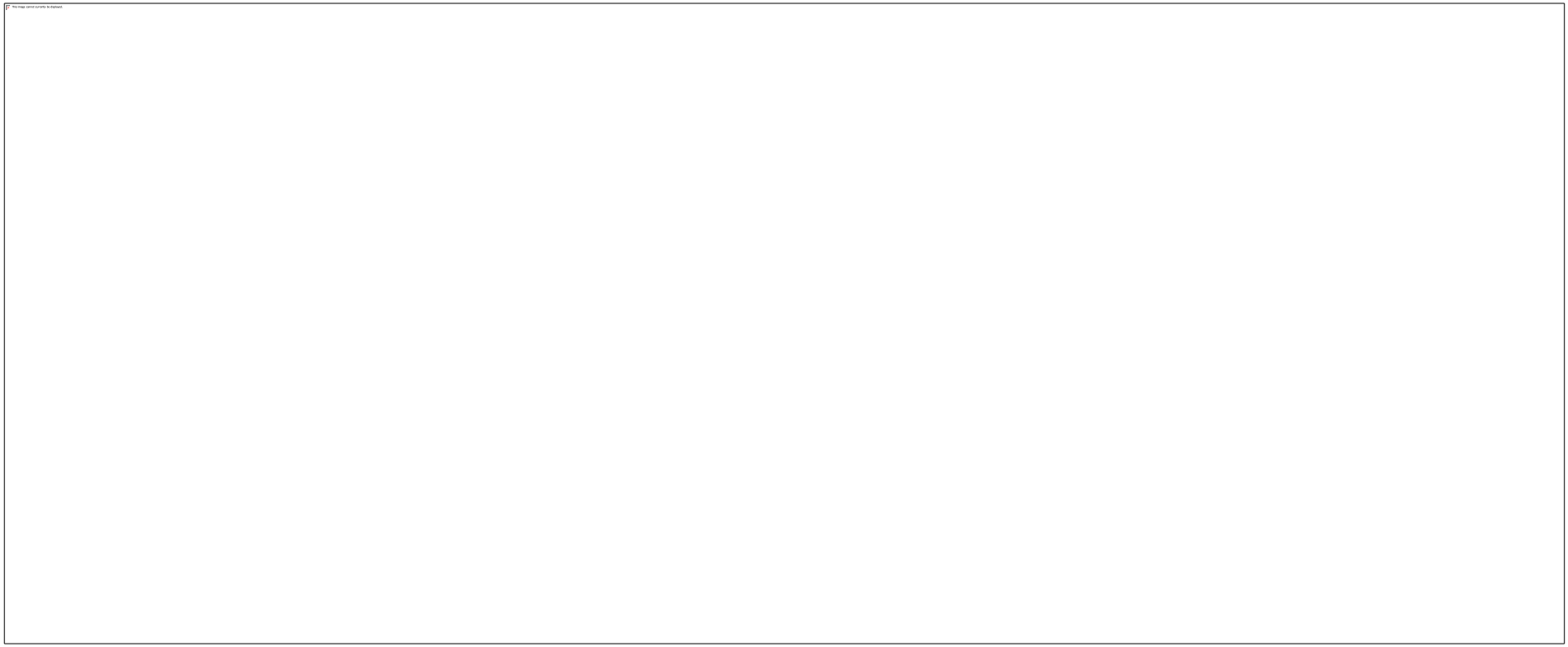

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Figure 2: Cost-effectiveness acceptability curves without the CODA samples with new ERG recommended sequences and revised base case for the severe cDMARD-iR population (MTX-tolerant)

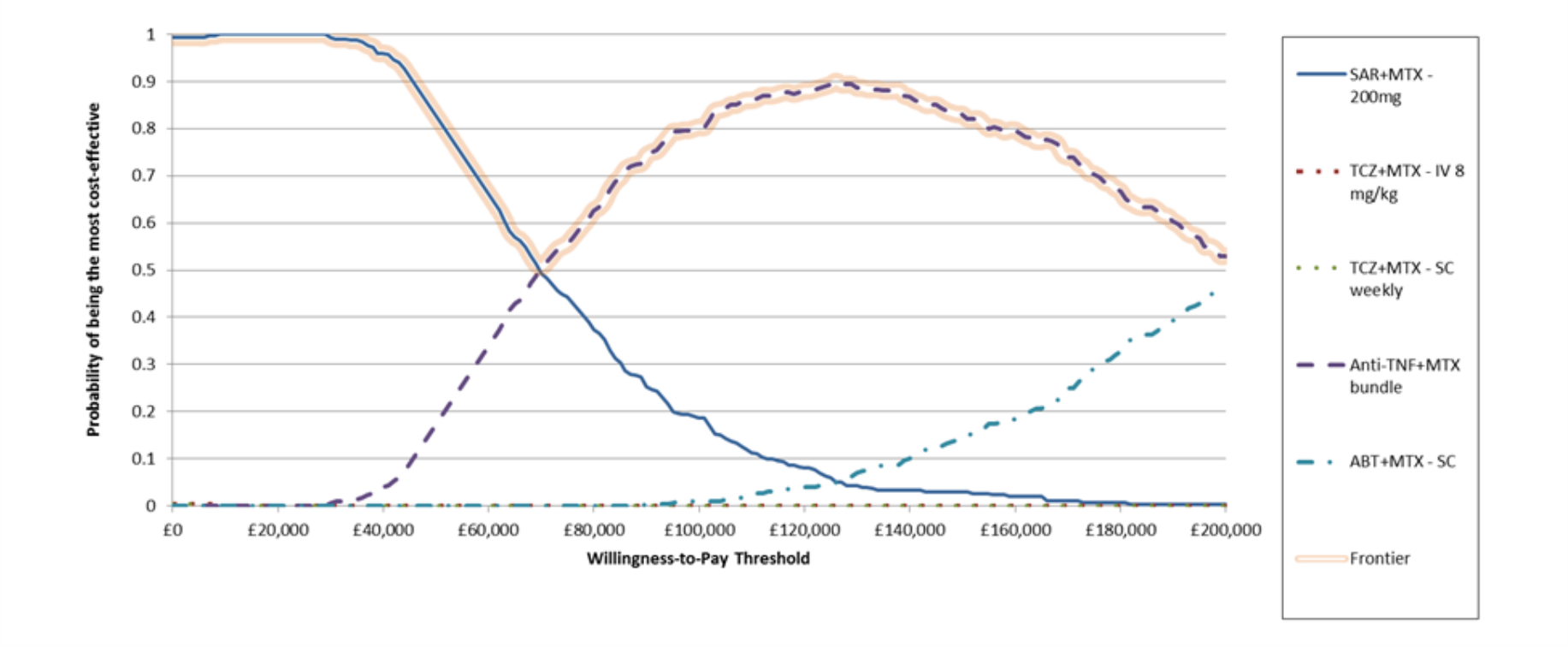

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Table B8: Probabilistic results without the CODA with new ERG recommended sequences and revised base case for the severe cDMARD-iR population (MTX-tolerant)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Sarilumab ICER (£) versus each alternative technology (QALYs)	ICER (£) incremental (QALYs)
SAR+MTX - 200mg	[redacted]	15.24	[redacted]	-	-	-	-	-
TCZ+MTX - IV 8 mg/kg	[redacted]	15.24	[redacted]	[redacted]	0.00	[redacted]	Dominant	Dominated
TCZ+MTX – SC weekly	[redacted]	15.24	[redacted]	[redacted]	0.00	[redacted]	Dominant	Dominated
Anti-TNF+MTX bundle	[redacted]	15.24	[redacted]	[redacted]	0.00	[redacted]	Less costly, less effective	£70,167
ABT+MTX - SC	[redacted]	15.24	[redacted]	[redacted]	0.00	[redacted]	Less costly, less effective	£199,331

B2. Please provide an incremental analysis for moderate cDMARD-IR patients with a DAS28 score between 4.0 and 5.1 with the sequences described in Table 2 so that patients receive the moderate treatment sequences until they progress to severe RA and then receive treatment for severe patients (severe sequences in Table 2). In order to do this a relationship between HAQ and DAS28 score would need to be estimated. If you do not have the data from your trials, assume a 1:1 mapping.

Population A2: Moderate cDMARD-IR population

Methods

To estimate the relationship between HAQ and DAS28, a mapping exercise was conducted. The analysis was done at baseline both on the pooled data from the three relevant studies (MOBILITY-B, TARGET and MONARCH) and also separately for each study. (For further details, please see Appendix A). Given a significant study effect, the separate regression was implanted for each study corresponding to each population in the model. However, the mapping has important limitations, that increase the uncertainty associated with the results. Firstly, there is only a weak correlation shown between HAQ and DAS28. In addition, using the mapping and the thresholds provided for the moderate population, only a small proportion of the patients in the trials can be considered moderate based on their HAQ score. In particular, for the MOBILITY-B study, the mapped threshold of severe RA was a HAQ score of 0.375 inclusive. This implied that approximately 90% of the patients who at baseline were considered moderate based on their DAS28 score, would be considered severe based on their HAQ score.

Results

The revision of the model and the new sequences has not resulted in major changes in the results (Table B10 vs. Table B11). While costs have remained similar, QALYs have increased mainly due to the new method for the estimation of utilities (use of the equation by Hernandez et al.). While the total QALYs increased, the advantage of the sarilumab combination sequence decreased [redacted] which may be a consequence of the shorter time on biologic treatment as a result of using the generalised gamma distribution for time to treatment discontinuation (Table B10 and Table B11). The addition of the switch to the severe sequence resulted in significantly longer time on biologic and cDMARD treatment for both sequences, resulting in higher costs, better HAQ scores, higher utilities, and thus higher QALYs for both sequences (Table B12). While the better HAQ scores resulted in lower disease management costs, this was offset by the higher drug costs.

These differences may be explained by the additional five lines of treatment. Due to the limitations of the HAQ – DAS28 mapping described above, the extended sequences with the switch were equivalent to a longer treatment sequence for the majority of simulated patients. The incremental outcomes for sarilumab vs. the methotrexate sequence decreased in terms of both costs and QALYs, resulting in an ICER of £29,864/QALY. The lower incremental outcomes may be due to longer time on the more efficacious biologic treatments in both sequences, limiting the time on non-biologics which is the main driver of the differences between sequences. In addition, using the extended sequences led to only a minor decrease in LYs (Table B11 vs Table B12) although, mortality is dependent on baseline HAQ.

Table B9: Sequences for the moderate cDMARD-IR population

	Moderate sequences	
1	*Sarilumab + MTX*	*MTX*
2	*MTX*	*BSC*
3	*BSC*	
	Severe sequences	
1	*TNFi bundle + MTX*	
2	*Rituximab + MTX*	
3	*Tocilizumab IV + MTX*	
4	*SSZ*	
5	*BSC*	

SSZ: sulfasalazine

Table B10: Original results for the moderate (DAS28 between 4.0 and 5.1) cDMARD-IR population

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Sarilumab ICER (£) versus each alternative technology (QALYs)	ICER (£) incremental (QALYs)	Sarilumab INB (£) at a threshold of £20,000	Sarilumab INB (£) at a threshold of £30,000
BSC	[redacted]	16.81	[redacted]	-	-	-	£22,275	-	-£5,461	£18,538
SAR + MTX	[redacted]	16.81	[redacted]	[redacted]	0.00	[redacted]	-	£22,275	-	-

Table B11: Revised model results for the moderate (DAS28 between 4.0 and 5.1) cDMARD-IR population (ERG moderate sequences only)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Sarilumab ICER (£) versus each alternative technology (QALYs)	ICER (£) incremental (QALYs)	Sarilumab INB (£) at a threshold of £20,000	Sarilumab INB (£) at a threshold of £30,000
MTX	[redacted]	16.80	[redacted]	-	-	-	£29,864	-	-£16,003	£221
SAR + MTX	[redacted]	16.80	[redacted]	[redacted]	0.00	[redacted]	-	£29,864	-	-

Table B12: Revised model results for the moderate (DAS28 between 4.0 and 5.1) cDMARD-IR population (ERG Sequences extended with severe sequence Table 8)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Sarilumab ICER (£) versus each alternative technology (QALYs)	ICER (£) incremental (QALYs)	Sarilumab INB (£) at a threshold of £20,000	Sarilumab INB (£) at a threshold of £30,000
MTX	[redacted]	16.80	[redacted]	-	-	-	£38,254	-	-£11,566	-£5,230
SAR + MTX	[redacted]	16.80	[redacted]	[redacted]	0.00	[redacted]	-	£38,254		

Population B: Severe cDMARD-IR MTX-intolerant population

Methods

In this population the same changes were implemented as for population A1 in the revised model. In this population however, the number of treatments in the sequences have increased for all comparators with the addition of sulfasalazine prior to BSC (Table B13).

Results

Due to the relatively low cost of sulfasalazine and the reduced treatment duration with the generalised gamma distribution, the changes in total costs were minor in the sarilumab and the TNFi bundle sequences (Table B14 and Table B15). In the tocilizumab sequences, there was a more notable change in the total costs due to exclusion of the exploratory PAS. Similarly as before, while the total QALYs increased, the differences decreased due to the shorter time on biologic treatment as a result of using the generalised gamma distribution for time to treatment discontinuation. The sarilumab sequence remained cost-effective compared with the TNFi bundle sequence (ICER of £17,123/QALY) and was less costly and less effective compared to the tocilizumab sequences.

Table B13: Sequences for the severe cDMARD-IR MTX-intolerant population

1	*Sarilumab*	*Tocilizumab IV*	*Tocilizumab SC*	*TNFi bundle*
2	*TNFi bundle*	*TNFi bundle*	*TNFi bundle*	*TNFi bundle*
3	*SSZ*	*SSZ*	*SSZ*	*SSZ*
4	*BSC*	*BSC*	*BSC*	*BSC*

SSZ: sulfasalazine

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Table B14: Original results for the severe cDMARD-IR MTX-intolerant population

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Sarilumab ICER (£) versus each alternative technology (QALYs)	ICER (£) incremental (QALYs)	Sarilumab INB (£) at a threshold of £20,000	Sarilumab INB (£) at a threshold of £30,000
TNFi Bundle	[redacted]	14.94	[redacted]	-	-	-	£12,995	-	£8,199	£19,903
SAR	[redacted]	14.94	[redacted]	[redacted]	0.00	[redacted]	-	£12,995	-	-
TCZ (IV)	[redacted]	14.94	[redacted]	[redacted]	0.00	[redacted]	Less costly, less effective	£1,013,528	£15,108	£14,956
TCZ (SC)	[redacted]	14.94	[redacted]	[redacted]	0.00	[redacted]	Less costly, less effective	Dominated	£15,651	£15,499

Table B15: Results for the severe cDMARD-IR MTX-intolerant population (ERG Sequences)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Sarilumab ICER (£) versus each alternative technology (QALYs)	ICER (£) incremental (QALYs)	Sarilumab INB (£) at a threshold of £20,000	Sarilumab INB (£) at a threshold of £30,000
TNFi bundle	[redacted]	14.94	[redacted]	-	-	-	£17,123	-	£2,039	£9,126
SAR	[redacted]	14.94	[redacted]	[redacted]	0.00	[redacted]	-	£17,123	-	-
TCZ (IV)	[redacted]	14.94	[redacted]	[redacted]	0.00	[redacted]	Less costly, less effective	£1,578,976	£23,109	£22,960
TCZ (SC)	[redacted]	14.94	[redacted]	[redacted]	0.00	[redacted]	Less costly, less effective	Dominated	£25,664	£25,515

Population C1: Severe TNFi-IR RTX-ineligible population

Methods

In this population the same changes were implemented as for population A1 in the revised model. In this population however, the second line treatment was changed to methotrexate from the abatacept combination for the sarilumab and the tocilizumab IV combination sequences reducing time spent on biologic treatment. The number of treatments in the sequence increased for the tocilizumab SC, TNFi bundle and abatacept combinations with the addition of methotrexate prior to BSC (Table B16).

Results

With the shorter duration of biologic treatment as a result of the shorter treatment sequence and the use of generalised gamma distribution for time to treatment discontinuation, the cost of the sarilumab and tocilizumab IV combination sequences decrease (Table B17 and Table B18). At the same time, due to the additional line of treatment, the costs for all other comparators increased.

Total QALYs have increased for all comparators due to the different estimation of utilities, however, as a result of the longer biologic sequence for tocilizumab SC, the TNFi bundle and the abatacept combinations QALYs have increased more for these sequences resulting in higher values than for those with shorter sequences. These different treatment sequences resulted in the sarilumab combination being less costly but also less effective compared to these treatment options.

With the above changes, the sarilumab combination sequence was less costly and less effective than the other sequences and was on the efficiency frontier with the TNFi bundle and the tocilizumab SC combinations.

Table B16: Sequences for the severe TNFi-IR RTX-ineligible population

1	*Sarilumab + MTX*	*Tocilizumab IV + MTX*	*Tocilizumab SC + MTX*	*TNFi bundle + MTX*	*Abatacept SC + MTX*
2	*MTX*	*MTX*	*Abatacept IV + MTX*	*Tocilizumab IV + MTX*	*Tocilizumab IV + MTX*
3	*BSC*	*BSC*	*MTX*	*MTX*	*MTX*
4			*BSC*	*BSC*	*BSC*

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Table B17: Original results for the severe TNFi-IR RTX-ineligible population

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Sarilumab ICER (£) versus each alternative technology (QALYs)	ICER (£) incremental (QALYs)	Sarilumab INB (£) at a threshold of £20,000	Sarilumab INB (£) at a threshold of £30,000
TNFi Bundle + MTX	[redacted]	14.34	[redacted]	-	-	-	£7,583	-	£9,922	£17,913
SAR + MTX	[redacted]	14.34	[redacted]	[redacted]	0.00	[redacted]	-	£7,583	-	-
TCZ (SC) + MTX	[redacted]	14.34	[redacted]	[redacted]	0.00	[redacted]	Less costly, less effective	£77,024	£12,293	£10,138
TCZ (IV) + MTX	[redacted]	14.34	[redacted]	[redacted]	0.00	[redacted]	Less costly, less effective	Dominated	£15,306	£13,150
ABT (SC) + MTX	[redacted]	14.34	[redacted]	[redacted]	0.00	[redacted]	Less costly, less effective	Dominated	£25,173	£23,265

Table B18: Results for the severe TNFi-IR RTX-ineligible population (ERG Sequences)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Sarilumab ICER (£) versus each alternative technology (QALYs)	ICER (£) incremental (QALYs)	Sarilumab INB (£) at a threshold of £20,000	Sarilumab INB (£) at a threshold of £30,000
SAR + MTX	[redacted]	14.33	[redacted]	-	-	-	-	-	-	-
TCZ (IV) + MTX	[redacted]	14.33	[redacted]	[redacted]	0.00	[redacted]	Less costly, less effective	Extended Dominated	£25,601	£23,493
TNFi Bundle + MTX	[redacted]	14.33	[redacted]	[redacted]	0.00	[redacted]	Less costly, less effective	£64,602	£26,924	£20,887
TCZ (SC) + MTX	[redacted]	14.33	[redacted]	[redacted]	0.00	[redacted]	Less costly, less effective	£69,306	£41,690	£32,659
ABT (SC) + MTX	[redacted]	14.33	[redacted]	[redacted]	0.00	[redacted]	Less costly, less effective	Dominated	£54,099	£45,153

Population C2: Severe TNFi-IR RTX-eligible population

Methods

In this population the same changes were implemented as for population A1 in the revised model. For treatment sequences, the second line treatment was changed to methotrexate from the abatacept combination for the sarilumab and rituximab combination sequences. Two additional sequences were modelled with the insertion of tocilizumab combination treatment in the second line (Table B19).

Results

The new sequences with only one biologic treatment followed by methotrexate allow for less time on biologic treatment than the original sequences and thus accumulate less drug costs. The number of treatments in sequence has increased for the sarilumab and rituximab 2 sequences with the addition of methotrexate prior to BSC as well as the replacement of abatacept with tocilizumab in the second line. Consequently both QALYs and total costs have increased. (Table B20 and Table B21).

The QALYs increased for all sequences due to the change in the utility equation. This was not offset by the reduced utilities for the shorter sequences due to spending less time on biologics.

The shorter sarilumab combination sequence was extended dominated, and the rituximab combinations sequences and the longer sarilumab combination sequence were on the efficiency frontier.

Table B19: Sequences for the severe TNFi-IR RTX-eligible population

1	*Sarilumab + MTX 2*	*Rituximab + MTX 2*	*Sarilumab + MTX 1*	*Rituximab + MTX 1*
2	*Tocilizumab IV + MTX*	*Tocilizumab IV + MTX*	*MTX*	*MTX*
3	*MTX*	*MTX*	*BSC*	*BSC*
4	*BSC*	*BSC*		

Table B20: Original results for the severe TNFi-IR RTX-eligible population

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Sarilumab ICER (£) versus each alternative technology (QALYs)	ICER (£) incremental (QALYs)	Sarilumab INB (£) at a threshold of £20,000	Sarilumab INB (£) at a threshold of £30,000
RTX + MTX	[redacted]	14.34	[redacted]	-	-	-	£104,012	-	-£13,173	-£11,605
SAR + MTX	[redacted]	14.34	[redacted]	[redacted]	0.00	[redacted]	-	£104,012	-	-

Table B21: Revised model results for the severe TNFi-IR RTX-eligible population (ERG Sequences)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Sarilumab* ICER (£) versus each alternative technology (QALYs)	ICER (£) incremental (QALYs)	Sarilumab* INB (£) at a threshold of £20,000	Sarilumab* INB (£) at a threshold of £30,000
RTX + MTX 1	[redacted]	14.33	[redacted]	-	-	-	£48,063	-	-£33,843	-£21,784
SAR + MTX 1	[redacted]	14.33	[redacted]	[redacted]	0.00	[redacted]	£39,814	Extended Dominated	-£20,301	-£10,055
RTX + MTX 2	[redacted]	14.33	[redacted]	[redacted]	0.00	[redacted]	£130,691	£39,994	-£11,877	-£10,804
SAR + MTX 2	[redacted]	14.33	[redacted]	[redacted]	0.00	[redacted]	-	£130,691	-	-

* SAR + MTX 2

Population C3: Severe TNFi-IR MTX-intolerant population

Methods

In this population the same changes were implemented as for population A1 in the revised model. For both treatment sequences, sulfasalazine was inserted as second line treatment before BSC (Table B22),

Results

The new sequences increase the number of lines of treatments and thus the time on active treatment. Consequently, both costs and QALYs increased for both sequences. However, as the cost of sulfasalazine is relatively low, the cost increase is also small. The increase is smaller in the sarilumab sequence potentially because IL6 has a longer time to discontinuation. Sulfasalazine is therefore initiated at a later time on average and so its additional cost is lower. The incremental cost of sarilumab therefore slightly decreased (Table B23 and Table 24). As with the previous populations, the QALYs increased for both sequences significantly due to the change in the utility equation. Also similarly to previous populations, the change in the time to discontinuation distribution implied shorter absolute time and smaller differences in time on both biologic treatments leading to a smaller incremental QALY difference. Sarilumab remained cost effective compared to the TNFi-bundle with a small increase in ICER to £17,794/QALY.

Table B22: Sequences for the severe TNFi-IR MTX-intolerant population

1	*Sarilumab*	*TNFi bundle*
2	*SSZ*	*SSZ*
3	*BSC*	*BSC*

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Table B23: Original results for the severe TNFi-IR MTX-intolerant population

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Sarilumab ICER (£) versus each alternative technology (QALYs)	ICER (£) incremental (QALYs)	Sarilumab INB (£) at a threshold of £20,000	Sarilumab INB (£) at a threshold of £30,000
TNFi Bundle	[redacted]	14.34	[redacted]	-	-	-	£13,878	-	£6,882	£18,125
SAR	[redacted]	14.34	[redacted]	[redacted]	0.00	[redacted]	-	£13,878	-	-

Table 24: Revised model results for the severe TNFi-IR MTX-intolerant population

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Sarilumab ICER (£) versus each alternative technology (QALYs)	ICER (£) incremental (QALYs)	Sarilumab INB (£) at a threshold of £20,000	Sarilumab INB (£) at a threshold of £30,000
TNFi Bundle	[redacted]	14.33	[redacted]	-	-	-	£17,794	-	£1,517	£8,393
SAR	[redacted]	14.33	[redacted]	[redacted]	0.00	[redacted]	-	£17,794	-	-

Population C4: Patients with severe, active disease despite treatment with bDMARDs recommended according to NICE guidance

Methods

In this population the same changes were implemented as for population A1 in the revised model. For each treatment sequence methotrexate was inserted as second line treatment before BSC (

Table B25), BSC as first line treatment was excluded among the comparators.

Results

The new sequences increase the number of lines of treatment and so increase the time on active treatment which is expected to increase both drug costs and QALYs for each sequence. However, as the cost of methotrexate is relatively low, the drug cost increase is also small. This change is fully offset by the shorter time to discontinuation potentially due to the use of the generalized gamma distribution in the revised model, and the decreased disease management costs due to the lower HAQ scores. The results show that the total cost of the sarilumab sequence has marginally decreased (Table B26 and Table B27). The similar effects with the tocilizumab sequences are offset by the removal of the exploratory PAS for tocilizumab, which increased the costs for both tocilizumab sequences therefore the incremental cost of the tocilizumab sequences compared to sarilumab increased.

As with the previous populations, the QALYs increased for each sequence due to the change in the utility equation. Also similarly to previous populations, the change in the time to discontinuation distribution in the revised base case implied shorter absolute time and smaller difference in time on biologic treatments, and therefore smaller incremental QALY differences. The overall result is that sarilumab remained less costly and less effective than both tocilizumab sequences, however, as incremental costs increased and incremental QALYs decreased, the ICER of tocilizumab combination versus sarilumab combination has more than doubled, to £133,548/QALY (Table B26 and Table B27).

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Table B25: Sequences for patients with severe active disease despite treatment with bDMARDs recommended according to NICE guidance

1	*Sarilumab + MTX*	*Tocilizumab IV + MTX*	*Tocilizumab SC + MTX*
2	*MTX*	*MTX*	*MTX*
3	*BSC*	*BSC*	*BSC*

Table B26: Original results for patients with severe active disease despite treatment with bDMARDs

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Sarilumab ICER (£) versus each alternative technology (QALYs)	ICER (£) incremental (QALYs)	Sarilumab INB (£) at a threshold of £20,000	Sarilumab INB (£) at a threshold of £30,000
BSC	[redacted]	14.34	[redacted]	-	-	-	£18,394	-	£3,185	£23,015
SAR + MTX	[redacted]	14.34	[redacted]	[redacted]	0.00	[redacted]	-	£18,394	-	-
TCZ (SC) + MTX	[redacted]	14.34	[redacted]	[redacted]	0.00	[redacted]	Less costly, less effective	£63,276	£13,250	£10,189
TCZ (IV) + MTX	[redacted]	14.34	[redacted]	[redacted]	0.00	[redacted]	Less costly, less effective	Dominated	£16,263	£13,201

Table B27: Revised model results for patients with severe active disease despite treatment with bDMARDs (ERG sequences)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Sarilumab ICER (£) versus each alternative technology (QALYs)	ICER (£) incremental (QALYs)	Sarilumab INB (£) at a threshold of £20,000	Sarilumab INB (£) at a threshold of £30,000
SAR + MTX	[redacted]	14.33	[redacted]	-	-	-	-	-	-	-
TZC (SC) + MTX	[redacted]	14.33	[redacted]	[redacted]	0.00	[redacted]	Less costly, less effective	£133,548	£23,943	£21,834
TCZ (IV) + MTX	[redacted]	14.33	[redacted]	[redacted]	0.00	[redacted]	Less costly, less effective	Dominated	£25,601	£23,493

*B3. **Priority question:** Please perform an analysis where the lowest acquisition and administration price is used for the TNFi bundle based on the analysis in question B1*

Table B28 presents the results with the analysis for Population A1. Infliximab biosimilar was selected as the lowest cost TNFi drug and was thus assigned a 100% weight in the TNFi bundle. However, the long term costs of TNF inhibitors do not differ significantly (

Table B29), therefore the change caused only a marginal decrease in the total cost of the TNFi bundle from [redacted] (Table B28). The tocilizumab combination sequences remained dominated, and the sarilumab combination sequence remained less effective and less costly compared to the TNFi bundle and the abatacept combination sequences.

Table B28: Incremental results of Population A1 with certolizumab pegol costs applied for TNFi bundle in the revised model

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Sarilumab ICER (£) versus each alternative technology (QALYs)	ICER (£) incremental (QALYs)	Sarilumab INB (£) at a threshold of £20,000	Sarilumab INB (£) at a threshold of £30,000
SAR + MTX	[redacted]	15.38	[redacted]	-	-	-	-	-	-	-
TNFi bundle + MTX	[redacted]	15.38	[redacted]	[redacted]	0.00	[redacted]	Less costly, less effective	£66,397	£14,334	£11,245
TCZ (SC) + MTX	[redacted]	15.38	[redacted]	[redacted]	0.00	[redacted]	Dominant	Dominated	£24,664	£25,388
TCZ (IV) + MTX	[redacted]	15.38	[redacted]	[redacted]	0.00	[redacted]	Dominant	Dominated	£24,414	£24,794
ABT (SC) + MTX	[redacted]	15.38	[redacted]	[redacted]	0.00	[redacted]	Less costly, less effective	£218,630	£51,986	£47,087

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Table B29: The costs comparison of TNFi drugs (without MTX costs)

	Annual costs (drug+administration+monitoring)	5-year costs (drug+administration+monitoring)
Adalimumab SC	£11,958	£56,691
Certolizumab pegol SC	£9,618	£54,911
Etanercept SC	£12,702	£60,413
Etanercept SC (biosimilar)	£11,530	£54,549
Golimumab SC	£11,818	£55,990
Infliximab	£13,677	£58,139
Infliximab (biosimilar)	£12,698	£53,877

Single Technology Appraisal (STA)

Sarilumab for treating moderate-to-severe rheumatoid arthritis [ID994]

Dear Frances,

> Further to Table A1 in our responses of 26th June, we mistakenly provided results from a fixed effects probit link model rather than random effects. Please find the results from the correct model in Table A1. The trend in the results remains unchanged to that which we previously presented, the NMA tends to under-predict for sarilumab and over-predict for tocilizumab compared with the observed trial results in the TNF-IR network.

Yours sincerely

[redacted]
Head of Health Outcomes UK & Ireland

Table A1: Comparison ACR20/50/70 responder rate as observed (direct results) and estimated from NMA using probit link approach in a random effects model at Week 24 in TNF-IR population

White cells mean NMA predicts well, hatched cells that the NMA over predicts, grey cells that the NMA under predicts

Within the UK, treatment of RA is based on NICE clinical guidelines (Figure 3.1)[4]. These emphasise timely access to assessment, diagnosis and treatment. The NICE RA Commissioning Guide recommends that treatment with DMARDs starts within six weeks of referral from a GP to prevent functional impairment and disability[82]. Drug management includes DMARDs (conventional [cDMARDs], biological [bDMARDs]) and glucocorticoids[9,17,101,102]. Recommended bDMARDs include tumour necrosis factor inhibitors (TNFi) (adalimumab, certolizumab pegol, etanercept, golimumab [Simponi®], and infliximab [Remicade®]), IL-6 receptor inhibitor (tocilizumab), T-cell co-stimulation inhibitor (abatacept), and B-cell depletion (rituximab)[9,17,101,102].

NICE recommend disease activity is measured by composite score such as DAS28 which may provide an objective indication of activity. Severe disease is defined as DAS28 >5.1, an adequate response as improvement in DAS28 ≥1.2 points, low disease activity as DAS28 <3.2 and remission as DAS28<2.6[9,17].

Recommended first-line treatment for people diagnosed with active RA is a combination of DMARDs, including methotrexate (MTX) and at least one other DMARD, ideally within 3 months of onset of persistent symptoms. In patients where combination therapy is not appropriate (e.g. comorbidities, pregnancy or contraindication) NICE recommends starting DMARD monotherapy with emphasis on dose escalation for clinical efficacy[4].

Treatment escalation may be required to rapidly control disease, lower disease activity, and therefore reduce the impact of the disease in terms of joint function and everyday living. The importance of disease control is highlighted by NICE Quality Standards for RA which recommend that patients with active RA are offered treatment escalation until the disease is controlled to an agreed “low disease activity target” for each patient[10].

Following cDMARDs, bDMARDs are recommended. Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab, abatacept, and biosimilars to originator where available, all in combination with MTX, are recommended as options for treating RA, if the disease is severe, i.e. a disease activity score DAS28 >5.1 and the disease is not responding to treatment with a combination of cDMARDs[4,17]. Adalimumab, etanercept, certolizumab pegol and tocilizumab are approved for use in combination with MTX or as monotherapy for patients intolerant to MTX or because it is contraindicated. Infliximab, golimumab and abatacept are approved for use only in combination with MTX.

In patients with severe RA who have had an inadequate response to, or are intolerant to, other bDMARDs including at least one TNFi, rituximab in combination with MTX is

- **MONARCH:** A randomised, double-blind, parallel-group study assessing the efficacy and safety of sarilumab monotherapy versus adalimumab monotherapy in patients with active RA who are inadequate responders to MTX therapy (Section **Error! Reference source not found.**)[1]

- All studies met their primary efficacy endpoints (Section **Error! Reference source not found.**), and overall, the clinical trial programme demonstrates that[1,55-59]:

  - Sarilumab provides reliable and significant response against moderate-to-severe disease activity regardless of patient treatment history (inadequate responders to or intolerant of MTX or TNFi)

  - Sarilumab provides rapid and sustained improvement in moderate-to-severe signs and symptoms and an increased probability of achieving and sustaining clinical remission, compared with MTX/cDMARD alone

  - Sarilumab significantly reduces structural joint damage. Reduction of radiographic progression should limit further functional decline

  - Sarilumab has demonstrated significant and clinically meaningful improvements across a broad range of patient-reported outcomes (PROs), including health-related quality of life (HRQoL), physical function, pain, fatigue, sleep, morning stiffness and participation

  - Sarilumab monotherapy was superior to adalimumab monotherapy in improving signs and symptoms and physical function in patients with severe active RA at Week 24, with a similar incidence of adverse events (AE) and infections between the treatments

Sarilumab and tocilizumab safety and tolerability was assessed in ASCERTAIN however, exploratory efficacy endpoints were evaluated and suggest that sarilumab efficacy is broadly comparable to that of tocilizumab

monotherapy. All patients were ≥18 years with severe, active RA with disease duration ≥3 months and were inadequate responders to or intolerant of MTX.

In MONARCH, 369 patients were randomised (1:1) to receive sarilumab 200 mg + placebo Q2W (n=184), or adalimumab 40 mg + placebo Q2W (n=185) (Figure **Error! No text of specified style in document.**.1).

After Week 16, dose escalation to weekly adalimumab or matching placebo in the sarilumab group was permitted for patients who did not achieve ≥20% improvement in TJC or SJC. All patients who completed the double-blind treatment period were eligible for inclusion in the long-term OLE safety study EXTEND.

The primary endpoint of MONARCH was the change from baseline in DAS28-ESR at Week 24 (**Error! Reference source not found.**). Secondary endpoints included proportion of patients achieving disease remission defined as DAS28-ESR <2.6 at Week 24, HAQ-DI at Week 24, ACR20/50/70 response rates at Week 24, Medical Outcomes Short Form 36 Health Survey (SF-36) (physical component summary score and mental component summary) at Week 24, and Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) at Week 24 (**Error! Reference source not found.**).

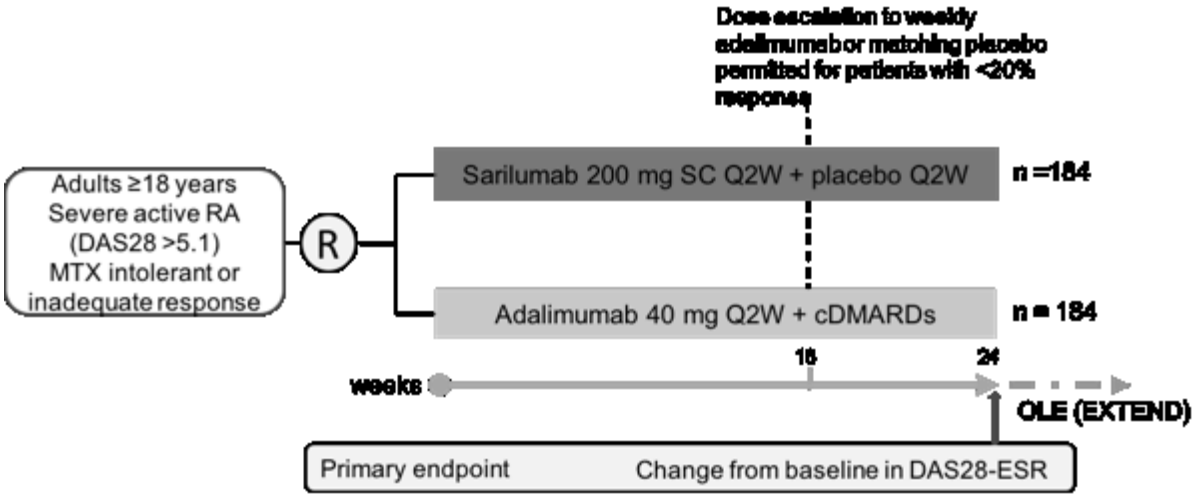
The TEAE period was defined for the 24-week randomised treatment period as the time from first dose of randomised study treatment up to the day of the first dose of the open-label treatment for patients who completed the randomised treatment and enrolled in the extension. For patients who did not enrol in the extension, the TEAE period was defined as the time from the first dose of randomised study treatment to the last dose date of investigational medicinal product (IMP) + 60 days. The occurrence of AEs, including SAEs and AEs of special interest (neutropenia, thrombocytopenia, and changes in hepatic enzymes, lipid levels, CV events, TB and other opportunistic infections) were reported. Laboratory analysis included:

- Haematology: haemoglobin, haematocrit, red blood cell count and morphology (if red blood cell count is abnormal), white blood cell count, white blood cell differential, platelet count, and ANC
- Full chemistry profiles including sodium, potassium, chloride, bicarbonate, BUN, creatinine and creatinine clearance, calcium, phosphate, total protein, albumin, ALT, AST, alkaline phosphatase, total bilirubin, conjugated bilirubin, unconjugated bilirubin, lactate dehydrogenase, uric acid, prothrombin time, and hs-CRP

- Fasting lipids: Triglycerides, total cholesterol, HDL, LDL and triglycerides

- Fasting glucose and HbA1c
- RF, ANA/dsDNA antibody, and anti-CCP
- ADAs to sarilumab

Figure Error! No text of specified style in document.**.1 MONARCH study design**[1]



cDMARD=conventional disease-modifying anti-rheumatic drug; DAS28-ESR=28-joint count disease activity score-erythrocyte sedimentation rate; MTX=methotrexate; OLE=open-label extension; Q2W=once every 2 weeks; R=randomisation; RA=rheumatoid arthritis; SC=subcutaneous

4.3.1.6 Eligibility criteria

Only subjects who fulfilled all the inclusion criteria and did not meet any of the exclusion criteria were included in the clinical trials. The full inclusion and exclusion criteria for the studies are provided in Table 4.5.

4.3.1.7 Endpoints

Error! Reference source not found. provides full details of primary outcomes measures and definitions. **Error! Reference source not found.** provides details of the primary and secondary efficacy endpoints for each trial.

Safety endpoints included incidence of TEAEs, serious AEs (SAEs), laboratory safety assessments and presence of sarilumab anti-drug antibodies (ADAs).

4.3.2 Comparative summary of trial methodology

A summary of the trial methodologies are presented in Table 4.8.

Table Error! No text of specified style in document..**1 Comparative summary of trial methodologies**[1,55-58]

	MOBILITY A	MOBILITY B	TARGET	ASCERTAIN	MONARCH
Setting	Secondary care (outpatient) Self-administered or administered by a caregiver	Secondary care (outpatient) Self-administered or administered by a caregiver	Secondary care (outpatient) Self-administered or administered by a caregiver	Secondary care (outpatient) Self-administered (whenever possible)	Secondary care (outpatient) Self-administered (whenever possible)
Trial design	12-week, multicentre, randomised, double-blind, placebo-controlled Phase II study	52-week, multicentre, randomised, double-blind, placebo-controlled Phase III study	24-week, multicentre, randomised, double-blind, placebo-controlled Phase III study	24-week, multicentre, randomised, double-blind, double-dummy, placebo-controlled Phase III study	24-week, multicentre, randomised, double-blind, double-dummy, Phase III superiority study
Patient population	N=306 MTX irresponsive adults (18–75 years) with moderate to severely active RA (SJC ≥6, TJC ≥8, hs-CRP ≥0.6 mg/dL) with disease duration ≥3 months despite treatment with MTX for a minimum of 12 weeks at a stable dosage (10–25 mg/week)	N=1,197 MTX irresponsive adults (18–75 years) with moderate to severely active RA (SJC ≥6, TJC ≥8, hs-CRP ≥0.6 mg/dL) with disease duration ≥3 months despite treatment with MTX for a minimum of 12 weeks at a stable dosage (10–25 mg/week)	N=546 TNFi irresponsive/intolerant adults (≥18 years) with moderate to severely active RA (SJC ≥6, TJC ≥8, hs-CRP ≥0.6 mg/dL) with disease duration ≥6 months and an inadequate response or intolerance to ≥1 TNFi therapy as defined by the investigator	N=202 TNFi irresponsive/intolerant adults (≥18 years) with moderate to severely active RA (SJC ≥4, TJC ≥4, hs-CRP ≥4 mg/L, with disease duration ≥3 months and an inadequate response or intolerance to ≥1 TNFi after being treated ≥3 consecutive months	N=369 MTX irresponsive/intolerant adults (≥18 years) with severely active RA (SJC ≥6, TJC ≥8, hs-CRP ≥8 mg/L/ESR ≥22 mm/hours, DAS28-ESR >5.1) with disease duration ≥3 months and an inadequate response or intolerance to MTX for a minimum of 12 weeks at a stable dosage (10–25 mg/week or 6–26 mg/week in the Asia-Pacific region)
Location of data collection	262 study locations in the US, Argentina, Australia, Austria, Belarus, Belgium, Brazil, Canada, Chile, Colombia, Czech Republic, Egypt, Estonia, Finland, Germany, Greece, Hungary, India, South Korea, Lithuania, Malaysia, Mexico, Netherlands, New Zealand, Norway, Philippines, Poland,	262 study locations in US, Argentina, Australia, Austria, Belarus, Belgium, Brazil, Canada, Chile, Colombia, Czech Republic, Egypt, Estonia, Finland, Germany, Greece, Hungary, India, South Korea, Lithuania, Malaysia, Mexico, Netherlands, New Zealand, Norway, Philippines, Poland,	196 study locations in US, Argentina, Australia, Austria, Brazil, Canada, Chile, Colombia, Czech Republic, Ecuador, Germany, Greece, Guatemala, Hungary, Israel, Italy, South Korea, Lithuania, Mexico, Netherlands, New Zealand, Peru, Poland, Portugal, Romania, Russia, Slovakia	78 study locations in US, Argentina, Belgium, Brazil, Czech Republic, Estonia, Finland, Hungary, Israel, Italy, Mexico, Netherlands, New Zealand, Norway, Poland, Romania, Russia, Spain, Sweden, UK	86 study locations in US, Chile, Czech Republic, Egypt, Estonia, Finland, Germany, Hungary, Israel, South Korea, Peru, Poland, Romania, Russia, South Africa, Spain, Ukraine, UK

4.7.5 MONARCH—sarilumab monotherapy versus adalimumab monotherapy in moderate-to-severe rheumatoid arthritis patients who were inadequate responders to or intolerant of methotrexate

The MONARCH monotherapy study met its primary endpoint demonstrating that sarilumab was superior to adalimumab in improving signs and symptoms (DAS28-ESR) at Week 24 in severe RA patients who were inadequate responders to or intolerant of MTX (**Error! Reference source not found.**). The MONARCH study also met important secondary endpoints; superiority over adalimumab in improvements in signs and symptoms of RA and physical function[1].

4.7.5.1 Superior reductions in disease activity

Sarilumab 200 mg Q2W was significantly superior to adalimumab 40 mg Q2W in LSM change from baseline to Week 24 in DAS28-ESR (−3.28 vs. −2.20; p<0.0001) (Table 4.22 and Figure 4.22)[1]. Superior improvements in DAS28-ESR were apparent by Week 12 with sarilumab vs. adalimumab (−2.77 vs −1.88; nominal p<0.0001 (**Error! Reference source not found.**)[1].

Sarilumab 200 mg Q2W was significantly superior to adalimumab 40 mg Q2W in terms of the proportion of patients achieving DAS28-ESR remission (26.6% vs. 7.0%; p<0.0001) (Table 4.22) and the odds of achieving DAS28-ESR remission with sarilumab were approximately three times greater than adalimumab at Week 12 (OR 2.61; 95% CI 1.31–5.20; nominal p=0.0051) and approximately five times greater at Week 24 (OR: 4.88; 95% CI 2.54–9.39; p<0.0001)[1].

The change in DAS28-CRP at Week 24 was consistent with DAS28-ESR in terms of superiority of sarilumab versus adalimumab (−2.86 vs. −1.97; nominal p<0.0001) (Table 4.22 and Figure 4.22) and sensitivity analyses were consistent with the primary analysis[1].

Sarilumab 200 mg Q2W was significantly superior to adalimumab 40 mg Q2W in CDAI, a measure of clinical response independent of acute-phase reactants that may favour IL-6 inhibition. Sarilumab 200 mg Q2W was significantly superior in terms of least mean squares (LSM) improvements in CDAI score from baseline to Week 24 versus adalimumab 40 mg Q2W at Week 24 (−28.9 vs. −25.2; nominal p=0.0013) and a greater proportion of patients receiving sarilumab achieved CDAI remission versus adalimumab [redacted] (Table 4.22)[1,63].

4.7.5.2 Superior improvements in signs and symptoms

Sarilumab 200 mg Q2W was significantly superior to adalimumab 40 mg Q2W in the proportion of patients achieving an ACR20/50/70 response at Week 24 (71.7%/45.7%/23.4%

Table Error! No text of specified style in document..**2 American College of Rheumatology 20% improvement response at Week 24 and Health Assessment Questionnaire Disability Index at Week 12 by prior tumour necrosis factor inhibitor — TARGET[57]**

	Sarilumab 150 mg Q2W + cDMARD(s) (n=181)	Sarilumab 200 mg Q2W + cDMARD(s) (n=184)
ACR20, OR (95% CI) vs. placebo at Week 24		
1 prior TNFi	3.11 (1.85–5.25)	2.90 (1.73–4.86)
> 1prior TNFi	1.82 (0.75–4.43)	4.66 (1.94–11.21)
HAQ-DI, difference in LS mean vs. placebo at Week 12 (95% CI)		
1 prior TNFi	-0.15 (−0.28 to −0.01)	−0.21 (−0.34 to −0.07)
> 1prior TNFi	-0.37 (−0.59 to −0.14)	−0.23 (−0.45 to −0.01)

ACR20=American College of Rheumatology 20% improvement; HAQ-DI=Health Assessment Questionnaire Disability Index; LS=least square; DMARD=disease-modifying anti-rheumatic drug; TNFi=tumour necrosis factor

4.8.3 Subgroups analysis for MONARCH

A pre-specified subgroup analysis of patients from MONARCH demonstrated greater a change from baseline in DAS28-ESR at Week 24 with sarilumab compared with adalimumab, regardless of previous MTX response (treatment-by-subgroup interaction: intolerant versus inadequate response, p=0.2163) (Table **Error! No text of specified style in document.**.3)[1].

Table Error! No text of specified style in document..**3 CFB in DAS28 with ESR at Week 24 by MTX response —MONARCH[1]**

	Adalimumab 40 mg Q2W (n=185)	Sarilumab 200 mg Q2W (n=184)
MTX inadequate responders		
Change from baseline in DAS28-ESR at Week 24, mean (SD)	4.4 (1.4)	3.6 (1.5)
Mean difference, 95% CI vs. adalimumab	-	−0.891 (−1.293 to −0.489)
MTX intolerant		
Change from baseline in DAS28-ESR at Week 24, mean (SD)	4.7 (1.3)	3.2 (1.4)
Mean difference, 95% CI vs. adalimumab	-	−1.253 (−1.660 to −0.846)

CFB=change from baseline; CI=confidence interval; DAS28= 28 joint disease activity score; ESR=erythrocyte sedimentation rate; HAQ-DI=Health Assessment Questionnaire Disability Index; LS=least square; MTX= methotrexate; Q2W=once every 2 weeks; SD=standard deviation

Tofacitinib oral 10 mg BID + MTX Tofacitinib oral 15 mg BID + MTX Tofacitinib oral 20 mg BID + MTX				
Tofacitinib oral 5 mg BID + MTX Tofacitinib oral 10 mg BID + MTX	MTX	104	797	Oral Scan (van der Heijde 2013[251])
Tofacitinib oral 5 mg BID + MTX Tofacitinib oral 10 mg BID + MTX Tofacitinib oral 40 mg BID + MTX Adalimumab SC 40 mg Q2W + MTX	MTX	52	717	Oral Standard (Van Vollenhoven 2012[252])
Tofacitinib oral 5 mg BID + cDMARD Tofacitinib oral 10 mg BID + cDMARD	cDMARD	53	636	Tofacitinib efficacy and safety study (Kremer 2013[253])
Baricitinib oral 2 mg OD + cDMARD Baricitinib oral 10 mg OD + cDMARD	cDMARD	24	684	RA-BUILD (Dougados 2017[254])
Biologic vs. same biologic				
Comparisons of different routes of administration				
Tocilizumab SC 162 mg QW+ cDMARDs	Tocilizumab IV 162 mg Q4W+ cDMARDs	104	1,262	SUMMACTA (Burmester 2014[255,256], Burmester 2013[257])
Head-to-head comparisons of bDMARDs				
TNF vs. non-TNF				
Adalimumab SC 40 mg Q2W + MTX	Abatacept SC 125 mg QW + MTX	104	646	AMPLE (Schiff 2014[258], Weinblatt 2013[259])
Adalimumab SC 40 mg Q2W + MTX	Baricitinib oral 4 mg OD + MTX	52	1307	RA-BEAM (Taylor 2017[260])
IL-6 vs. TNF				
Tocilizumab IV 8 mg/kg Q4W	Adalimumab SC 40 mg Q2W	32	326	ADACTA (Gabay 2013[33])
Sarilumab SC 200 mg Q2W	Adalimumab SC 40 mg Q2W	24	369	MONARCH (Burmester 2016[1])

BID=Twice a day; BIW=twice weekly; cDMARD= disease-modifying anti-rheumatic drugs; HCQ= hydroxychloroquine; IL-6=interleukin-6; IV=intravenous; MTX=methotrexate; OD=once daily; OLE=open labelled extension; QW=once a week; Q2W=every 2 weeks; Q4W=every 4 weeks; Q8W=once every 8 weeks; SC=subcutaneous

4.11 Non-randomised and non-controlled evidence

4.11.1 EXTEND

4.11.1.1 Study design

EXTEND (NCT01146652) is an ongoing, Phase III, multi-national, open-label extension study to assess long-term efficacy and long-term safety associated with long-term use of sarilumab with or without concomitant DMARDs, including MTX[59,142].

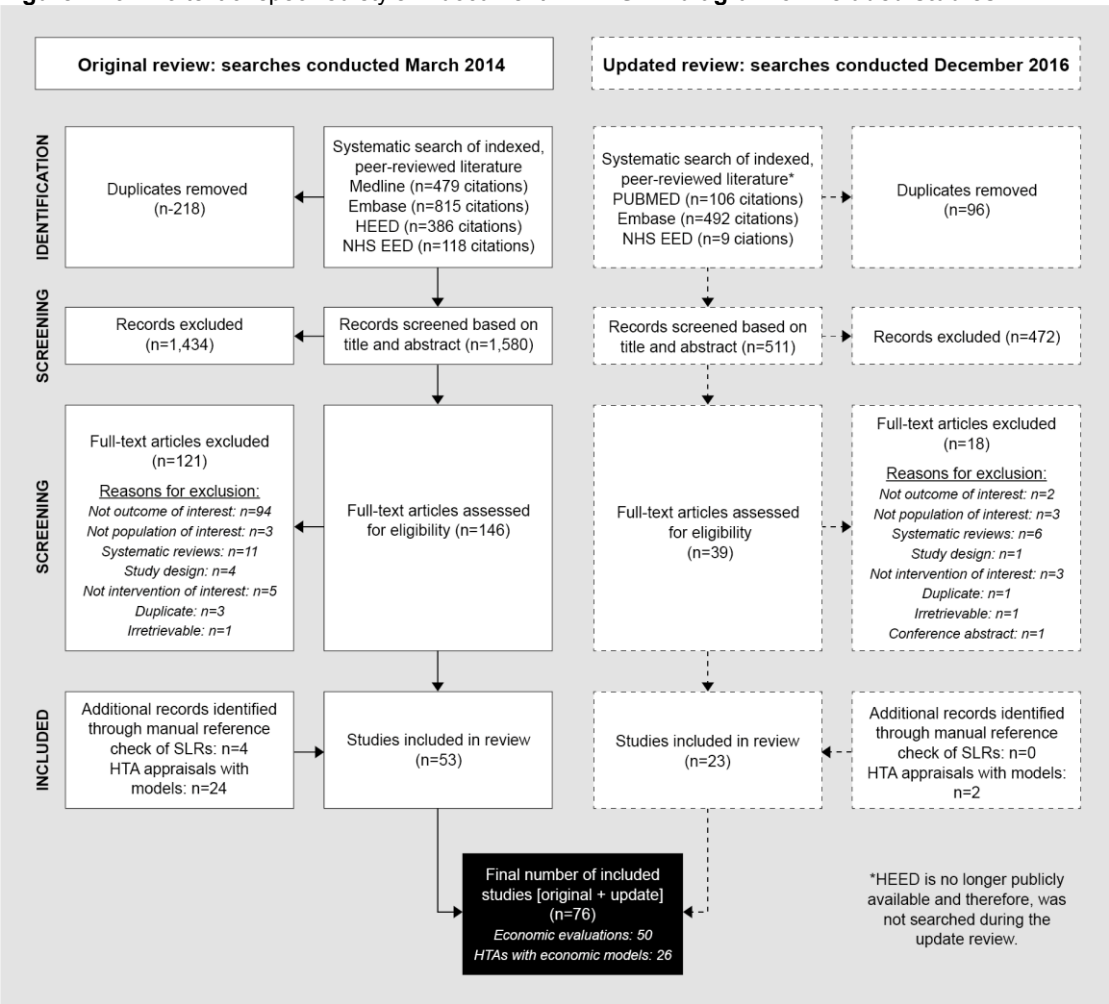
All patients who completed the double-blind treatment period of MOBILITY [redacted], TARGET [redacted], ASCERTAIN [redacted], ONE (see below [redacted] and [redacted] (study investigating clinical benefit of sarilumab plus cDMARD in patients who are inadequate responders to or intolerant of up to [redacted] were eligible for inclusion in the long-term OLE safety study EXTEND [redacted] where they would receive open-label sarilumab until commercial availability of sarilumab in their country, or until 2020 at the latest [redacted] when the study is to be closed[59]. At the time of the EXTEND data cut, MONARCH had not yet reached completion and patients had not entered the OLE phase.

At the time of their inclusion in the initial study, patients were either inadequate responders to MTX (MOBILITY), inadequate responders to or intolerant of TNFis (TARGET, ASCERTAIN), inadequate responders to TNF-α antagonists who had failed up to 2 TNF-α antagonists (ACT11575), or inadequate responders to or intolerant of non-biologic DMARDs (ONE). Patients were allowed to continue their background medication as per the initial study. Patients who received sarilumab monotherapy in ONE continued sarilumab monotherapy in EXTEND[59].

Only subjects who fulfilled all the inclusion criteria and did not meet any of the exclusion criteria were included in the clinical trial. The full inclusion and exclusion criteria for MOBILITY, TARGET and ASCERTAIN are provided in **Error! Reference source not found.**.

The primary endpoint of EXTEND was to evaluate the long-term safety of sarilumab. The secondary objective was to evaluate the long-term efficacy of sarilumab on moderate-to-severe RA patients and the study included assessments of the ACR core set and X-rays.

Figure Error! No text of specified style in document.**.2 PRISMA diagram of included studies**



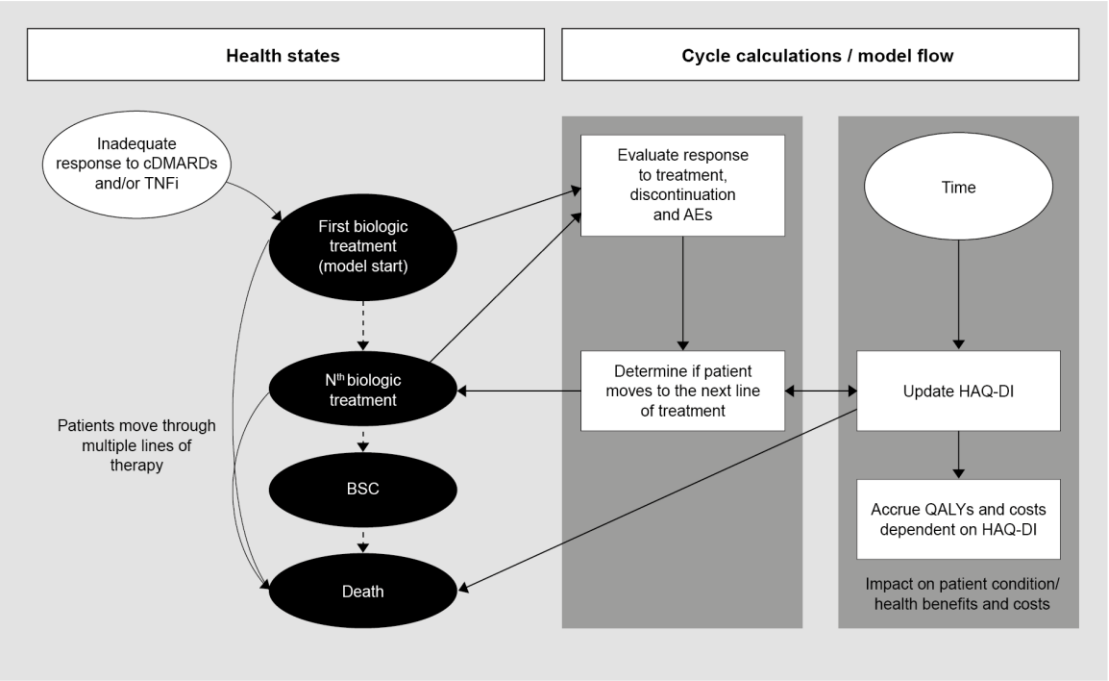
HEED=Health Economic Evaluation Database; HTA=Health Technology Assessment; NHS EED=NHS Economic Evaluation Database; SLR=systematic literature review

An additional non-systematic search of technology appraisals involving bDMARDs in patients with moderate-to-severe RA irresponsive/intolerant to cDMARDs or bDMARDs was performed to further inform the model.

5.1.2 Results

The SLR identified 50 published economic evaluations and 26 HTA reports (with economic models) that were relevant to all licensed biologics in RA. The original review identified 29 published economic evaluations and 24 HTA reports (three which were resubmissions to the SMC), while the update of the SLR identified 21 published economic evaluations and 2 HTA reports. Findings are summarised in **Error! Reference source not found.**

Figure Error! No text of specified style in document..**3 Model flow schematic**



BSC=best supportive care; HAQ-DI=Health Assessment Questionnaire Disability Index; TNFi=tumour necrosis factor inhibitor

Comparators are assessed within a sequence of treatments representing typical pathways followed by patients with RA in the UK. It should be noted that the sequence of treatments patients receive in clinical practice is made on a case-by-case basis and considers multiple factors including patient suitability, preference and clinician judgement. The sequences used in these analyses therefore represent a simplified pathway to enable evaluation, as is common practice in RA modelling. The first treatment in a sequence signifies the comparator being assessed for the sequence in question, the treatments in subsequent lines of therapy are held constant wherever possible for all comparator sequences being assessed (see **Error! Reference source not found.–Error! Reference source not found.**).

The economic model aimed to reflect the clinical care pathway and uses a decision tree/'tunnel state' structure until the first assessment of treatment response at the end of the initial six months for each treatment line. At this point the model decision tree assigns one of three possible outcomes to each patient:

Cycle 1 of each treatment:

Response: Patients achieve at least moderate European League Against Rheumatism (EULAR) response and continue with the treatment. If so, the

Table Error! No text of specified style in document.**.4 cDMARD-IR monotherapy population treatment response based on NMA and TA375 mapping matrix**

Comparator	Treatment response with EULAR moderate, % (95%CI)	Treatment response with EULAR good, % (95%CI)
Sarilumab	[redacted]	[redacted]
TNFi bundle	[redacted]	[redacted]
Tocilizumab (IV)	[redacted]	[redacted]
Tocilizumab (SC)	[redacted]	[redacted]

cDMARD=conventional disease modifying anti-rheumatic drug; CI=confidence interval; EULAR= European League Against Rheumatism; IV=intravenous; SC=subcutaneous

Table Error! No text of specified style in document.**.5 TNF-IR combination therapy population treatment response based on NMA and TA375 mapping matrix**

Comparator	Treatment response with EULAR moderate, % (95%CI)	Treatment response with EULAR good, % (95%CI)
Sarilumab + MTX	[redacted]	[redacted]
TNFi bundle + MTX	[redacted]	[redacted]
Tocilizumab (IV) + MTX	[redacted]	[redacted]
Tocilizumab (SC) + MTX	[redacted]	[redacted]
Abatacept (SC) + MTX	[redacted]	[redacted]
Rituximab (IV) + MTX	[redacted]	[redacted]

bDMARD=biological disease-modifying anti-rheumatic drug; CI=confidence interval; EULAR= European League Against Rheumatism; IV=intravenous; MTX=methotrexate; SC=subcutaneous

It is important to note that the credible intervals of ACR responses from the NMA, which are used to derive the EULAR responses shown below, of sarilumab vs. all comparators overlap indicating no statistically significant differences. The only exception is with adalimumab in monotherapy where sarilumab showed superior ACR response. The EULAR estimates shown below should therefore be interpreted with caution as numerical difference in EULAR may not indicate MCID. A cost-minimisation scenario based on the assumption of no MCID between sarilumab and the other bDMARD treatment options is presented in sensitivity analysis justified by the overlapping credible intervals in the NMA. One further significant assumption affects all bDMARDs for population C3 (evaluating second-line bDMARDs in monotherapy). No RCT has been conducted to specifically investigate any bDMARD in monotherapy following failure of a previous bDMARD. As such, response for the comparators in this population can be based on evidence from the cDMARD-IR monotherapy population, or, the TNF-IR combination therapy population. We make the conservative assumption that response for population C3 should be informed by the TNF-IR evidence for the following reasons:

5.3.6 Time to treatment discontinuation

Data on long-term treatment duration is not available from clinical trials and published data is very limited and generally focuses on TNFis. Two approaches for modelling treatment duration were implemented in our model. The base-case used a time-to-event analysis of patients from the RHUMADATA registry. The approach used by the AG in TA375 was implemented in sensitivity analysis. The base-case approach is considered more appropriate because it takes into account differences in retention among different classes of therapy which was established in TA195 and acknowledged in TA375[67,68].

The time-to-event (discontinuation) analysis produced separate Kaplan-Meier curves by drug class: TNFis, IL-6 inhibitors, and other modes of action. Parametric curves were then fitted from six distributions (Weibull, log-normal, log-logistic, exponential, generalised gamma, and Gompertz) to obtain long-term discontinuation curves. Details of the analysis are provided in Appendix 16. The base-case parametrisation is the Gompertz distribution which provided the best fit, the resultant curves for each treatment class are shown in Figure Error**! No text of specified style in document.**.4. The results showed a statistically significant advantage for non-TNFis over TNFis, and a non-significant advantage for IL-6 over OMAs in terms of treatment duration. In sensitivity analysis, we also test the impact of applying the curve associated with the TNFis (worst observed retention) to all comparators.

Figure Error! No text of specified style in document.**.4 Treatment discontinuation curves by drug class from RHUMADATA fitted with Gompertz distribution**

IL6=interleukin 6; TNFi=tumour necrosis factor inhibitor

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

Sarilumab for previously treated moderate to severe active rheumatoid arthritis

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

1. About you and your organisation

Your name : [redacted]

Name of your organisation: National Rheumatoid Arthritis Society

Your position in the organisation: [redacted]

Brief description of the organisation: We are the national organisation representing people with RA and children and young people and their families living with JIA. We also support the health professionals who treat those with RA and JIA.

(For example: who funds the organisation? How many members does the organisation have?)

We have approx 5,500 members including health professional members. We have a wide range of income streams with the majority of our funding coming from grant-giving trusts and foundations, events, legacy income and a maximum cap which we impose of 15% of annual income comes from projects funded by pharmaceutical industry, although to date such funding has never reached as much as 15%.

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None

Living with the condition

What is it like to live with the condition or 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), 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 particularly 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. 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 a lot of pain and distress at all stages of this disease.

Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

People simply want their life back. They want a reduction in pain, want to prevent permanent disability, want reduction in fatigue, and above all want to maintain independence and ability to work, if of working age, and carry out all the normal activities of daily living. Side effects of some drugs can be quite debilitating, however, by comparison to methotrexate for example, side effects from biologics are generally fewer in our experience. In my own experience and also listening to many thousands of people over the last 15.5 years running NRAS, one of the most important things people want is to be able to

maintain their independence. Pain and fatigue are the two most common symptoms and therefore the most major barriers to being able to live independently and without having to rely heavily on others for a myriad of things.

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

One of the key issues associated with current care is the variability of access to best, evidence-based care and access to all the relevant members of a consultant-led multi-disciplinary team. This has been demonstrated in the past by the Kings Fund and National Audit Office reports into services for people with RA and most recently by the 3-year audit results from the HQIP audit into early RA. People do experience different levels of care and not all, by any means, have access to research studies for example. In the early stages of their disease, people don't know what good looks like or what they should be able to ask for or expect and they are also vulnerable at that time as a consequence. This is where we come in – our goal is to be there at the start of everyone's journey and whenever they need us along the way. We try to emphasise the importance of supported self-management early on as the more you know about the disease and the more you can do to help yourself in a positive way, the better your outcomes are likely to be. Unfortunately, whilst there is a lot of rhetoric about self-management for people with LTCs, we still live in a very medical management model where investment in patient education, support and self-management by commissioners is far too low. That's one of the reasons it is essential that health professionals sign-post patients to organisations who can help and support like NRAS. Access to treatment where there are specific eligibility criteria – ref the biologics and biosimilars – is better than pre-NICE, however, with the introduction of biosimilars, the market has changed and there is a lot of confusion at the moment with local procurement deals ensuring that what is available in one area, may not be the same as the next. Even with all the new treatments available, the heterogeneity of this disease syndrome means that there remains unmet need. Even with cheaper drugs available and many people thinking that therefore more people will be able to get the treatment they need,

this is not the case unless NICE change the eligibility criteria which currently apply.

What do patients or carers consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

2. the course and/or outcome of the condition
3. physical symptoms
4. pain
5. level of disability
6. mental health
7. quality of life (such as lifestyle and work)
8. other people (for example, family, friends and employers)
9. ease of use (for example, tablets rather than injection)
10. where the treatment has to be used (for example, at home rather than in hospital)
11. any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

For someone who has uncontrolled moderate to severe disease and has failed on DMARDs or a TNF, the benefits that they might expect to gain from using this drug would be reduction in the physical symptoms of pain and fatigue in particular which are the most debilitating, and impact in all of the areas mentioned above. Basically, getting the disease under good control and enabling them to get on with life/work etc.

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

I am not aware of any as all the biologics as a class have similar efficacy and safety but I believe that for patients with high levels of inflammation, an IL6 blocker might be more advantageous post TNF failure.

What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

12. aspects of the condition that the treatment cannot help with or might make worse
13. difficulties in taking or using the treatment (for example, injection rather than tablets)
14. side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
15. where the treatment has to be used (for example, in hospital rather than at home)
16. impact on others (for example, family, friends and employers)
17. financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
18. any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

I am not aware of any that are over and above issues which are already known, well documented or evidenced.

Please list any concerns patients or carers have about the treatment being appraised.

Not aware of anything as this product is not yet available.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

No.

Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

Not aware of any

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

I am not aware of any

Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

☐ Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.

This drug is not part of routine care yet so this question is superfluous

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

N/A

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

Our own social research includes

- Family Matters NRAS 2012
- I want to work NRAS 2007
- RA Fatigue Survey and Report 2014
- The Mapping Project, Sue Oliver and Ailsa Bosworth, 2009
- Scotland Work survey, NRAS 2010
- Who Cares Report, Scotland NRAS 2015
- Emotions, Relationships and Sexuality Survey & Report, NRAS 2013
- RA and physiotherapy NRAS 2011
- Wales State of Play Report, BSR and NRAS, 2015

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

19. excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
20. having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
21. any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

No

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

Not that I am aware of

Other issues

Do you consider the treatment to be innovative?

☐ Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

We have 5 different TNF drugs all of which are in use and have made significant difference to thousands of lives. Whilst they are all TNFs, they are subtly different and whilst people may not respond to one TNF, they may respond to another. I am one such individual. There is only one existing IL6 drug on the market and this one may equally have subtle differences and in that sense it is innovative.

Are there any other issues that you would like the Appraisal Committee to consider?

Not that I can think of

Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- This is an innovative new therapy which could help a lot of people with RA
- It is injected by patients themselves so keeps them out of hospital
- RA is a complex and painful disease with unmet need
- It can be used in different places in the pathway

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)
Sarilumab for previously treated moderate to severe active rheumatoid arthritis

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation:
Robert Jones & Agnes Hunt Orthopaedic Hospital
UK Clinical Pharmacy Association & RPUK

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? **Yes**
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? **Yes**
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)? **Member, Pharmacist**
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)
Sarilumab for previously treated moderate to severe active rheumatoid arthritis

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

The management of RA is predominately covered by NICE Clinical Guidance CG79. Progression of the disease requires rapid intervention to prevent irreversible joint damage, and multiple therapy options are available and outlined in NICE TA375.

Implementation of NICE TA375 is funded by local CCGs – which results in geographic differences in implementation in regard to the time taken to initiate treatment and the choice of therapy. Choice of therapy is based upon the least expensive option available – which generally is assumed to be the lowest acquisition cost. However, there is a paucity of evidence to demonstrate the relative costs of achieving and maintaining disease remission. There is also insufficient evidence to show if there are any diagnostic tests, genetic phenotyping, biomarkers or other forms of assessment which may identify which specific treatment an individual patient may respond well to. Consequently, TA375 covers the use of several biologic immune modulators covering very different pharmacological pathways; namely: TNFα, IL-6 and CTLA-4, but makes no recommendations regarding the choice of therapy.

Sarilumab is a monoclonal antibody targeting the IL-6 receptor – thus should be considered along-side tocilizumab against which it will probably be a direct competitor and used in clinically similar circumstance. In addition, additional medications targeting IL-6 are also being investigated and appraised. Current evidence suggests that all the IL-6 inhibitors and IL-6-receptor antagonists appear to have broadly similar in clinical effectiveness and adverse effect profile, and that there is little to advantage of one over the other in general clinical practice.

Professional differences of opinion exist over which particular biologic agent should be considered first-line after failure of traditional DMARDS. Historically, since TNFα inhibitors were the first available option, these remain the first-line agents. However, the availability of other treatment options is a vital resource in the rheumatologist's arsenal, allowing effective treatment when patients fail to respond to other options.

Despite broadly similar efficacy and side-effect profile, the availability of multiple options provides effective market competition, allowing for local contract negotiation. There are also subtle differences of formulation, and the technologies employed for the injection device, which may affect patient concordance.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)
Sarilumab for previously treated moderate to severe active rheumatoid arthritis

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In contrast with some other biologics, Sarilumab is licensed for monotherapy in patients where co-administration of methotrexate is contraindicated or not tolerated.
Differences in the genetic coding of the IL-6 receptor have been noted between various ethnic populations. These differences may result in variations in efficacy observed between similar therapeutic agents, but it is currently unclear how this might translate into clinical practice.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

Secondary care clinics specialising in musculoskeletal/rheumatology.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Sarilumab is not currently approved by NICE for any indication.
Tocilizumab, its closest competitor, may potentially be used off-licence for other immune-mediated inflammatory diseases such as Behçet's disease and Takayasu arteritis.
There is insufficient evidence available to determine whether disease remission can be maintained using doses lower than those specified within the manufacturer's SPC, or with an extended dosing interval – however some trials have started to consider this scenario.

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

NICE CG79; NICE QS33.
SIGN Guidance 123.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

Sarilumab will be compared directly with Tocilizumab which is currently approved for the treatment of moderate to severe RA (and also, potentially, Sirukumab and other IL-6 inhibitors) – and should be similar in clinical practice. There is no evidence at this time to suggest that there will be any differences in monitoring requirements, or patient support.

Subtle differences in formulation, injection device, and drug half-life (resulting in variations of frequency of administration between therapeutic options) may help with patient concordance.

It is currently unknown how this agent will directly compare to other drugs – either within the same IL-6 class, or generally within the biologic immune-modulators. One head-to-head trial in patients where co-administration with Methotrexate was unsuitable suggests that monotherapy with Sarilumab may be superior to Adalimumab (MONARCH trial).

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

There is currently insufficient data published on the choice of first-line biologic agent – leading to differences in geographic implementation of treatment regimens (as noted above) as a result of guidelines imposed by commissioners. "Patient Profiling" through the use of biomarkers and/or genetic testing has been hypothesised, but this has not yet been shown to be practical or cost-effective. Therefore, we are limited to using disease activity scores to demonstrate that any course of biologic drug is effective in a particular patient, or if a treatment switch is required. This, by design, will require between 3-6 months of treatment (and funding) per patient before clinical outcome is assessed.

In an ideal situation, the time between diagnosis and initiating treatment should be as short as possible. However, in order to maintain cost-effectiveness, continued patient monitoring must be maintained, with an intention to treat-to-target and options to switch to alternative pharmacological options in the event of inadequate response. We have seen difficulties with the transition period between the initial point where current treatment is assessed to be no longer effective, and the final approval to initiate alternative treatment – leading to a waste of NHS resources due to the assumption (by patient or clinician) that some treatment, even if already demonstrated to be insufficient at maintaining remission, is better than no treatment at all whilst funding approval is pending.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

Clinical trial design generally appropriate, using DAS28 as an indicator of outcome efficacy.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Incidence and severity of adverse reactions appear to be in line with those exhibited by tocilizumab. Long-term monitoring and analysis would reveal any differences, but following past experience with the TNF-inhibitors, it is not anticipated that sarilumab would differ significantly from tocilizumab.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

None noted

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

A positive decision by NICE on this STA would provide additional choice to clinicians regarding which therapeutic options can be considered. Since arrangements for disease treatment are already in place with other biologic agents to support the provision, training and support of patients, no extra education and training would be required.
No additional (non-budgetary) resources should be required to implement.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)
Sarilumab for previously treated moderate to severe active rheumatoid arthritis

Equality
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Nothing noted.

NICE National Institute for Health and Care Excellence

Clinical expert statement

Sarilumab for previously treated moderate to severe active rheumatoid arthritis [ID994]

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

- 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	**Dr Marwan Bukhari**
2. Name of organisation	**University Hospitals of Morecambe bay NHS foundation trust**
3. Job title or position	**Consultant rheumatologist**
4. Are you (please tick all that apply):	**x**☐ an employee or representative of a healthcare professional organisation that represents

	clinicians? ☐**x** a specialist in the treatment of people with this condition? ☐ **x** 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.)	☐ **x** 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.)	

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.)	
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	
• 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.)	
• What impact would the technology have on the current pathway of care?	
11. Will the technology be used (or is it already	

used) in the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	

13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	
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 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?	
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?	
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	
• Does the use of the technology address any particular unmet need of the patient population?	
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?	
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	
• 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?	
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
21. How do data on real-world experience compare with the trial data?	
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	
22b. Consider whether these issues are different from issues with current care and	

why.	
Key messages	
25. In up to 5 bullet points, please summarise the key messages of your statement. • • • • •	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer expert statement (STA)

Sarilumab for previously treated moderate to severe active rheumatoid arthritis [ID994]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, including health-related quality of life)
- preferences for different treatments and how they are given
- expectations about the risks and benefits of the treatment.

We have already asked your nominating organisation to provide an organisation's view. We are asking you to give your views as an individual whether you are:

- a patient
- a carer (who may be voicing views for a patient who is unable to) or
- somebody who works or volunteers for a patient organisation.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The response area will expand as you type. The length of your response should not normally exceed 10 pages.

1. About you

Your name: Jennie Jones
Name of your nominating organisation: National Rheumatoid Arthritis Society
Do you know if your nominating organisation has submitted a statement?

X Yes ☐ No

Do you wish to agree with your nominating organisation's statement?

X Yes ☐ No

(We would encourage you to complete this form even if you agree with your nominating organisation's statement.)

Are you:

- a patient with the condition?

X Yes ☐ No

- a carer of a patient with the condition?

☐ Yes X No but I have been in the past.

- a patient organisation employee or volunteer?

X Yes ☐ No

Do you have experience of the treatment being appraised?

☐ Yes X No

If you wrote the organisation submission and do not have anything to add, tick here ☐ (If you tick this box, the rest of this form will be deleted after submission.)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: No

2. Living with the condition

What is your experience of living with the condition as a patient or carer?

RA has had a devastating impact on my life and life expectations. It has affected my family, my working life and prospects and my emotional well being. When initially diagnosed, my disease was aggressive and getting worse through a number of years while drugs were tried and found not to be effective in controlling my disease. I had to stop my full time work as the travel and hours involved couldn't be sustained with the pain, chronic fatigue and unreliability of my body. It has taken years to get to a steady state of remission and Humira has helped me get a life back (although not as it was before RA). Psychologically getting to a point of acceptance that this disease is here to stay is very difficult. My Mother also had the disease and I cared for her until she passed away, so I am also aware that the effectiveness of drugs and sensitivity to side effects etc can change over time, so no one knows what the future holds. I just have to live as well as possible today. It is particularly hard on your family who have to witness your pain, accommodate your lack of energy and help you when you cannot manage to do even basic tasks. Loss of independence and having to ask for help I have found very hard, even when it is offered freely and with much love.

3. Current practice in treating the condition

Which treatment outcomes are important to you? (That is, what would you like treatment to achieve?) Which of these are most important? If possible, please explain why.

Achieving a target of remission or as close to it as possible with reduced inflammations/joint damage, pain and less chronic fatigue, in the least possible time to avoid loss of work and independence.

What is your experience of currently available NHS care and of specific treatments? How acceptable are these treatments – which did you prefer

and why?

The quality of care available in the NHS is inconsistent and I had to move hospitals to avoid poor practice. The rationing of Biologic drugs combined with the fact that it usually takes at least 3 months to determine whether a DMARD is working meant for me that my life was on a total downward spiral physically and emotionally for a few years before I got treatments that made a significant difference (steroids work, but they are not sustainable long term without side effects). I have used Methotrexate, Prednisolone, Hydroxychloroquine and Sulphasalazine and Humira. It should be noted that even using a biologic is not without problem as normal infections mean the drug has to be stopped and then a period of inflammations etc are likely again until the RA settles down.

The Humira has been the only thing that really works for me, but injecting is not ideal and arranging deliveries, etc takes significant time. Methotrexate I find very unpleasant to take orally with bad effects on my stomach even now.

4. What do you consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that you expect to gain from using the treatment being appraised.

This disease specific treatment should deliver another option for reducing pain and inflammation at any stage of the disease, but especially for those whose

disease has not been controlled through existing treatments for whatever reason. This drug acts as an IL6 inhibitor rather than a TNF inhibitor which may suit some patients better. I am likely to be living with this disease for the rest of my life, and I am aware drugs can become less effective, other illness or side effects may mean changes in medication has to happen in response. The more effective alternatives available, the better for every patient

Please explain any advantages that you think this treatment has over other NHS treatments in England.

I believe the drug should be part of the range of drugs available as it acts in a different way to the existing drugs which may benefit some patients who cannot tolerate/do not respond to those drugs currently available.

If you know of any differences in opinion between you and other patients or carers about the benefits of the treatment being appraised, please tell us about them.

Not aware

5. What do you consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns you have about current NHS treatments in England.

Limiting access to Biologic drugs via strict rationing criteria means many patients endure life changing levels of pain and inflammation and still do not

qualify for that therapy. All aspects of their lives are affected – family, work, relationships and emotional well being. This is a great loss to society as a whole, and devastating for those individuals who have to live with this disease for the rest of their lives.

Please list any concerns you have about the treatment being appraised.

None known

If you know of any differences in opinion between you and other patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

None known

6. Patient population

Do you think some patients might benefit more from the treatment than others? If so, please describe them and explain why.

This drug should benefit patients at as an alternative treatment.

Do you think some patients might benefit less from the treatment than others? If so, please describe them and explain why.

Not known

7. Research evidence on patient or carer views of the treatment

Are you familiar with the published research literature for the treatment?

☐ Yes X No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether your experience of using the treatment as part of routine NHS care reflects the experience of patients in the clinical trials.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

If the treatment being appraised is already available in the NHS, are

there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments?

X Yes ☐ No

If yes, please provide references to the relevant studies.

National Rheumatoid Association

- Family Matters NRAS 2012
- I want to work NRAS 2007
- RA Fatigue Survey and Report 2014
- The Mapping Project, Sue Oliver and Ailsa Bosworth, 2009
- Scotland Work survey, NRAS 2010
- Who Cares Report, Scotand NRAS 2015
- Emotions, Relationships and Sexuality Survey & Report, NRAS 2013
- RA and physiotherapy NRAS 2011
- Wales State of Play Report, BSR and NRAS, 2015

8. Equality

NICE is committed to promoting equality of opportunity and eliminating discrimination. Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, who they are and why.

No

9. Other issues

Do you consider the treatment to be innovative?

X Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

IL6 inhibitor – precise blocking of inflammatory signal cascade.

Is there anything else that you would like the Appraisal Committee to

consider?

No

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- This is a new class of therapy not previously available which will provide help to some patients who currently cannot tolerate or do not respond to existing mediceines
- It is innovative – a targeted drug attacking the disease directly
- It adds to the armoury of drugs that may be needed to meet changing requirements during a lifetime of living with this chronic disease.

Sarilumab for previously treated moderate or severe rheumatoid arthritis: A Single Technology Appraisal

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
Authors	Iñigo Bermejo, Research Associate, ScHARR, University of Sheffield, Sheffield, UK Shijie Ren, Research Fellow, ScHARR, University of Sheffield, Sheffield, UK Emma Simpson, Research Fellow, ScHARR, University of Sheffield, Sheffield, UK Mark Clowes, Information Specialist, ScHARR, University of Sheffield, Sheffield, UK David L Scott, Department of Rheumatology, King's College Hospital NHS Foundation Trust, London, UK Adam Young, Department of Rheumatology, West Hertfordshire Hospital NHS Trust, Hertfordshire, UK Matt Stevenson, Professor of Health Technology Assessment, ScHARR, University of Sheffield, Sheffield, UK
Corresponding Author	Iñigo Bermejo, Research Associate, ScHARR, University of Sheffield, Sheffield, UK
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Declared competing interests of the authors

David Scott has no conflicts of interest relating to sarilumab. He has undertaken work for the following companies in rheumatology and related areas in the last 3 years:

1. Eli Lilly And Co. Autumn 2014: Advisory Board Baricitinib, summer 2015: Educational meeting on rheumatoid arthritis
2. Roche Products Ltd. Summer 2014: Advisory Board Biologics in Arthritis
3. Napp Pharmaceuticals. Summer 2014: Advisory Board Biosimilars in Arthritis
4. Baxalta. Autumn 2015: Advisory Board Biosimilars in Arthritis
5. Novartis. Spring 2016: Advisory Board Assessment of Multiple Sclerosis

He was paid between £1000 and £3300 for these various activities.

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

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Rider on responsibility for report

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

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Contributions of authors

Inigo Bermejo acted as the project lead and critiqued the health economic analysis submitted by the company. Emma Simpson summarised and critiqued the clinical effectiveness data reported within the company's submission. Shijie Ren critiqued the company's network meta-analysis. Ruth Wong critiqued the company's search strategy. David Scott and Adam Young provided clinical advice to the

team. Matt Stevenson critiqued and summarised the cost-effectiveness model. All authors were involved in drafting and commenting on the final report.

CONTENTS

List of Tables

List of Figures

ABBREVIATIONS

ABT	Abatacept
AC	Appraisal Committee
ACR	American College of Rheumatology
ACR20	20% improvement in the ACR score
ACR50	50% improvement in the ACR score
ACR70	70% improvement in the ACR score
ADA	Adalimumab
AE	Adverse event
AG	Assessment Group
AiC	Academic-in-confidence
AIC	Akaike Information Criterion
ALT	Alanine transaminase
AST	Aspartate transaminase
AZA	Azathioprine
AUC	Area under the curve
BAR	Baricitinib
BD	Twice per day
bDMARD	Biologic disease-modifying antirheumatic drug
BIC	Bayesian Information Criterion
BIW	Twice weekly
BNF	British National Formulary
BSC	Best supportive care
BSRBR	British Society for Rheumatology Biologics Register
cDMARD	Conventional disease-modifying antirheumatic drug
CDAI	Clinical Disease Activity Index
CG	Clinical Guideline
CI	Confidence interval
CIC	Commercial-in-confidence
CODA	Convergence diagnostic and output analysis
CRD	Centre for Reviews and Dissemination
CRP	C-reactive protein
CrI	Credible interval
CS	Company's submission
CSR	Clinical study report
CTZ	Certolizumab pegol

DAS28	Disease Activity Score 28
DAS-CRP	Disease Activity Score C-reactive protein
DES	Discrete event simulation
DSU	Decision Support Unit
DMARD	Disease-modifying antirheumatic drug
eGFR	Estimated glomerular filtration rate
EAIR	Exposure adjusted incidence rate
EMA	European Medicines Agency
EQ-5D	EuroQol 5 Dimensions
EQ-5D-5L	EuroQol 5 Dimensions 5 levels
ERAS	Early RA Study
ERG	Evidence Review Group
ESR	Erythrocyte Sedimentation Rate
ETN	Etanercept
ETN-b	Etanercept biosimilar
EULAR	European League Against Rheumatism
FAD	Final Appraisal Determination
GDG	Guideline Development Group
GLD	Gold injections
GOL	Golimumab
HAQ	Health Assessment Questionnaire
HAQ-DI	Health Assessment Questionnaire Disability Index
HCQ	Hydroxychloroquine
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IFX	Infliximab
IFX-b	Infliximab biosimilar
IL-6	Interleukin-6
INB	Incremental net benefit
IPS	Individual patient simulation
ITT	Intention-to-treat
IV	Intravenous infusion
JAK	Janus kinase
LDA	Low disease activity
LDL	Low-density lipoprotein

LOCF	Last observation carried forward
MACE	Major adverse cardiovascular event
MD-HAQ	Multidimensional HAQ
mITT	Modified intention-to-treat
MJS	Morning joint stiffness
MTA	Multiple Technology Appraisal
mTSS	Modified Total Sharp Score
MTX	Methotrexate
NBT	Non-biologic treatment
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NOAR	Norfolk Arthritis Register
NR	Not reported
NRI	Non-responder imputation
NSAIDs	Non-steroidal anti-inflammatory drugs
OLE	Open-label extension
ONS	Office for National Statistics
PAS	Patient Access Scheme
PASLU	Patient Access Schemes Liaison Unit
PBO	Placebo
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QD	Once a day
QW	Once weekly
Q2W	Every two weeks
Q4W	Every four weeks
Q8W	Every eight weeks
RA	Rheumatoid arthritis
RCT	Randomised controlled trial
RF	Rheumatoid factor
RR	Rate ratio
RTX	Rituximab
SAE	Serious adverse event
SAR	Sarilumab

SC	Subcutaneous
SD	Standard deviation
SDAI	Simplified Disease Activity Index
SE	Standard error
SF-36	Short Form (36) Health Survey
SIR	Sirukumab
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
STA	Single Technology Appraisal
SSZ	Sulfasalazine
SW28	Swelling 28 joints
TA	Technology Appraisal
TCZ	Tocilizumab
TEN28	Tenderness 28 joints
TNF	Tumour necrosis factors
TNFi	Tumour necrosis factors inhibitor
TNFi-IR	TNFi inadequate response
TOF	Tofacitinib
TSD	Technical Support Document
VARA	Veteran's Affairs Rheumatoid Arthritis Registry
WPAI-RA	Work Productivity and Activity Index-Rheumatoid Arthritis

1 SUMMARY

1.1 Critique of the decision problem in the company's submission

The Evidence Review Group (ERG) considers the company's description of the underlying health problem in the company's submission (CS) to be appropriate, mostly up-to-date and relevant to the decision problem set out in the final National Institute for Health and Care Excellence (NICE) scope. The decision problem assesses sarilumab (SAR) for previously treated moderate-to-severe active rheumatoid arthritis (RA). SAR is a new interleukin-6 (IL-6) pathway inhibitor,

1.2 Summary of clinical effectiveness evidence submitted by the company

The key clinical effectiveness evidence for SAR was based on five randomised controlled trials (RCTs). Additionally, one long-term extension study was included. There were three RCTs in methotrexate (MTX) intolerant or inadequate response (MTX-IR) patients with RA (MOBILITY-A, MOBILITY-B, MONARCH). Two RCTs (TARGET and ASCERTAIN) were in patients with RA who had had an inadequate response or were intolerant to biologic disease-modifying antirheumatic drug (bDMARD-IR). One RCT (ASCERTAIN) compared SAR with tocilizumab (TCZ), another study (MONARCH) compared it against adalimumab (ADA), and the remainder compared SAR against placebo (PBO).

Three RCTs had 20% improvement in the American College of Rheumatology (ACR) score (ACR20) as their primary endpoint (MOBILITY-A, MOBILITY-B, TARGET). In the MTX-IR population, the RCTs showed a significant advantage ($p \leq 0.05$) in ACR responses for licensed doses of SAR with concomitant MTX (SAR+MTX) over PBO + MTX (MOBILITY-A, MOBILITY-B), and a significant advantage ($p<0.01$) for SAR monotherapy over ADA monotherapy (MONARCH). In the bDMARD-IR population, TARGET reported a significant advantage for SAR with a concomitant conventional disease-modifying antirheumatic drug (cDMARD) over PBO+cDMARD on ACR20 ($p<0.0001$), ACR50 ($p \leq 0.005$) and ACR70 ($p \leq 0.005$).

[redacted] The most frequent serious adverse event (SAEs) were [redacted] The most common adverse events (AEs) [redacted]

Network meta-analyses (NMA) were performed to assess the relative efficacy and safety of SAR versus the relevant comparators in patients with moderate-to-severe RA who were inadequate responders to cDMARDs (cDMARD-IR) or to tumour necrosis factor inhibitors (TNFi-IR). The efficacy outcome

measures used in the NMA were ACR responses, the Health Assessment Questionnaire Disability Index (HAQ-DI), European League Against Rheumatism (EULAR) responses, Disease Activity Score 28 (DAS28) remission and modified Total Sharp Score (mTSS)). The safety outcome measures included in the NMA were serious infections (SI) and SAEs. In the cDMARD-IR population, separated networks were used for the combination therapies and monotherapies.

In the base case NMA for the cDMARD-IR population, SAR 200mg in combination with cDMARD demonstrated statistically superiority to cDMARD for all the efficacy outcome measures at 24 weeks. SAR 200mg combination therapy was comparable to other bDMARD combination therapies on ACR responses, DAS28 remission and HAQ-DI (subcutaneous [SC] TCZ combination therapy was not included in the HAQ-DI network). SAR 200mg combination therapy showed statistical superiority to ABT combination, infliximab (IFX) combination and intravenous (IV) TCZ 4mg/kg, rituximab (RTX) and SAR 150mg on good EULAR response at 24 weeks, and was comparable to golimumab (GOL) and TCZ IV 8mg/kg, all in combination with cDMARDs. SAR 200mg combination therapy was statistically inferior to certolizumab pegol (CTZ) combination on moderate to good EULAR response at 24 weeks, but comparable to GOL, IFX, TCZ IV 4mg/kg and 8mg/kg, RTX and SAR 150mg all in combination with cDMARDs. For mTSS at 24 weeks, SAR 200mg combination therapy was statistically superior to baricitinib (BAR) 2mg, tofacitinib (TOF) and CTZ all in combination with cDMARDs, and comparable to BAR 4mg, ADA, GOL, TCZ SC 162mg all in combination with cDMARD. For mTSS at 52 weeks, SAR 200mg combination therapy was comparable to ABT, ADA, CTZ and etanercept (ETN) all in combination with cDMARDs, and superior to SAR 150mg combination therapy.

In the NMA evaluating monotherapies in the cDMARD-IR population, all outcome measures were assessed at 24 weeks. SAR 200mg monotherapy showed statistically superiority to placebo and cDMARDs for all efficacy outcome measures, except that it was comparable to cDMARDs on HAQ-DI, and an analysis of DAS28 remission was not performed for placebo. SAR 200mg monotherapy was also statistically superior to ADA on all ACR responses, and sirukumab (SIR) 50mg on ACR20 and ACR50 responses. SAR 200mg was comparable to CTZ, ETN, SIR 100mg, TCZ IV 8mg/kg and TOF on all ACR responses. SAR 200mg was statistically superior to ADA and SIR 50mg on DAS28 remission, and comparable to SIR 100mg and TCZ IV 8mg/kg. SAR 200mg was statistically superior to ADA on HAQ-DI, and comparable to CTZ, ETN and TCZ IV 8mg/kg. SAR 200mg was statistically superior to ADA on EULAR responses, and comparable to TCZ 8mg/kg.

In the NMA for the TNFi-IR population, the outcome measures were all assessed at 24 weeks. SAR 200mg combination therapy showed statistically superiority to cDMARDs for all efficacy outcome measures. SAR 200mg combination was statistically superior to BAR 2mg combination, SIR 50mg combination on ACR50, and comparable to other bDMARD combination therapies on all ACR

responses. SAR 200mg combination therapy was statistically superior to ABT, BAR 2mg, GOL, SIR 50mg, TCZ IV 4mg/kg, and RTX combination therapies on DAS28 remission, and comparable to other bDMARD combination therapies. SAR 200mg was not statistically significantly different to other bDMARDs on changes in HAQ-DI. For good EULAR response, SAR 200mg combination therapy was statistically superior to RTX combination therapy, and comparable to ABT and SAR 150mg combination therapies. For at least a moderate EULAR response, SAR 200mg combination therapy was statistically inferior to TCZ 8mg/kg and RTX combination therapies, and comparable to ABT, GOL and SAR 150mg combination therapies.

Regarding safety, SAR 200mg combination therapy was associated with significantly higher odds of SAEs at 52 weeks when compared to cDMARDs in the cDMARD-IR population. All other outcomes were not statistically significant.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The ERG believes that all available RCTs informing on the clinical effectiveness of SAR were included in the CS. The eligibility criteria applied in the selection of evidence for the clinical effectiveness review were considered by the ERG to be reasonable and consistent with the decision problem outlined in the final NICE scope. The quality of the included RCTs was assessed using well-established and recognised criteria.

The ERG believes that the results presented in the NMAs of clinical effectiveness should be treated with caution, as the statistically significant results of SAR 200mg compared with other bDMARD treatments (both as combination therapy and monotherapy) may be a consequence of underestimating the uncertainty in treatment effects resulting from the use of a fixed effect model. The ordered categorical ACR response and EULAR response data were dichotomised in the NMA, which ignores the natural ordering and correlations between the categories within the outcome measure. When a risk difference model was used for binary data, the probability of response was not constrained to be below or equal to 1, potentially producing invalid probability values. Furthermore, the MOBILITY B and TARGET trial designs allowed patients who did not achieve a ≥20% improvement from baseline at two consecutive assessments in the swollen joint count or tender joint count to switch to open-label SAR 200mg at 16 and 12 weeks, respectively. Non-responder imputation was carried out for the control arm, assuming none of the non-responders in the cDMARD control group would become responders at 24 weeks, which may overestimate the relative treatment effect of SAR combination therapy versus cDMARDs.

1.4 Summary of cost effectiveness submitted evidence by the company

The company supplied a *de novo* individual patient-level Markov model constructed in Microsoft Excel®. The model, which has a cycle length of 6 months, simulates patients' disease progressions through the sequences of treatments being compared. For each treatment, patients may achieve good, moderate or no EULAR response: this is assessed at 6 months. The EULAR response rates for each treatment are based on the ACR response rates calculated using the company's NMA. Patients who achieve moderate or good EULAR response are assumed to have an improvement in Health Assessment Questionnaire (HAQ) score and remain on treatment until loss of efficacy (as assessed by a clinician), or until they experience an AE or death. Patients who fail to achieve a moderate or good EULAR response discontinue treatment at 6 months and initiate the next treatment in the sequence. HAQ progression whilst on treatment is assumed to be constant on bDMARDs and SAR; conversely, whilst on cDMARDs and best supportive care (BSC), HAQ progression is assumed to be linear. Time to treatment discontinuation for responders is dependent on the type of treatment (TNFi, IL-6, others) and is modelled using survival curves fitted to treatment discontinuation data from the Canadian observational database RHUMADATA. Upon treatment discontinuation, patients are assumed to experience a rebound in HAQ equal to that achieved on treatment initiation and then start on the next treatment in the sequence. The mortality rate is assumed to be affected by the HAQ score of a patient at treatment initiation. The model estimates the costs and quality-adjusted life years (QALYs) accrued over patients' remaining lifetimes. EuroQol 5 Dimensions (EQ-5D) values are estimated based on a mapping algorithm from HAQ scores and patient characteristics. Hospitalisation costs and resource use estimates were based on HAQ score bands as in previous NICE technology appraisals. Unit costs were taken from the British National Formulary and NHS Reference Costs. Serious infection were the only AE included in the analyses.

The company's analyses relate to seven different populations of rheumatoid arthritis patients: (1) cDMARD-IR patients with severe RA who can tolerate MTX; (2) cDMARD-IR patients with severe RA for whom MTX is contraindicated or not tolerated; (3) TNFi-IR patients with severe RA and who are rituximab (RTX) eligible; (4) TNFi-IR patients with severe RA for whom RTX is not an option; (5) TNFi-IR patients with severe RA for whom MTX is contraindicated or not tolerated; (6) TNFi-IR patients with severe RA after treatment with RTX+MTX; and, (7) a subgroup of cDMARD-IR patients with moderate RA whose DAS28 scores are between 4.0 and 5.1. The definition of severe RA was a DAS28 score higher than 5.1, whilst moderate RA was defined as a DAS28 > 3.2 and ≤ 5.1. Baseline characteristics of patients are based on the relevant clinical SAR trials.

The company presented analyses in the CS and in the clarification response as per the ERG's request. The ERG believes that the analyses presented by the company in the clarification responses are closer to the company's intended base case than those reported in the CS. According to the company's revised

probabilistic analysis, in the cDMARD-IR population of patients with severe RA who could tolerate MTX, SAR with concomitant MTX (SAR+MTX) dominated both indications of TCZ with concomitant MTX and the incremental cost-effectiveness ratios (ICERs) for SAR+MTX compared with a weighted average of TNFi-s (TNFi bundle) and ABT (SC) + MTX were £69,884 and £117,482 per QALY gained respectively. In cDMARD-IR patients with severe RA who could not tolerate MTX, the deterministic ICER for SAR monotherapy compared with the TNFi bundle was estimated to be £17,123 per QALY gained, whilst the ICER for both TCZ indications compared with SAR was in excess of £1,000,000 per QALY gained. In TNFi-IR patients for whom RTX+MTX was an option, the ICER for SAR+MTX compared with RTX+MTX was estimated to be £130,691 per QALY gained. In patients for whom RTX is not an option, the ICER for the comparators versus SAR+MTX in TNFi-IR patients was greater than £60,000 per QALY. For TNFi-IR patients who cannot tolerate MTX, the ICER for SAR monotherapy compared with a TNFi bundle was estimated to be £17,794 per QALY gained. In patients who have received RTX+MTX, the ICER for both indications of TCZ compared with SAR+MTX were estimated to be greater than £130,000 per QALY gained. Finally, in cDMARD-IR patients with moderate RA and a DAS28 score higher than 4.0, the ICER for SAR+MTX was estimated to be £38,254 per QALY gained.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The company's model was based on the model developed by the Assessment Group (AG) in NICE Technology Appraisal 375 (TA375) but was an individual patient level Markov model rather than a discrete event simulation (DES). The ERG believes that the conceptual model was broadly appropriate.

After an initial evaluation of the company's analyses, the ERG requested that the company perform new analyses after addressing a number of issues. The company presented new analysis after addressing the following issues: (i) inadequate treatment sequences that did not reflect NICE recommendations; (ii) omission of the possibility of patients with moderate RA to progress to the severe state; (iii) use of Malottki *et al.* instead of Hernandez *et al.* for the mapping of HAQ scores to EQ-5D; (iv) limitations in the company's NMA explained in Section 1.3; (v) using percentages of improvement of HAQ instead of absolute mean changes; (vi) omission of rounding to the nearest valid HAQ score; (vii) use of an implausible extrapolation of time to treatment discontinuation; (viii) using independent samples for the probabilities of ACR responses in the PSA instead of correlated samples from the CODA of the NMA; (ix) assuming 9 free doses of CTZ instead of 10; and, (x) the inclusion of the speculative Patient Access Scheme (PAS) discount of 15% applied to TCZ and ABT.

The main issue remaining in the company's analyses after these amendments is the assumption that the HAQ score of patients on cDMARDs and BSC follow a linear trajectory. The ERG notes that there is extensive evidence that shows that the HAQ trajectory for these patients is not linear and that the appraisal committee for TA375 accepted the non-linear trajectory of HAQ scores using the latent class

approach used by the AG. The ERG notes that the company's assumption of linear HAQ increase is likely to lead to lower ICER estimations for SAR+MTX in the moderate RA population with a DAS28 score between 4.0 and 5.1 compared with a non-linear trajectory approach.

A further issue in the company's amended model is the inadequate implementation of the transition from moderate to severe RA. The ERG notes that patients should progress to the severe sequences at the point when their DAS28 score increases above 5.1, without waiting until they have reached the end of the moderate sequence.

The company did not present analyses comparing SAR to all other recommended bDMARDs independently; instead, the company created a blended comparator grouping all the TNFi-s together. The ERG believes that presenting analyses including the TNFi-s independently would have been more informative, given the differences in cost and efficacy of different TNFi-s and the fact that their market shares are currently changing.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

The ERG believes that all available RCTs of SAR were included in the CS. The five SAR RCTs included were considered to be of good methodological quality in terms of randomisation, blinding and performing intention-to-treat analyses.

The ERG notes that the model and analyses submitted after the clarification process appears to be conceptually appropriate with only two relevant limitations.

1.6.2 Weaknesses and areas of uncertainty

The ERG notes that the natural comparators for SAR are the other biologic agents specifically targeting the IL-6 pathway, e.g. TCZ, SIR, olokizumab, and clazakizumab. Of these IL-6 pathway inhibitors, only TCZ was approved by the European Medicines Agency at the time of writing, and prior to the start of the SAR trials. Therefore, TCZ should be the main comparator of SAR, but only one head-to-head comparison study (ASCERTAIN) was identified. The ERG notes that the primary endpoint of this study relates to safety, rather than efficacy outcomes. In addition, the ERG notes that some patients on the TCZ arm of ASCERTAIN received only half the recommended dose according to UK prescription guidance (4mg/kg instead of 8mg/kg). Only one head-to-head efficacy RCT was identified against another bDMARD, a monotherapy study against ADA. The ERG notes that in the ADACTA study, ADA monotherapy had previously been shown to be statistically significantly inferior to TCZ monotherapy in terms of DAS28 and ACR and EULAR responses.

The ERG believes that the DES paradigm is more appropriate to represent the disease than the individual patient Markov model approach used by the company.

In the company's amended model HAQ progression is still assumed to be linear for patients on cDMARDs and on BSC. This approach was used in previous appraisals but there has been since extensive evidence published against the appropriateness of this assumption. In line with this evidence, the AG in TA375 used a latent class approach of non-linear trajectories.

The company used a blended comparator grouping all the TNFi-s together, which may obscure the cost-effectiveness of SAR. This weakness has been alleviated by the company to a certain extent by including sensitivity analyses where TNFi-s have been considered separately in some of the populations in the CS but not in the clarification response.

In some populations the company used effectiveness estimates calculated from similar but different populations due to lack of available evidence: in TNFi-IR patients who could not tolerate MTX, the company used the effectiveness of therapies in combination with MTX; and in TNFi-IR patients who had received RTX + MTX, the effectiveness estimates calculated from the general TNFi-IR population were used.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG undertook exploratory analyses after implementing the latent class approach of non-linear HAQ trajectories used in TA375 and amending the transition of moderate RA patients to the severe state.

According to the ERG's exploratory analyses, in cDMARD-IR patients with severe RA who can tolerate MTX, SAR + MTX was estimated to dominate both indications of TCZ with concomitant MTX and the ICERs for TNFi bundle + MTX and ABT (SC) + MTX compared with SAR + MTX are estimated to be in excess of £150,000 per QALY gained. In cDMARD-IR patients with severe RA for whom MTX was contraindicated or not tolerated, the ICER for SAR monotherapy compared with TNFi bundle monotherapy was estimated to be £34,422 per QALY gained, whilst the ICERs for both indications of TCZ compared with SAR monotherapy where estimated to be in excess of £1,500,000 per QALY gained. In TNFi-IR patients with severe RA who can tolerate RTX and MTX the ICER for SAR+MTX compared with RTX+MTX was estimated to be £171,466 per QALY gained. In TNFi-IR patients with severe RA for whom RTX is not an option, SAR + MTX was estimated to result in an ICER of £34,979 per QALY gained compared with TNFi bundle whilst the ICER for both TCZ indications with concomitant MTX compared with SAR + MTX was estimated to be in excess of £195,000. In TNFi-IR patients with severe RA for whom MTX is contraindicated or not tolerated, the ICER for SAR monotherapy compared with TNFi bundle was estimated to be £31,433 per QALY

gained. In TNFi-IR patients who have already received RTX+MTX, the ICERs for both indications of TCZ with concomitant MTX compared with SAR+MTX were estimated to be in excess of £200,000 per QALY gained. In cDMARD-IR patients moderate RA and a DAS28 higher than 4.0, a sequence starting with SAR+MTX compared with MTX was estimated to result in an ICER of £63,438 per QALY gained.

The ERG notes that the confidential PASs in place for ABT and TCZ were not included in these analyses. The ERG presents the analyses including the confidential PASs in a confidential appendix.

2 BACKGROUND

2.1 Critique of company's description of underlying health problem

The Evidence Review Group (ERG) considers the company's description of the underlying health problem in the company's submission (CS)[2] to be appropriate, mostly up-to-date and relevant to the decision problem set out in the final National Institute for Health and Care Excellence (NICE) scope.[3] The ERG provides a brief summary of the underlying health problem. Epidemiological numbers provided by the ERG may differ from those presented in the CS but do not affect the broad messages.

Clinical features of rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterised by: progressive, irreversible, joint damage; impaired joint function; pain and tenderness caused by swelling of the synovial lining of joints.[4] The condition is associated with increasing disability and reduced health-related quality of life.[4] The primary symptoms are: pain; morning stiffness; swelling; tenderness; loss of movement; redness of the peripheral joints; and fatigue.[5, 6] RA is associated with substantial direct costs (including drug acquisition and hospitalisation) and indirect costs (including reduced productivity).[7] RA has long been reported as being associated with increased mortality,[8, 9] particularly due to cardiovascular events.[10]

Epidemiology

NICE estimates that there are 400,000 people in the UK with RA,[11] based on a prevalence of 0.8% reported by Symmons *et al*.[12] The incidence of RA is greater in females (3.6 per 100,000 per year) than in males (1.5 per 100,000 per year).[13] For both genders, the peak age of incidence in the UK is in the eighth decade of life, but all ages can develop the disease.[13]

Aetiology

There is no identified specific cause for RA, but there seems to be a variety of contributing factors such as genetic and environmental influences. Genetic factors have a substantial contribution to RA. The heritability of RA is estimated to be between 53 and 65%[14] and family history of RA has a corresponding risk ratio of 1.6 compared with the general population.[15] Many genes associated with RA susceptibility are concerned with immune regulation. Infectious agents have been suspected but no consistent relationship with an infective agent has been proven. Similarly, sex hormones have been suspected due to the higher prevalence of RA in women and a tendency for the disease to improve during pregnancy. However, a precise relationship has not been identified. There is no proof of any causal link with lifestyle factors such as diet, smoking, or occupation.

Management of rheumatoid arthritis

Traditionally, patients have been treated with conventional disease-modifying anti-rheumatic drugs (cDMARDs) which include methotrexate (MTX), sulfasalazine (SSZ), hydroxychloroquine (HCQ), leflunomide (LEF), and gold injections as well as corticosteroids, analgesics and non-steroidal anti-inflammatory drugs (NSAIDs). However, more recently, a group of biologic immunosuppressant drugs have been developed that specifically modify the disease process by blocking key protein messenger molecules (such as cytokines) or cells (such as B-lymphocytes).[11] Such drugs have been labelled as biologic disease-modifying anti-rheumatic drugs (bDMARDs): certolizumab pegol (CTZ); adalimumab (ADA); etanercept (ETN); golimumab (GOL); and infliximab (IFX) are tumour necrosis factor (TNF) inhibitors (or antagonists) (TNFi). Of the remaining bDMARDs, tocilizumab (TCZ) is a cytokine interleukin-6 (IL-6) inhibitor; abatacept (ABT) is a selective modulator of the T lymphocyte activation pathway; and rituximab (RTX) is a monoclonal antibody against the CD20 protein. For patients who have exhausted all NICE recommended treatments, palliative care, also known as best supportive care (BSC), is the final treatment option.

Assessment of response to therapy

The initial response criteria for RA were produced in 1987 by the American College of Rheumatology[16] (ACR). NICE Clinical Guideline (CG) 79 provides a summary of the ACR criteria, namely that patients must have at least four of seven criteria: (i) morning stiffness lasting at least 1 hour; (ii) swelling in three or more joints; (iii) swelling in hand joints; (iv) symmetric joint swelling; (v) erosions or decalcification on X-ray of hand; (vi) rheumatoid nodules; (vii) and abnormal serum rheumatoid factor. For the first four criteria, these must have been present for a period of at least six weeks. However, in NICE CG 79, the Guideline Development Group (GDG) preferred a clinical diagnosis of RA rather than the ACR criteria referencing recommendations from the European League Against Rheumatism (EULAR)[17] stating that "*an early persistent synovitis where other pathologies have been ruled out needs to treated as if it is RA to try to prevent damage to joints. Identification of persistent synovitis and appropriate early management is more important than whether the disease satisfies classification criteria*".

In 2010, the ACR and EULAR jointly published RA classification criteria, which focussed on the features at earlier stages of disease which are associated with persistent and/or erosive disease, rather than defining the disease by its late stage features.[18] The classification criteria allocate scores to characteristics of joint involvement, serology, acute-phase reactants, and duration of symptoms, to produce a score between 0 and 10 inclusive. Those patients scoring 6 or greater and with obvious clinical synovitis being defined as having "definite RA" in the absence of an alternative diagnosis that better explains the synovitis.

Two classifications have dominated the measurement of improvement in RA symptoms: ACR responses[19] and EULAR responses.[20]

The initial ACR response 'ACR20', required: a 20% improvement in tender joint counts; a 20% improvement in swollen joint counts; and a 20% improvement in at least three of the following five 'core set items': physician global assessment; patient global assessment; patient pain; self-reported disability (using a validated instrument), and; erythrocyte sedimentation rate (ESR) / C-reactive protein (CRP).

ACR response has been widely adopted in randomised controlled trials (RCTs) although studies have shown that the value of the measure can vary between trials due to the timing of the response.[21] Since the inception of the ACR20, two further response criteria (ACR50 and ACR70) have become widely used. These are similar to ACR20 and differ only in the level of percentage improvements required to be classified as a responder. These are nested responses, thus patients who achieve ACR70 will also achieve ACR20 and ACR50.

In the UK, monitoring the progression of RA is often undertaken using the disease activity score of 28 joints (DAS28) in terms of swelling (SW28) and of tenderness to the touch (TEN28). The DAS28 score incorporates measures of the ESR and a subjective assessment on a scale of 0-100 made by the patient regarding disease activity in the previous week.

The equation for calculating DAS28 is as follows:[22]

$$DAS28 = 0.56 * TEN28^{0.5} + 28 * SW28^{0.5} + 0.70 * \ln(ESR) + 0.014 * \text{subjective assessment}$$

The DAS28 can be used to classify both the disease activity of the patient and the level of improvement estimated within the patient.

A second version of DAS28, using C-reactive protein (CRP) rather than ESR exists. However, as the majority of studies have used DAS28 ESR, this is the metric used by the company in assessing comparative effectiveness between interventions.

The EULAR response criteria use the individual change in DAS28 and the absolute DAS28 score to classify a EULAR response as: good; moderate; or none.[20] The EULAR response criteria and the ACR20 improvement criteria were found to have reasonable agreement in the same set of clinical trials, although van Gestel *et al.* state that the EULAR response criteria showed better construct and discriminant validity than ACR20.[23] EULAR response has been reported less frequently in RCTs than ACR responses,[24] although EULAR is much more closely aligned to the treatment continuation rules

stipulated by NICE for treatment in England. These rules require either a moderate or good EULAR response or a DAS28 improvement of more than 1.2 to continue treatment, with the latter criterion applying to RTX. The relationship between change in DAS28 and the absolute DAS28 score and EULAR response is shown in Table 1.

Table 1: Determining EULAR response based on DAS28[23]

	Improvement in DAS 28		
DAS28 at endpoint	>1.2	>0.6 and ≤1.2	≤0.6
≤ 3.2	Good	Moderate	None
>3.2 and ≤5.1	Moderate	Moderate	None
>5.1	Moderate	None	None

Patients with a DAS28 ≤3.2 are regarded as having low disease activity, those with a DAS28 > 3.2 and ≤ 5.1 are regarded as having moderate disease and >5.1 as having very active disease.[22] Within NICE Technology Appraisal (TA) 375, patients with a DAS28 > 3.2 and ≤ 5.1 were considered as having moderate to severe disease whilst those with a DAS28 > 5.1 were denoted as having severe disease.[25]

A widely used measure of patient disability is the Health Assessment Questionnaire (HAQ). The HAQ score is a patient completed disability assessment which has established reliability and validity.[26] HAQ scores range from 0 to 3, with higher scores indicating greater disability, and is a discrete scale with step values of 0.125, resulting in the HAQ scale containing 25 points. The HAQ has been used in many published RCTs in RA.[24]

2.2 Critique of company's overview of current service provision

The company's overview of current service but appropriate and relevant to the decision problem set out in the final NICE scope. The ERG provides a summary of current service provision below.

Clinical guidelines

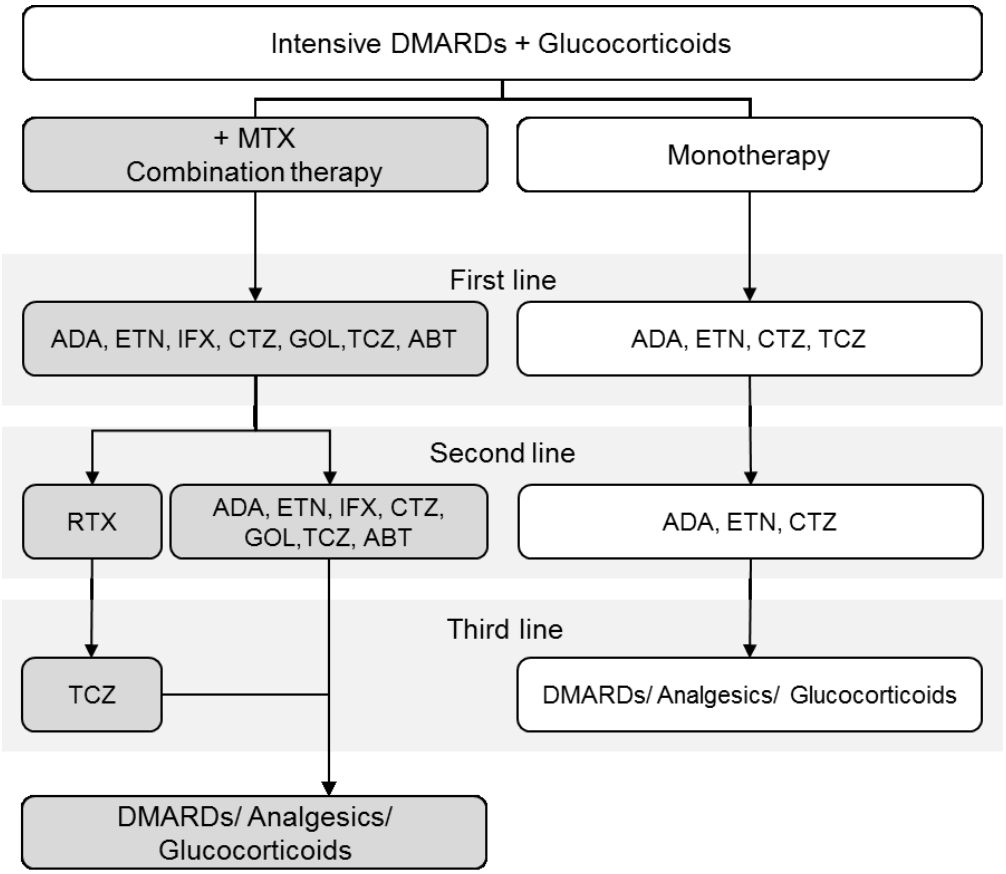
For people with newly diagnosed RA, NICE CG79[11] recommends a combination of cDMARDs (including MTX and at least one other cDMARD plus short-term glucocorticoids) as first-line treatment, ideally beginning within 3 months of the onset of persistent symptoms. Where combination therapies are not appropriate, for example, where there are comorbidities or pregnancy, cDMARD monotherapy is recommended. Where cDMARD monotherapy is used, efforts should be made to increase the dose quickly to obtain best disease control. For the purposes of this assessment, the term "intensive cDMARDs" has been used to denote that this involves treatment with multiple cDMARDs simultaneously.

NICE guidance (TA375)[25] recommends the use of ABT, ADA, CTZ, ETN, GOL, IFX, and TCZ in combination with MTX in people with RA after the failure to respond to intensive cDMARD treatment and who have severe active RA (defined as a DAS28 score > 5.1). For people who meet these criteria but cannot take MTX because it is contraindicated or because of intolerance, TA375[25] recommends the following bDMARDs as monotherapy options: ADA; CTZ; ETN; or TCZ.

After the failure of the first TNF-inhibitor, TA195[27] recommends RTX in combination with MTX for the treatment of severe active RA. If RTX is contraindicated or withdrawn because of an adverse event (AE), TA195 recommends ABT, ADA, ETN, or IFX in combination with MTX. If MTX is contraindicated, or withdrawn because of an AE, TA195 recommends ADA or ETN as monotherapy. TA247[28] recommends TCZ, and TA415[29] recommends CTZ as alternatives to TNF-inhibitors in the same circumstances as TA195, that is, after the failure of a TNF-inhibitor in patients with severe active RA, in combination with MTX when RTX is contraindicated or withdrawn and as monotherapy if MTX is contraindicated or withdrawn. In addition, TA247 recommends TCZ in combination with MTX in patients in whom TNF-inhibitors and RTX have not worked.

The summary of the NICE recommended treatment pathway for RA presented in the CS is reproduced in Figure 1.

Figure 1: Treatment pathway presented in the CS modified by the ERG



ABT=abatacept; ADA=adalimumab; CTZ=certolizumab pegol; DMARD=disease-modifying anti-rheumatic drug; ETN=etanercept; GOL=golimumab; IFX=infliximab; MTS=methotrexate; RTX=rituximab; TCZ=tocilizumab.

A key pathway for those who are RTX and MTX tolerant is a sequence of an initial bDMARD+MTX, followed by RTX+MTX and then TCZ+MTX, which typically uses three different classes of intervention. However, for those that cannot receive RTX+MTX, it is possible that a second TNFi would be used. In Figure 3.2 (p43) of the CS the company report evidence that the effectiveness of TNFi in terms of EULAR response diminishes as the number of prior TNFis used increases. Clinical advice provided to the ERG states that this result is not unexpected and that clinicians would try to avoid using a second TNFi where possible.

NICE criteria for continuing treatment

NICE TA375[25] states that for patients to continue treatment with their first bDMARD treatment they must maintain at least a moderate EULAR response. TA195,[27] which for all bDMARDs excluding RTX was updated in TA375[25], states that bDMARD treatment after the failure of a TNFi should be continued only if there is an adequate response (defined as an improvement in the DAS28 score of ≥ 1.2 points) at initiation of treatment and as long as this adequate response is maintained. If the criterion of having

at least a moderate EULAR response at six months has not been met, then treatment should be stopped and the next intervention in the sequence should be initiated.

3 CRITIQUE OF COMPANY'S DEFINITION OF THE DECISION PROBLEM

3.1 Population

Sarilumab (Kevzara®) is licensed in the UK 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 DMARDs. Treatment can be provided with MTX or as a monotherapy if a patient is intolerant to MTX or where treatment with MTX is inappropriate. The target population in the company's decision problem aligns with the populations described in the final scope issued by NICE, although only a subgroup of patients with moderate RA have been evaluated. The company describe the patient populations analysed in the model in Table 5.3 of the CS; the company have assigned alpha-numeric codes for each population, although the ERG did not find these overly helpful and have renamed the populations. The populations are as follows:

- Patients with severe RA who have had an inadequate response to cDMARDs (cDMARD-IR) who can tolerate MTX
- Patients with severe RA who are cDMARD-IR who cannot tolerate MTX
- Patients with severe RA who have are TNFi-IR who can tolerate RTX
- Patients with severe RA who are TNFi-IR who cannot tolerate RTX
- Patients with severe RA who are TNFi-IR who cannot tolerate MTX
- Patients with severe RA who are RTX+MTX-IR
- Patients with moderate RA with DAS28> 4.0 who are cDMARD-IR who can tolerate MTX

Within the categorisation of patients, the company have assumed that severe disease is represented by a DAS28 >5.1. The ERG comments that this is in line with TA375.[25] The company have presented analyses for a subgroup of moderate patients, determined by having a DAS28 score of 4.0, considered by the company of being "*at risk of rapid progression*". The company argue that there is an unmet need in this population, where biologics are not recommended. The ERG notes that although the wording is similar, the definition of this subgroup is unrelated to the "fast progressors" discussed in work by the NICE Decision Support Unit (DSU).[30] The ERG also notes that moderate patients at risk of rapid progression are likely to progress to the severe state, where sequences of bDMARDs are recommended.

3.2 Intervention

Sarilumab (SAR) is a fully human immunoglobulin G1 monoclonal antibody that inhibits interleukin-6 (IL-6) mediating signalling. SAR is administered subcutaneously (SC) every other week (Q2W) and has two doses (200mg and 150mg). The contraindications to SAR listed in the draft Summary of Product Characteristics (SmPC) are hypersensitivity to the active substance or any of the excipients—histidine,

arginine, polysorbate 20 and sucrose. Reduction of dose from 200mg Q2W to 150mg Q2W is recommended for management of neutropenia, thrombocytopenia, and liver enzyme elevations. The efficacy and safety of SAR has not been studied in patients with hepatic impairment or in children aged up to 18 years of age, although paediatric studies are ongoing.

The list price for SAR is [redacted] per pen or syringe, the prices for both the 150mg and 200mg doses being the same. A Patient Access Scheme (PAS) in the form of a simple discount ([redacted]) has been agreed with the Department of Health which reduces the cost per pen or syringe to [redacted]. The cost-effectiveness results presented by the company are based on the PAS price.

3.3 Comparators

The comparators considered in the decision problem are shown in

Table **2**.

Table 2: Comparators to SAR considered in the CS (adapted from Table 5.5 of the CS)

Drug	Dose	Frequency
SAR SC[b]	200mg	Every other week
ABT IV[a]	500mg if <60 kg, 750mg if 60–100 kg, 1,000mg if > 100 kg	Week 0, 2, 4, then every 4 weeks
ABT SC[a]	125mg SC injections	Once per week
GOL SC[a]	50mg	Once per month
ETN SC[a]	25mg	Twice weekly
ETN biosimilar SC[a]	50mg	Every week
ADA SC[a]	40mg	Every other week
RTX IV[c]	2,000mg	Two 1,000mg IV infusions separated by 2 weeks (one course) every 9 months
CTZ SC[a]	400mg induction dose, 200mg maintenance dose	400mg dose at week 0, 2, and 4, followed by maintenance dose every other week
TCZ IV[a]	8mg/kg	Every 4 weeks
TCZ SC[a]	162mg SC	Every week
IFX IV[a]	3mg/kg	Week 0, 2 and 6, then every 8 weeks.
IFX biosimilar IV[a]		

a https://www.medicines.org.uk/emc/ b Draft SmPC c. TA375
ABT= abatacept; ADA= adalimumab; CTZ= certolizumab pegol; ETN: etanercept; GOL= golimumab; IFX= infliximab; IV = intravenous; RA = rheumatoid arthritis; Q2W, once every 2 weeks; RTX= rituximab; SAR= sarilumab; SC = subcutaneous; TCZ= tocilizumab

The comparators in the CS are largely in line with the final scope issued by NICE although biosimilars for ADA and RTX were not considered. MTX alone was not included as a comparator in the cDMARD-IR with severe RA population or the TNFi-IR population with severe RA, presumably because bDMARDs are recommended by NICE in this population. BSC was used as a comparator in the cDMARD-IR with moderate RA population and included at the end of every sequence in all populations but was omitted from

Table **2**.

3.4 Outcomes

The outcomes contained in the final scope issued were all addressed in the CS with the exception of extra-articular manifestations of disease where no data related to SAR were identified.

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

This chapter presents a review of the clinical effectiveness evidence provided in the CS for SAR for treating RA. The clinical evidence provided in the CS comprised a systematic review of SAR and comparators for treating RA, used to provide effectiveness and safety data for SAR, and to populate a network meta-analysis (NMA).

4.1.1 Searches

The search strategies are reproduced in the Appendices (Section 5) of the CS. The company's searches were well-designed and are appropriately structured to include population, interventions of interest (SAR and comparator drugs) and study types (using a recognised RCT filter). An appropriate range of databases was searched (Medline; EMBASE and the Cochrane Library) in accordance with (NICE) guidelines. The ERG queried whether any additional steps had been taken to capture the latest evidence and the company confirmed that Medline In Process had been included in the search (see clarification response[31] – Literature searching, Q1). Initial searches covered the period from inception to March 2015 whilst update searches undertaken in December 2016 covered the period since March 2015. The ERG is broadly confident that all relevant published studies have been identified by the search process.

4.1.2 Inclusion criteria

The CS review (

Table 3) was carried out in two stages, based on initial and update searches. The update differed from the initial search in being restricted to "investigational drugs to those likely to be relevant future comparators for" SAR (page 54 of the CS). In practice, these were baricitinib and sirukumab (CS Table 4.2). The update was also limited to studies of 12 weeks or more duration (see clarification response[31] – question A5). These restrictions were appropriate given the decision problem. Inclusion/exclusion criteria are shown in the CS as Table 4.1 for the initial search, and CS Table 4.2 for the update search. The intervention (technology of interest) was SAR monotherapy or in combination with cDMARDs. Other interventions / comparators of cDMARDs and bDMARDs were included to populate the NMA. Selection criteria were in accordance with the decision problem in the final NICE scope. Inclusion and exclusion criteria are shown in

Table 3 of the ERG report.

Table 3: CS Review inclusion/exclusion criteria (Reproduced from CS Table 4.4)

Criteria		Inclusion	Exclusion
STUDY DESIGN	Abstract selection	RCTs above Phase I	• Case series/reports, letters to editor, commentary, editorials • Observational and registry studies • Non-English publications • Preclinical/Pharmacokinetic/ Pharmacogenomic studies • Animal or in vitro studies • Literature review/meta-analysis[a] • Phase I study • Prognostic study • Retrospective study • Open-label extension and extended access studies • *Post hoc* studies and pooled analyses[a] • Any other type of non-randomised study
	Full-text selection	RCT above Phase I	
POPULATION	Abstract and full-text selection	• Adult patients (≥18 years) with moderately to severely active RA who have had inadequate response to one or more cDMARDs • Adult patients (≥18 years) with moderately to severely active RA who have had inadequate response to one or more bDMARDS (TNFi or another MoA) • Adult patients (≥18 years) intolerant to MTX or for whom continued MTX is inappropriate	• Patients without RA • Patients with diseases other than RA • Patients with rheumatic diseases other than RA • Patients not being treated with an intervention of interest • Patients naïve for cDMARD
TREATMENT / INTERVENTION	Abstract and full-text selection	The following interventions are of interest at any dosage or administration type: • Sarilumab (REGN88, sarilumab153191) • Etanercept (Enbrel) • Tocilizumab (RoActemra/Actemra) • Adalimumab (Humira) • Abatacept (Orencia) • Infliximab (Remicade) • Rituximab	Other treatments

Criteria		Inclusion	Exclusion
		(MabThera/Rituxan) • Tofacitinib (Xeljanz) • Anakinra (Kineret) • Certolizumab (Cimzia) • Golimumab (Simponi) • Biosimilar DMARDs (CS Appendix 5.3) • Investigational drugs (CS Appendix 5.4)	
COMPARATOR	Abstract and full-text selection)	Placebo or any of the above listed treatments as monotherapy or in combination with a cDMARD(s) (i.e. MTX, leflunomide, hydroxychloroquine, minocycline, sulfasalazine, azathioprine, sodium aurothiomalate, and auranofin) or cDMARD as monotherapy or in combination with other cDMARD(s)	Other treatments not in the above listed treatments
OUTCOMES	Abstract and full-text selection	No selection was made on outcomes. *After the screening phase top-line data extraction was performed to detect which outcomes were selected for data extraction*	None[b]
Timepoint		No start limit – 31st March 2015[c]	
Language		English language	Non-English language

[a]Systematic literature reviews and meta-analyses (2010 – present) will be noted in a separate "study design" exclusion column; using this list of reviews, we will select the most recent and relevant systematic literature reviews/meta-analyses and check the reference lists of the reviews for relevant studies. For *post hoc* and pooled analyses, the reference list was also checked for relevant studies.

[b]Studies were not excluded based on the outcomes at the screening phase. Outcomes were selected during the top-line data extraction phase.

PICOS-T = population, intervention, comparison, outcomes, study, and time horizon.

bDMARD= biological disease-modifying anti-rheumatic drug; cDMARD=conventional disease-modifying anti-rheumatic drug; MoA=mode of action; MTX=methotrexate; RA=rheumatoid arthritis; RCT=randomised controlled trial

Note: These exclusion criteria, along with the PICOS-T criteria noted in Table 4.1 were applied during the abstract and full-text screening process to select appropriate studies.

[c]Update searches up to 6th December 2016

The population was adults with moderate to severe, active rheumatoid arthritis, whose disease has not responded adequately to, or who are intolerant of cDMARDs or bDMARDs. The intervention was SAR as monotherapy or in combination with cDMARDs.

Comparators included were: etanercept (Enbrel); tocilizumab (RoActemra/Actemra); adalimumab

(Humira); abatacept (Orencia); infliximab (Remicade); rituximab (MabThera/Rituxan); tofacitinib (Xeljanz); anakinra (Kineret); certolizumab (Cimzia); golimumab (Simponi); biosimilars. Investigational drugs were sought in the initial search, this was restricted to baricitinib and sirukumab in the update search. Investigational drugs were not mentioned in the final NICE scope. All comparators mentioned in the final NICE scope were included in the CS inclusion criteria.

Study designs for effectiveness data were restricted to RCTs and their long-term extension studies. This was appropriate given the availability of RCTs meeting the inclusion criteria.

The study selection process described in the CS (Section 4.1.3 of the CS) describes study selection by two reviewers, as is good practice in systematic reviews. A third and fourth reviewer were employed to resolve discrepancies.

4.1.3 Critique of data extraction

Data were extracted by two reviewers (CS Section 4.1.3) as is good practice. Data extracted for the SAR trials by the CS, and reported below, were checked by the ERG against published trial papers where available (MOBILITY-A Huizinga 2014,[32] MOBILITY-B Genovese 2015,[33] TARGET Fleischmann 2017,[34] MONARCH Burmester 2016[35]), and the clinical study report (CSR) for ASCERTAIN.[36]

4.1.4 Quality assessment

The CS Section 4.1.3 states that a quality assessment was performed using the methods recommended in the current NICE specification. Quality items assessed were taken from the Centre for Reviews and Dissemination (CRD) guidelines for undertaking reviews in health care.[37] These are standard and appropriate criteria for assessing the risk of bias in RCTs.

Table 4 of the ERG report shows quality assessment for the SAR trials (reproduced from Table 4.13 of the CS). The ERG checked the quality assessment against the publications of the trials where available, and the CSR for ASCERTAIN, and agreed with the assessment in the CS.

Table 4: Quality assessment of included SAR trials (Reproduced from CS Table 4.13)

Trial name	MOBILITY-A [32]	MOBILITY-B [33]	TARGET [34]	ASCERTAIN [36]	MONARCH [35]
Was randomisation carried out appropriately?	YES	YES	YES	YES	YES
Was the concealment of treatment allocation adequate?	YES	YES	YES	YES	YES
Were the groups similar at the outset of the study in terms of prognostic factors?	YES	YES	YES	YES	YES
Were the care providers, participants and outcome assessors blind to treatment allocation?	YES	YES	YES	YES	YES
Were there any unexpected imbalances in drop-outs between groups?	NO	NO	NO	NO	NO
Is there any evidence to suggest that the authors measured more outcomes than they reported?	NO**	NO**	NO**	Not yet published***	NO***
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	YES	YES	YES (mITT)	YES (mITT)	YES

Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination)

**from CS Appendix 6, some results not yet published, but in the process of being published

***from CS Appendix 6, some results not yet analysed

The five included SAR RCTs were generally at low risk of bias, in the view of both the company and the ERG. All five RCTs used central allocation generated by interactive voice response system (MOBILITY-A, MOBILITY-B, TARGET, MONARCH, ASCERTAIN).

In all five RCTs, randomisation was stratified by region, and there was also stratification by prior bDMARD use in MOBILITY-A and MOBILITY-B, number of prior bDMARDs in TARGET, and screening value of absolute neutrophil count in ASCERTAIN. All five RCTs were blinded.

Three of the RCTs planned an intent-to-treat (ITT) analysis with all randomised patients (MOBILITY-A, MOBILITY-B, MONARCH). The other two RCTs (TARGET and ASCERTAIN) planned a modified ITT, analysing all randomised patients who received at least one dose of study drug,[34] [36] however in practice all randomised patients were treated and included in the analysis. All five included RCTs used a non-responder imputation for categorical data, in which patients who discontinued, received rescue therapy or otherwise had missing data were assumed to be failures.

Quality assessments of the trials in the NMA are presented in Appendix 8.7 of the CS. The same quality assessment items were used as above, as is appropriate for RCTs. There was some variation in quality, but the majority were blinded and reported ITT analyses.

4.2 Critique of trials of the technology of interest, their analysis and interpretation

SAR trials included in the CS

Five RCTs and one long-term extension study of SAR were included in the CS (Table 5). Three RCTs had populations of cDMARD experienced RA patients (MOBILITY-A, MOBILITY-B, MONARCH), and two RCTs had TNFi experienced RA patients (TARGET, ASCERTAIN).

Table 5: Included SAR trials (Reproduced from CS Table 4.3)

Study	Study population	Intervention	Comparator	Reference
MOBILITY A NCT01061736	MTX-IR	SAR + MTX	PBO + MTX	*Huizinga 2014*[32] *Sanofi Genzyme Data on File*[38]
MOBILITY B NCT01061736	MTX-IR	SAR + MTX	PBO + MTX	*Genovese 2015*[33] *Sanofi Genzyme Data on File*[39]
TARGET NCT01709578	TNFi-IR/ intolerant	SAR + cDMARD	PBO + cDMARD	*Fleischmann 2017*[34] *Sanofi Genzyme Data on File*[40]
MONARCH NCT02332590	MTX-IR/ intolerant	SAR	ADA	*Burmester 2016*[35] *Sanofi Genzyme Data on File*[41]
ASCERTAIN (safety study) NCT01768572	TNFi-IR/ intolerant	SAR + cDMARD	TCZ + cDMARD	*Sanofi Genzyme Data on File* [36]
EXTEND (Long-term extension safety study) NCT01146652	cDMARD/TNFi-IR/ intolerant	SAR + cDMARD, SAR monotherapy	NA, Extension study	*Sanofi Genzyme Data on File*[42]

ADA=adalimumab; cDMARD=conventional disease-modifying anti-rheumatic drugs; cDMARD = conventional disease-modifying anti-rheumatic drug; IR=inadequate response; MTX=methotrexate; NA=not applicable; PBO=placebo; SAR= sarilumab; TCZ= tocilizumab; TNFi =tumour necrosis factor inhibitor.

SAR trials excluded from the CS

Two trials of SAR were terminated early: NCT01764997 with comparators ADA and ETN, and NCT01217814 with comparator GOL. The company's clarification response[31] (question A2) states that these trials were terminated due to study delays. The company's clarification response to question A2 states that for NCT01217814 no effectiveness analyses were conducted, and that safety analyses were conducted but no conclusions were drawn due to the small sample size (16 patients randomised).

Two studies were excluded from the CS for being uncontrolled, ONE **(**NCT02121210) and EASY (NCT02057250). However, the company's clarification response[31] (question A3) states that safety data from these studies were included in the pooled safety analysis of SAR for the EMA license application.

Two studies were excluded from the CS for having exclusively Japanese populations. KAKEHASI (NCT02293902) was conducted in an MTX-IR population, and compared SAR+MTX with placebo + MTX. HARUKA (NCT02373202) compared SAR monotherapy with SAR +cDMARDs (non-MTX) in a population of MTX-IR, MTX intolerant, or non-MTX cDMARD experienced. The company's clarification response[31] states that this is due to the trials not being generalisable to the UK population, and suggests that

"[redacted]".

SAR trials included in the CS – trial characteristics

Trial characteristics for the studies included in the CS are shown in Table 6.

Table 6: Included SAR trials (Adapted from CS Tables 1.3, 4.3 and 4.7)

Study	Study population	Intervention	Comparator	Follow-up (weeks)	Primary endpoint	Used in NMA?
MOBILITY A NCT01061736	N=306 MTX-IR [24.5% prior bDMARDs]	SAR + MTX SAR doses: 100mg QW, 150mg QW, 100mg Q2W, 150mg Q2W, 200mg Q2W	PBO + MTX	12	ACR20 Week 12	No (12 week study)
MOBILITY B NCT01061736	N=1197 MTX-IR [27.9% prior bDMARDs]	SAR + MTX SAR doses: 150mg Q2W, 200mg Q2W	PBO + MTX	52	ACR20 at Week 24 Change in HAQ-DI from baseline to Week 16 Change in mTSS from baseline to Week 52	cDMARD-IR combination therapy
MONARCH NCT02332590	N=369 MTX-IR/ intolerant	SAR monotherapy SAR dose 200mg Q2W	ADA monotherapy ADA dose 40mg Q2W	24	Change in DAS28-ESR from baseline to Week 24	cDMARD-IR monotherapy
TARGET NCT01709578	N=546 TNFi-IR/ intolerant	SAR + cDMARD SAR doses: 150mg Q2W, 200mg Q2W	PBO + cDMARD	24	ACR20 response at Week 24 Change in HAQ-DI from baseline to Week 12	TNFi-IR
ASCERTAIN (safety study) NCT01768572	N=202 TNFi-IR/ intolerant	SAR + cDMARD SAR doses: 150mg Q2W, 200mg Q2W	TCZ + cDMARD TCZ dose 4-8mg/kg	24	Safety	TNFi-IR
EXTEND (Long-term extension safety study) NCT01146652	N=2023 cDMARD/TNFi-IR/ intolerant	SAR + cDMARD, SAR monotherapy	NA, Extension study	264 (at least)	Safety	No (extension study)

ADA: adalimumab; cDMARD: conventional disease-modifying antirheumatic drug; IR: inadequate response; MTX: methotrexate; PBO: placebo; SAR: sarilumab; TCZ: tocilizumab; TNFi: tumour necrosis factor inhibitor

All trials recruited adult populations. ASCERTAIN and EXTEND assessed safety, whereas the other included trials assessed effectiveness and safety. EXTEND was an open-label extension study, MOBILITY A was a Phase II RCT, and the other trials were Phase III RCTs. The RCTs were all international, multi-centre studies including centres in the US, South America and Europe. Two of the RCTs had centres in the UK (1 centre for Monarch and six centres for ASCERTAIN, see CS Section 4.5) however only ASCERTAIN recruited patients from the UK (n=14) (see clarification response[31] – question A4).

EXTEND was an open-label extension study of SAR (either monotherapy or in combination with cDMARDs). Patients in the EXTEND study were recruited from MOBILITY A and B ([redacted]), TARGET ([redacted]), ASCERTAIN ([redacted]), ONE ([redacted]) and [redacted] ([redacted]).

Of the five RCTs, three had a PBO comparator (MOBILITY-A, MOBILITY-B, TARGET). The monotherapy trial, MONARCH, compared SAR with ADA at its licensed UK dose. The ASCERTAIN trial compared SAR with TCZ 4-8mg/kg Q4W. The UK recommended dose of IV TCZ for adults is "8mg/kg every 4 weeks (max. per dose 800mg), for dose adjustments in patients with liver enzyme abnormalities, or low absolute neutrophil or platelet count, consult product literature."[43] The primary endpoint of ASCERTAIN was safety rather than effectiveness. The company's clarification response[31] (question A6) states that comparative effectiveness data were not provided as ASCERTAIN was not powered for effectiveness endpoints.

Baseline characteristics of patients included in the RCTs are shown in Table 7. Across trials, patients had a mean DAS of >5.1, had a mean age of 52.2, and were mostly female and Caucasian. There were no imbalances within trials between treatment groups at baseline.

Table 7: Baseline characteristics of included SAR trials (reproduced from CS Table 4.12)

	MOBILITY A N=306* [32;38]	**MOBILITY B N=398**[33;39]	**TARGET N=546**[34;40]	**ASCERTAIN** [redacted][36]	**MONARCH N=369**[35;41]
Age, mean (SD)	52.2 (12.5)	50.8 (11.7)	52.9 (12.4)	[redacted]	52.2 (12.3)
Males, %	20.6	18.3	18.1	[redacted]	16.8
Race, %					
Caucasian/ White	93.8	86.4	71.1	[redacted]	90.8
Black	2.6	2.4	3.7	[redacted]	1.1
Asian/ Oriental	2.0	8.0	0.9	[redacted]	3.0
Other	1.6	3.2	24.4	[redacted]	5.1

	MOBILITY A N=306* [32;38]	MOBILITY B N=398[33;39]	TARGET N=546[34;40]	ASCERTAIN [redacted][36]	MONARCH N=369[35;41]
Weight kg, mean (SD)	74.86 (15.27)	74.39 (18.52)	78.22 (21.52)	[redacted]	72.05 (17.15)
BMI kg/m², mean (SD)	28.28 (5.64)	28.26 (6.34)	29.53 (7.17)	[redacted]	27.18 (6.05)
Duration of RA in years, mean (SD)	7.81 (8.08)	9.03 (7.85)	12.09 (9.40)	[redacted]	7.33 (7.99)
RA functional class, %					
I	6.2	11.7	9.5	[redacted]	17.9
II	70.3	67.2	57.7	[redacted]	65.0
III	23.5	21.2	32.8	[redacted]	17.1
IV	0	0	0	[redacted]	0
RF +ve, %	79.7	84.9	75.5	[redacted]	65.8
Anti-CCP +ve, %	82.0	86.9	78.1	[redacted]	76.0
TJC (0–68), mean (SD)	27.39 (14.93)	26.85 (14.07)	28.88 (15.22)	[redacted]	27.32 (13.41)
SJC (0–66), mean (SD)	17.38 (9.73)	16.82 (9.49)	19.93 (11.49)	[redacted]	18.04 (10.50)
CRP inmg/L, mean (SD)	2.78 (2.96)	22.23 (23.69)	26.82 (25.89)	[redacted]	20.71 (26.78)
HAQ-DI (0–3), mean (SD)	1.59 (0.62)	1.64 (0.64)	1.78 (0.63)	[redacted]	1.64 (0.60)
DAS28-CRP, mean (SD)	6.11 (0.84)	5.96 (0.90)	6.20 (0.91)	[redacted]	6.01 (0.89)
Prior cDMARD use, %	100	100	100	[redacted]	100
Number of cDMARDs, %					
0	0	0	0	[redacted]	0
1	92.8	NR	53.5	[redacted]	46.3
2	4.9	NR	27.5	[redacted]	31.2
≥3	2.3	NR	19.0	[redacted]	22.5
Prior bDMARD use, %	24.5	27.9	100	[redacted]	0
Prior TNFi use, %	NR	NR	100%	[redacted]	0
Number of TNFi, %					

	MOBILITY A N=306* [32;38]	MOBILITY B N=398[33;39]	TARGET N=546[34;40]	ASCERTAIN [redacted][36]	MONARCH N=369[35;41]
1	NR	NR	76.8	[redacted]	0
≥1	NR	NR	23.2	[redacted]	0

*includes groups with unlicensed doses of SAR

RF rheumatoid factor, CCP anti-cyclic citrullinated peptide, CRP high-sensitivity C reactive protein

Discontinuation rates are shown in Table 8 and Table 9. At 24 weeks discontinuation rates for SAR ranged from 10.3% to [redacted]. In MONARCH, there was a discontinuation rate of 15.1% for the licensed dose of ADA, and 10.3% for SAR 200mg Q2W.

[redacted]

Table 8: Discontinuation during cDMARD-IR trials[38, 39, 41 32 33 35]

	MOBILITY-A 12weeks			MOBILITY-B 52 weeks			MONARCH 24 weeks	
	PBO + MTX (n=52)	SAR 150mg Q2W + MTX (n=51)	SAR 200mg Q2W + MTX (n=52)	Placebo + MTX (n=428)	SAR 150mg Q2W + MTX (n=430)	SAR 200mg Q2W + MTX (n=427)	ADA 40mg Q2W (n=185)	SAR 200mg Q2W (n=184)
Discontinuation during double blind period, n (%)	3 (5.8)	3 (5.9)	6 (11.5)	62 (14.5)	78 (18.1)	88 (20.6)	28 (15.1)	19 (10.3)
Any AE leading to treatment discontinuation, n (%)	1 (1.9)	2 (3.8)	4 (7.8)	20 (4.7)	54 (12.5)	59 (13.9)	15 (8.1)	11 (6.0)

AE: adverse events; PBO: placebo: MTX: methotrexate; SAR: salirumab; ADA: adalimumab; Q2W: every other week

Table 9: Discontinuation during TNFi-IR trials at week 24 [34 36 40]

	TARGET			ASCERTAIN		
	PBO + cDMARD (n=181)	SAR 150mg Q2W + cDMARD (n=181)	SAR 200mg Q2W + cDMARD (n=181)	TCZ IV 4–8mg/kg Q4W + cDMARD (n=102)	SAR 150mg Q2W + cDMARD (n=49)	SAR 200mg Q2W + cDMARD (n=51)
Discontinuation, n (%)	17 (9.4)	31 (17.1)	25 (13.6)	[redacted]	[redacted]	[redacted]
Any AE leading to treatment discontinuation, n (%)	8 (4.4)*	14 (7.7)	17 (9.2)	[redacted]	[redacted]	[redacted]

*additionally 1 PBO and 4 SAR 150mg, abnormal laboratory values at baseline [34]

AE: adverse events; PBO: placebo: SAR: salirumab; TCZ: tocilizumab; IV: intravenous; Q2W: every 2 weeks; Q4W: every 4 weeks; cDMARD: conventional disease-modifying antirheumatic drug

Effectiveness results from the included SAR RCTs

ACR response data

The five included SAR RCTs reported ACR data. ACR20 was the primary outcome for MOBILITY-A, MOBILITY-B and TARGET.

ACR response data from the cDMARD-IR trials

ACR response data for the cDMARD-IR RCTs are shown in Table 10 to Table 12. At 12 weeks, MOBILITY-A showed a statistically significant advantage for both licensed doses of SAR+MTX over PBO+MTX in ACR20 and ACR50 ($p<0.05$). A significantly higher proportion of patients in the SAR 200mg Q2W group, than the PBO group, achieved ACR70. At 24 weeks, MOBILITY-B showed a significant advantage for SAR 200mg Q2W+MTX and SAR 150mg Q2W+MTX over PBO for ACR20 (66.4%, 58.0% and 33.4%), respectively ($p<0.0001$). Both licensed doses also showed a significant advantage over PBO in AC50 and ACR70 at 24 weeks, and ACR20 at 52 weeks ($p<0.0001$). MONARCH reported a significantly ($p<0.01$) higher proportion of patients in the SAR 200mg Q2W monotherapy group, than the ADA 40mg Q2W monotherapy group, achieved ACR20 (71.7% versus 58.4%).

Table 10: ACR response rates in MOBILITY-A at 12 weeks (adapted from CS Section 4.7.1[32])

	PBO +MTX (n=52)	**SAR 150mg Q2W +MTX (n=51)**	***p*-value**	**SAR 200mg Q2W +MTX (n=52)**	***p*-value**
ACR20 response	46%	67%	0.0363	65%	0.0426
ACR50 response	15%	35%	0.0163	40%	0.0038
ACR70 response	2%	12%	0.0574	17%	0.0078

Table 11: ACR response rates in MOBILITY-B data at week 24 (adapted from Table 4.16 of the CS)

	PBO + MTX (N=398)	**SAR 150mg Q2W + MTX (N=400)**	***p*-value**	**SAR 200mg Q2W + MTX (N=399)**	***p*-value**
ACR20 response, n (%)	133 (33.4)	232 (58.0)	< 0.0001	265 (66.4)	< 0.0001
ACR50 response, n (%)	66 (16.6)	148 (37.0)	< 0.0001	182 (45.6)	<0.0001
ACR70 response, n (%)	29 (7.3)	79 (19.8)	< 0.0001	99 (24.8)	<0.0001
ACR20 response at Week 52, n (%)	126 (31.7)	214 (53.5)	<0.0001	234 (58.6)	<0.0001

Table 12: ACR response rates in MONARCH at Week 24 (adapted from CS Table 4.22)

	ADA 40mg Q2W (N=185)	SAR 200mg Q2W (N=184)	*p*-value
ACR20 response, n (%)	108 (58.4)	132 (71.7)	0.0074
ACR50 response, n (%)	55 (29.7)	84 (45.7)	0.0017
ACR70 response, n (%)	22 (11.9)	43 (23.4)	0.0036

ACR response data from the TNFi-IR trials

ACR response data from the TARGET and ASCERTAIN TNFi-IR trials are shown in Table 13 and Table 14, respectively. TARGET reported a significant (p<0.0001) advantage for SAR 200mg Q2W+ cDMARD and SAR 150mg Q2W+ cDMARD over PBO+ cDMARD for ACR20 (60.9%, 55.8% and 33.7% respectively) at 24 weeks. At 24 weeks, TARGET also reported a significant advantage for the SAR+ cDMARD doses over PBO+ cDMARD in ACR50 and ACR70 (p≤0.0002). [redacted]

Table 13: ACR response rates in TARGET at week 24 (adapted from CS Table 4.19)

	PBO + cDMARD (N=181)	SAR 150mg Q2W + cDMARD (N=181)	*p*-value	SAR 200mg Q2W + cDMARD (N=184)	*p*-value
ACR20 response n (%)	61 (33.7)	101 (55.8)	<0.0001	112 (60.9)	<0.0001
ACR50 response n (%)	33 (18.2)	67 (37.0)	<0.0001	75 (40.8)	<0.0001
ACR70 response n (%)	13 (7.2)	36 (19.9)	0.0002	30 (16.3)	0.0056

Table 14: ACR response rates in ASCERTAIN at week 24 (adapted from CS Table 4.2)

	TCZ Q4W + cDMARD (N=102)	SAR 150mg Q2W + cDMARD (N=49)	SAR 200mg Q2W + cDMARD (N=51)
ACR20 response %	[redacted]	[redacted]	[redacted]
ACR50 response %	[redacted]	[redacted]	[redacted]

ACR70 response %	[redacted]	[redacted]	[redacted]

EULAR response data from the cDMARD-IR trials

[redacted]

Table 15: EULAR response rates in MOBILITY-A at 12 weeks[38]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

*[redacted]

Table 16: EULAR response rates in MOBILITY-B at week 24 (adapted from CS Appendix Tables 8.23 and 8.24)

	PBO + MTX (N=398)	**SAR 150mg Q2W + MTX (N=400)**	**SAR 200mg Q2W + MTX (N=399)**
EULAR good response (%)	[redacted]	[redacted]	[redacted]
EULAR moderate to good response (%)	[redacted]	[redacted]	[redacted]

Table 17: EULAR response rates in MONARCH at week 24 (adapted from CS Appendix Table 8.33)

	ADA 40mg Q2W (N=185)	**SAR 200mg Q2W (N=184)**
EULAR good (%)	[redacted]	[redacted]
EULAR moderate to good response (%)	[redacted]	[redacted]

EULAR response data from the from the TNFi-IR trials

[redacted]

[redacted]

Table 18: EULAR response rates in TARGET at week 24 (adapted from CS Table 8.43 and 8.44)

	Placebo + cDMARD (N=181)	SAR 150mg Q2W + cDMARD (N=181)	SAR 200mg Q2W + cDMARD (N=184)
EULAR good response (%)	[redacted]	[redacted]	[redacted]
EULAR moderate to good response (%)	[redacted]	[redacted]	[redacted]

HAQ-DI, DAS28 and mTSS effectiveness outcomes

HAQ-DI, DAS28 and mTSS outcomes are shown in Tables 19-21 for the cDMARD-IR trials, and in Table 22 and Table 23 for the TNFi-IR trials. The MOBILITY-A, MOBILITY-B, MONARCH and TARGET trials reported significantly favourable results for licensed doses of SAR over their comparators for improvement in HAQ-DI ($p \leq 0.0037$). SAR had a significant advantage over its comparator for DAS28-CRP in the MOBILITY-B and TARGET trials ($p < 0.0001$), and for DAS28-ESR in the MONARCH trial ($p < 0.0001$). MOBILITY-B measured radiographic progression by mTSS, and reported a significantly lower deterioration from baseline for SAR over comparator ($p \leq 0.01$). Comparative statistics were not available for ASCERTAIN.

Table 19: Efficacy results from MOBILITY-A (adapted from CS Table 4.14)

	PBO (n=52) LS Mean (SE)	SAR 150mg Q2W (n=51) LS Mean (SE)	SAR200mg Q2W (n=52) LS Mean (SE)
HAQ-DI	−0.26 (0.07)	−0.62 (0.07)	−0.57 (0.07)
***p*-value vs. placebo**		0.0003	0.0019
CRP (mg/L)	−3.1 (2.8)	−21.9 (2.8)	−21.9 (2.8)
***p*-value vs. placebo**		<0.0001	<0.0001

Table 20: Efficacy results from MOBILITY-B (adapted from CS Table 4.16)

	Placebo + MTX (N=398)	SAR 150mg Q2W + MTX (N=400)	*p*-value	SAR 200mg Q2W + MTX (N=399)	*p*-value
HAQ-DI	−0.33 ± 0.03	−0.53 ± 0.03	<0.0001	−0.55 ± 0.03	<0.0001
CRP,mg/dL	−0.0 ± 0.12	−1.3 ± 0.12	<0.0001	−1.7 ± 0.12	<0.0001
Major clinical response (ACR70 response maintained for ≥24 weeks), n (%)[a]	12 (3.0)	51 (12.8)	<0.0001	59 (14.8)	<0.0001
DAS28-CRP, LS mean change from baseline to Week 24 (SE)	−1.17(0.080)	−2.45(0.076)	< 0.0001	−2.82(0.075)	<0.0001
DAS28-CRP response at Week 24, n (%)					
Score <2.6[b]	40 (10.1)	111 (27.8)	<0.0001	136 (34.1)	<0.0001
Score ≤3.2	67(16.8)	159 (39.8)	<0.0001	196 (49.1)	<0.0001
Physical function (HAQ-DI)					
HAQ-DI, adjusted mean change from baseline at Week 16, using MMRM[a]	−0.29 ± 0.03	−0.53 ± 0.03	<0.0001	−0.55 ± 0.03	<0.0001
HAQ-DI response (MCID ≥0.3), n (%)					
At Week 16	169 (42.5)	215 (53.8)	<0.01	229 (57.4)	<0.0001
At Week 24	133 (33.4)	204 (51.0)	<0.0001	205 (51.4)	<0.0001
At Week 52	104 (26.1)	188 (47.0)	<0.0001	190 (47.6)	<0.0001
Radiographic progression (mTSS)					
Mean change from baseline in mTSS at week 52, using rank ANCOVA[b]	2.78 ± 7.73	0.90 ± 4.66	<0.0001	0.25 ± 4.61	<0.0001
No radiographic progression, n (%)					
At Week 24	158 (39.7)	185 (46.3)	<0.0001	226 (56.6)	<0.0001
At Week 52[a]	154 (38.7)	191 (47.8)	<0.01	222 (55.6)	<0.0001

Table 21: Efficacy results from MONARCH at week 24 (adapted from CS Table 4.22)

	ADA 40mg Q2W (N=185)	SAR 200mg Q2W (N=184)	*p*-value
Disease activity			
DAS28-ESR, mean (SD)	4.5 (1.4)	3.5 (1.4)	
DAS28-ESR, LSM change from baseline (SE)	−2.20 (0.106)	−3.28 (0.105)	<0.0001
DAS28-ESR <2.6 (remission), n (%)	13 (7.0)	49 (26.6)	<0.0001
Physical function and PROs			
HAQ-DI, mean (SD)	1.2 (0.7)	1.0 (0.7)	
HAQ-DI, LSM change from baseline (SE)	−0.43 (0.05)	−0.61 (0.05)	0.0037

ACR20/50/70=American College of Rheumatology 20%/50%/70% improvement; DAS28-ESR=28-joint disease activity score-erythrocyte sedimentation rate; EQ-5D= EuroQol five dimensions' questionnaire; FACIT=Functional Assessment of Chronic Illness Therapy; HAQ-DI=Health Assessment Questionnaire Disability Index; LSM=least square mean; Q2W=every 2 weeks; SF-36=Medical Outcomes Short Form 36 Health Survey.

Table 22: Efficacy results from TARGET (adapted from CS Table 4.19)

	Placebo + cDMARD (N=181)	SAR 150mg Q2W + cDMARD (N=181)	*p*-value	SAR 200mg Q2W + cDMARD (N=184)	*p*-value
Physical function at Week 12					
HAQ-DI, LSM change from baseline (SE)	−0.26 (0.04)	−0.46 (0.04)	<0.001	−0.47 (0.04)	<0.001
Physical function at Week 24					
HAQ-DI, LSM mean change from baseline (SE)	−0.3 (0.05)	−0.5 (0.05)	0.0078	−0.6 (0.05)	0.0004

HAQ-DI change from baseline >3.0, n (%)	57 (31.5)	78 (43.1)	<0.05	87 (47.3)	<0.01
DAS28-CRP, LS mean change from baseline (SE)	−1.38 (0.119)	−2.35 (0.111)	<0.0001	−2.82 (0.108)	<0.0001
Disease activity and remission at Week 24					
DAS28-CRP<2.6, n (%)	13 (7.2)	45 (24.9)	<0.0001	53 (28.8)	<0.0001

Table 23: Efficacy results from ASCERTAIN (adapted from CS Table 4.21)

	TCZ Q4W + cDMARD (N=102)	SAR 150mg Q2W + cDMARD (N=49)	SAR 200mg Q2W + cDMARD (N=51)
HAQ-DI, LSM change from baseline (SE)	[redacted]	[redacted]	[redacted]
CRP (mg/dL)	[redacted]	[redacted]	[redacted]
DAS28 remission <2.6, %	[redacted]	[redacted]	[redacted]
DAS28-CRP	[redacted]	[redacted]	[redacted]

HRQoL

Table 24 and
Table 25 show the HRQoL outcomes from cDMARD-IR trials. [redacted] **** **** [redacted]. MONARCH found no significant treatment effect for SF-36 MCS, EQ-5D single index utility or EQ-5D VAS, but reported a significantly (p=0.006) greater improvement in SF-36 PCS in the SAR 200mg Q2W monotherapy group than in the ADA 40mg Q2W monotherapy group.

TARGET reported a significant (p<0.0001) advantage for SAR 200mg Q2W+ cDMARD and SAR 150mg Q2W+ cDMARD over PBO+ cDMARD for SF36-PCS at 12 weeks and 24 weeks, and an advantage (p<0.05) in MCS at 12 weeks. There was no statistically significant treatment effect for SF-36 MCS at week 24[redacted].[40]

Table 24: HRQoL results from MOBILITY-B (adapted from CS Table 4.17)

	Placebo + MTX (N= 398)	SAR 150mg Q2W + MTX (N=400)	*p*-value	SAR 200mg Q2W + MTX (N=399)	*p*-value
Week 24					
SF-36 Physical	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SF-36 Mental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 52					
SF-36 Physical	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SF-36 Mental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

SF-36=Medical Outcomes Short Form 36 Health Survey

Table 25: HRQoL results from MONARCH (adapted from Table 4.22)

	ADA 40mg Q2W (N=185)	SAR 200mg Q2W (N=184)	*p*-value
SF-36 PCS, LSM change from baseline (SE)	6.1 (0.6)	8.7 (0.6)	0.0006
SF-36 MCS, LSM change from baseline (SE)	6.8 (0.8)	7.9 (0.8)	0.3319
EQ-5D single index utility, LSM change from baseline (SE)	0.26 (0.35)	0.32 (0.35)	0.0382

EQ-5D VAS, LSM change from baseline (SE)	19.94 (1.720)	24.22 (1.686)	0.0699

SF-36=Medical Outcomes Short Form 36 Health Survey, EQ-5D= EuroQol five dimensions' questionnaire

Table 26 shows HRQoL from the TNFi-IR trial TARGET.

Table 26: HRQoL results from TARGET (adapted from CS Table 4.20)

LSM change from baseline (SE)	**Week 12**					**Week 24**				
	Placebo + cDMARDs (N =181)	**SAR 150mg Q2W + cDMARDs (N=181)**	***p*-value**	**SAR 200mg Q2W + cDMARDs (N=184)**	***p*-value**	**Placebo + cDMARDs (N =181)**	**SAR 150mg Q2W + cDMARDs (N=181)**	***p*-value**	**SAR 200mg Q2W + cDMARDs (N=184)**	***p*-value**
SF-36 PCS	3.7±0.6	6.9±0.6	<0.0001	6.8±0.6	<0.0001	4.4±0.7	7.7±0.7	<0.001	8.5±0.6	<0.0001
SF-36 MCS	3.5±0.7	5.1±0.8		6.5±0.7	<0.05	4.7±0.9	6.3±0.8		6.8±0.8	

SF-36=Medical Outcomes Short Form 36 Health Survey

Effectiveness data from the EXTEND study

At the time of writing, the EXTEND study was ongoing (see Table 27 and Table 28). The CS provided results of an interim analysis of EXTEND (see CS, Section 4.11).

[redacted]

Table 27: ACR response and DAS28-CRP remission rates from the interim analysis in EXTEND (reproduced from CS Table 4.38)

	ACR20 (%)	ACR50 (%)	ACR70 (%)	DAS28 remission (%)
SAR + cDMARD				
Week 0,	[redacted]	[redacted]	[redacted]	[redacted]
Week 24,	[redacted]	[redacted]	[redacted]	[redacted]
Week 48	[redacted]	[redacted]	[redacted]	[redacted]
Week 96	[redacted]	[redacted]	[redacted]	[redacted]
Week 144	[redacted]	[redacted]	[redacted]	[redacted]
Week 192	[redacted]	[redacted]	[redacted]	[redacted]
Week 216	[redacted]	[redacted]	[redacted]	[redacted]
Week 240	[redacted]	[redacted]	[redacted]	[redacted]
Week 264	[redacted]	[redacted]	[redacted]	[redacted]
SAR monotherapy				
Week 0	[redacted]	[redacted]	[redacted]	[redacted]
Week 24	[redacted]	[redacted]	[redacted]	[redacted]
Week 48	[redacted]	[redacted]	[redacted]	[redacted]

Table 28: Changes from baseline in mTSS from the interim analysis in EXTEND (reproduced from CS Table 4.39)

	2-year analysis SAR + DMARD (n=889)	3-year analysis SAR + DMARD (n=796)
CFB in mTSS, mean (SD)		
Week 0 (52 weeks from baseline)	[redacted]	[redacted]
Week 48 (100 weeks from baseline)	[redacted]	[redacted]

	2-year analysis SAR + DMARD (n=889)	3-year analysis SAR + DMARD (n=796)
Week 96 (148 weeks from baseline)	[redacted]	[redacted]

CFB=change from baseline, mTSS=modified Total Sharp Score

Adverse events

Adverse event rates from the included trials are shown in Table 29 and Table 30. AE rates were higher in SAR than PBO groups. For the cDMARD-IR trials, AE rates in the SAR groups ranged from 53.8% to 78.1%. In the MONARCH trial, ADA and SAR had similar AE rates (63.6% and 64.1% respectively).

[redacted]

Table 29: AEs in cDMARD-IR trials (adapted from CS Tables 4.41, 4.42 and 4.45)[32 33 35 38, 39, 41]

	MOBILITY-A 12weeks			MOBILITY-B 52 weeks			MONARCH 24 weeks	
	PBO + MTX (n=52)	SAR 150mg Q2W + MTX (n=51)	SAR 200mg Q2W + MTX (n=52)	PBO + MTX (n=427)	SAR 150mg Q2W + MTX (n=431)	SAR 200mg Q2W + MTX (n=424)	ADA 40mg Q2W (n=184)	SAR 200mg Q2W (n=184)
Any AE, n (%)	24 (47.1)	28 (53.8)	33 (64.7)	263 (61.6)	321 (74.5)	331 (78.1)	117 (63.6)	118 (64.1)
Any SAE, n (%)	2 (3.9)	0	0	23 (5.4)	38 (8.8)	48 (11.3)	12 (6.5)	9 (4.9)
Any AE leading to treatment discontinuation, n (%)	1 (1.9)	2 (3.8)	4 (7.8)	20 (4.7)	54 (12.5)	59 (13.9)	15 (8.1)	11 (6.0)
Deaths, n	0	0	0	2 (0.5)	2 (0.5)	1 (0.2)	0	1 (0.5)

AE: adverse events; SAE: serious AE; PBO: placebo: MTX: methotrexate; SAR: salirumab; ADA: adalimumab; Q2W: every other week

Table 30: AEs in TNFi-IR trials[34 40 36]

	TARGET 24 weeks			ASCERTAIN 24 weeks		
	PBO + cDMARD (n=181)	SAR 150mg Q2W + cDMARD (n=181)	SAR 200mg Q2W + cDMARD (n=184)	TCZ IV 4–8mg/kg Q4W + cDMARD (n=102)	SAR 150mg Q2W + cDMARD (n=49)	SAR 200mg Q2W + cDMARD (n=51)
Any AE, n (%)	90 (49.7)	119 (65.7)	120 (65.2)	[redacted]	[redacted]	[redacted]
Any SAE, n (%)	6 (3.3)	6 (3.3)	10 (5.4)	[redacted]	[redacted]	[redacted]
Any AE leading to treatment discontinuation, n (%)	8 (4.4)	14 (7.7)	17 (9.2)	[redacted]	[redacted]	[redacted]
Deaths, n (%)	1 (0.6)	0	0	[redacted]	[redacted]	[redacted]

AE: adverse events; SAE: serious AE; PBO: placebo: SAR: salirumab; TCZ: tocilizumab; IV: intravenous; Q2W: every 2 weeks; Q4W: every 4 weeks; cDMARD: conventional disease-modifying antirheumatic drug

The SmPC (published by the EMA after company submission, but draft provided by company in CS Appendix 1.2) provides the tabulated summary of AEs of SAR (Table 31). Data were provided for 2,887 patients receiving SAR in combination with cDMARDs, and 467 patients receiving SAR monotherapy.

AEs for SAR+cDMARDs are shown in Table 32 (from the EPAR) and for SAR monotherapy in

Table 33 (from the EPAR).[1] The most frequent SAEs were infections and laboratory abnormalities (changes in absolute neutrophil count and alanine aminotransferase).[1]

As of the data extraction dates for the EPAR, there were 27 deaths in the SAR treated patients, the most common causes were cardiovascular, infections and malignancies.[1] The most common AEs were infections: the most common of these were nasopharyngitis, bronchitis, upper respiratory tract infections, and urinary tract infections. [1]

Table 31: Summary of AEs in controlled clinical studies (as published in SmPC)

System Organ Class	Frequency	Adverse Reaction
Infections and Infestations	Common	Upper respiratory tract infection
		Urinary tract infection
		Nasopharyngitis
		Oral herpes
Blood and Lymphatic System Disorders	Very common	Neutropenia
	Common	Thrombocytopenia
Metabolism and Nutrition Disorders	Common	Hypercholesterolemia
		Hypertriglyceridemia
Hepatobiliary Disorders	Common	Transaminases increased
General Disorders and Administration Site Conditions	Common	Injection site erythema
		Injection site pruritus

Very common: ≥ 1/10; Common:≥ 1/100 to < 1/10

Table 32: Percentages of patients with AEs on SAR+cDMARDs (≥2% in at least one treatment group) (adapted from the EPAR)[1]

Primary System Organ Class **Preferred Term**	**SAR+DMARD** **(N=2887)** **n (%)**
Any class	2418 (83.8%)
Infections and infestations	1428 (49.5%)
Upper respiratory tract infection	325 (11.3%)
Urinary tract infection	252 (8.7%)
Nasopharyngitis	237 (8.2%)
Bronchitis	196 (6.8%)
Sinusitis	110 (3.8%)
Influenza	107 (3.7%)
Pharyngitis	104 (3.6%)
Cellulitis	85 (2.9%)
Pneumonia	80 (2.8%)
Gastroenteritis	76 (2.6%)
Blood and lymphatic system disorders	670 (23.2%)
Neutropenia	507 (17.6%)
Leukopenia	111 (3.8%)
Thrombocytopenia	80 (2.8%)
Metabolism and nutrition disorders	338 (11.7%)
Hypertriglyceridaemia	97 (3.4%)
Hypercholesterolaemia	79 (2.7%)
Dyslipidaemia	65 (2.3%)
Nervous system disorders	311 (10.8%)
Headache	115 (4.0%)
Vascular disorders	279 (9.7%)
Hypertension	204 (7.1%)
Gastrointestinal disorders	553 (19.2%)
Diarrhoea	135 (4.7%)
Nausea	83 (2.9%)
Musculoskeletal and connective tissue disorders	599 (20.7%)
Rheumatoid arthritis	175 (6.1%)

Back pain	116 (4.0%)
Arthralgia	68 (2.4%)
Osteoarthritis	66 (2.3%)
General disorders and administration site conditions	474 (16.4%)
Injection site erythema	214 (7.4%)
Injection site pruritus	105 (3.6%)
Investigations	571 (19.8%)
Alanine aminotransferase increased	289 (10.0%)
Transaminases increased	75 (2.6%)
Aspartate aminotransferase increased	53 (1.8%)
Injury, poisoning and procedural complications	644 (22.3%)
Accidental overdose	316 (10.9%)
Fall	98 (3.4%)

Table 33: Percentages of patients with AEs on SAR monotherapy (≥2% in at least one treatment group) (adapted from EPAR)[1]

Primary System Organ Class **Preferred Term**	**SAR monotherapy** **(N=467)** **N (%)**
Any class	285 (61.0%)
Infections and infestations	135 (28.9%)
Nasopharyngitis	28 (6.0%)
Bronchitis	16 (3.4%)
Upper respiratory tract infection	16 (3.4%)
Urinary tract infection	15 (3.2%)
Blood and lymphatic system disorders	82 (17.6%)
Neutropenia	73 (15.6%)
Nervous system disorders	32 (6.9%)
Headache	15 (3.2%)
Vascular disorders	18 (3.9%)

Hypertension	11 (2.4%)
Musculoskeletal and connective tissue disorders	51 (10.9%)
Rheumatoid arthritis	11 (2.4%)
General disorders and administration site conditions	49 (10.5%)
Injection site erythema	29 (6.2%)
Investigations	36 (7.7%)
Alanine aminotransferase increased	15 (3.2%)
Injury, poisoning and procedural complications	45 (9.6%)
Accidental overdose	22 (4.7%)

4.3 Critique of trials identified and included in network meta-analysis

Trials included in the NMA are listed in Table 34 and Table 35. Trial characteristics of these studies are included in the CS Appendix 8.6 and were considered appropriate by the ERG to permit inclusion in the NMA, with the exceptions of the Fleischmann 2009,[44] Choy 2012[45] and Go-FURTHER,[46,] studies where unlicensed doses were used and Kay 2008[47] where there were no eligible data owing to treatment crossover. The quality of the included RCTs was assessed using well-established and recognised criteria and is reported in Appendix 8.7 of the CS.

In the cDMARD-IR NMAs, multiple trials (ASSET[48], Chen 2009[49], Lan 2004[50], Weinblatt 1999[51], Taylor 2004[52], Maini 1998[53], Tam 2012[54], Tanaka 2011[55], Smolen, 2014[56] (part A) and Smolen, 2014[56] (part B)) were excluded because these trials included fewer than 30 patients per arm. In the TNF-IR NMAs, two trials (Schiff 2014[57] and Genovese 2014[58]) were excluded because of small sample sizes. The ERG argues that all evidence is relevant unless there is a reason to assume that a study has questionable quality. The company justified the exclusion of RACAT[59] and Machado 2014[60] stating that it was unable to link them in the network. The ERG disagrees with the decision because both trials had ETN 50mg every week plus MTX, which can be linked to the network. Three studies assessing monotherapy versus combination therapy (SURPRISE,[61-63] ACT-RAY,[64] and JESMR[65, 66]) were excluded because the company stated that they '*were not part of either of the population network diagrams*'. The ERG notes that if all studies had been included within one network, there would have been no need to exclude these trials.

Table 34: Studies included in the NMA for the cDMARD-IR population: Updated review (reproduced from Table 4.27 of the CS)

Intervention arm(s)	Control arm	Duration of study (weeks)	Number of patients	References
Monotherapy studies vs. (placebo or cDMARD)				
TNF studies				
ADA SC 20mg QW ADA SC 20mg Q2W ADA SC 40mg QW ADA SC 40mg Q2W	Placebo	26	544	ADA efficacy and safety study (van de Putte 2004[67])
ADA SC 20mg Q2W ADA SC 40mg Q2W ADA SC 80mg Q2W	Placebo	24	352	CHANGE (Miyasaka 2008[68])
CTZ SC 400mg Q4W	Placebo	24	220	FAST4WARD (Fleischmann 2009[44])
ETN SC 25mg BIW ETN SC 25mg BIW + SSZ	SSZ	104	254	ETN study 309 (Combe 2006,[49] Combe 2009[69, 70]
ETN SC 10mg BIW ETN SC 25mg BIW	Placebo	26	234	ETN monotherapy study (Moreland 1999[71])
IL-6 studies				
TCZ SC 8mg/kg Q4W	MTX	24	125	SARTORI (Nishimoto 2009[72])
TCZ IV 8mg/kg Q4W	ADA SC 40mg Q2W	32	325	ADACTA (GABAY 2013[73])
SIR SC 50mg Q4W SIR SC 100mg Q2W	ADA SC 40mg Q2W	24	559	SIRROUND-H (Taylor 2016[74])
SAR SC 200mg Q2W	ADA SC 40mg Q2W	24	369	MONARCH (Burmester 2016[35])
JAK inhibitors studies				
TOF oral 1mg BID TOF oral 3mg BID TOF oral 5mg BID	Placebo	24	384	Efficacy and safety of TOF vs. ADA (Fleischmann 2012[75])

Intervention arm(s)	Control arm	Duration of study (weeks)	Number of patients	References
TOF oral 10mg BID TOF oral 15mg BID ADA SC 40mg QW for 12 weeks followed by oral TOF 5mg BID for 12 weeks				
Combination studies vs. (placebo or cDMARD)				
TNF studies				
ADA SC 20mg QW + MTX ADA SC 40mg Q2W + MTX	MTX	52 (plus 10 year OLE)	619	DE019 (Keystone 2013,[76] Keystone 2011,[77] Keystone 2004[76])
ADA SC 40mg Q2W + MTX	MTX	24	128	ADA efficacy and safety study (Kim 2007[78])
ADA SC 20mg Q2W + MTX ADA SC 40mg Q2W + MTX ADA SC 80mg Q2W + MTX	MTX	24	271	ARMADA (Weinblatt 2003[79])
ADA SC 40mg Q2W + standard treatment	Placebo + standard treatment	24	636	STAR (Furst 2003[80])
CTZ SC 200mg Q2W + MTX CTZ SC 400mg Q2W + MTX	MTX	52	982	RAPID (Keystone 2008,[81] Strand 2009[82])
CTZ SC 100mg Q2W + MTX CTZ SC 200mg Q2W + MTX CTZ SC 400mg Q2W + MTX	MTX	24	316	J-RAPID (Yamamoto 2014[83])
CTZ SC 200mg Q2W + MTX CTZ SC 400mg Q2W + MTX	MTX	24	619	RAPID-2 (Smolen 2009[84])
CTZ SC 400mg Q2W + MTX	MTX	24	247	CTZ efficacy and safety study (Choy 2012[45])
CTZ SC 400mg Q2W + cDMARD	cDMARD	24	194	CERTAIN (Smolen 2015[85])

Intervention arm(s)	Control arm	Duration of study (weeks)	Number of patients	References
ETN SC 25mg BIW ETN SC 25mg BIW + SSZ	SSZ	104	254	ETN 309 study (Combe 2006,[70] Combe 2009[69])
ETN SC 25mg BIW + MTX	MTX	104	222	ENCOURAGE (Yamanka 2016[86])
GOL SC 50mg Q4W + MTX GOL SC 100mg Q4W + MTX	MTX	24	269	GO-FORTH (Tanaka 2012[87])
GOL SC 50mg Q2W + MTX GOL SC 50mg Q4W + MTX GOL SC 100mg Q2W + MTX GOL SC 100mg Q4W + MTX	MTX	52	172	GOL efficacy and safety study (Kay 2008[47])
GOL SC 50mg Q4W + MTX	MTX	52	264	GOL efficacy and safety study (Li 2016[88])
GOL SC 2mg/kg Q8W+ MTX	MTX	112	592	GO-FURTHER (Weinblatt 2014,[89] Bingham 2014,[46] Weinblatt 2013[90])
GOL SC 100mg Q4W GOL SC 50mg Q4W + MTX GOL SC 100mg Q4W + MTX	MTX	312	444	GO-FORWARD (Keystone 2016,[91] Keystone 2013,[92] Genovese 2012,[93] Keystone 2010,[94] Keystone 2009[95])
IFX IV 3mg/kg Q8W + MTX IFX IV 3mg/kg Q4W + MTX IFX IV 10mg/kg Q8W + MTX IFX IV 10mg/kg Q4W + MTX	MTX	54 (plus 1 year OLE)	428	ATTRACT (Maini 1999,[96] Lipsky 2000,[97] Maini 2004[98])
IFX IV 3mg/kg Q8W + MTX IFX IV 10mg/kg Q8W + MTX	MTX	54	1084	START (Westerhovens 2006[99])
IFX IV 3mg/kg Q8W + MTX ABT IV 8–10mg/kg + MTX	MTX	52	431	ATTEST (Schiff 2008[100])

Intervention arm(s)	Control arm	Duration of study (weeks)	Number of patients	References
IFX IV 3mg/kg Q8W + MTX	SSZ 1000mg (oral) BID + HCQ 400mg (oral) BID + MTX	104	245	SWEFOT (Karlsson 2013,[101] Rezaei 2013,[102] van Vollenhoven 2012,[103] van Vollenhoven 2009,[104] Eriksson 2013[105])
Non-TNFi studies				
ABT IV 8–10mg/kg Q4W + MTX	MTX	52	652	AIM (Russell 2007,[106] Kremer 2006[107])
ABT IV 2mg/kg Q4W + MTX ABT IV 10mg/kg Q4W + MTX	MTX	52	339	ABT efficacy and safety study (Emery 2006,[108] Kremer 2005,[109] Kremer 2003[110])
ABT IV 2mg/kg Q4W + MTX ABT IV 10mg/kg Q4W + MTX	MTX	32	194	ABT efficacy and safety study (Takeuchi 2013[111])
IFX IV 3mg/kg Q8W + MTX ABT IV 8–10mg/kg + MTX	MTX	52	431	ATTEST (Schiff 2008[100])
ABT IV 8–10mg/kg Q4W + cDMARD	cDMARD	52	1456	ASSURE (Weinblatt 2006[112])
RTX IV 2 x 500mg at days 1 and 15 + MTX RTX IV 2 x 1,000mg at days 1 and 15 + MTX	MTX	48	511	SERENE (Emery 2010[113])
RTX IV 2 x 500mg at days 1 and 15 + MTX RTX IV 2 x 1000mg at days 1 and 15 + MTX	MTX	24	367	DANCER (Mease 2008[114])
RTX IV 1,000mg days 1 and 15 RTX IV 1,000mg days 1 and 15 + MTX RTX IV 1,000mg days 1 and 15 + CYC 750mg days 3 and 17	MTX	104	161	RTX efficacy and safety study (Strand 2006,[115] Edwards 2004[116])
RTX IV 500mg + MTX RTX IV 1,000mg + MTX	MTX	52	185	RA-SCORE (Peterfy 2016[117])

Intervention arm(s)	Control arm	Duration of study (weeks)	Number of patients	References
RTX IV 1,000mg + LEF	LEF	52	140	AMARA (Behrens 2016[118])
IL-6 studies				
SAR SC 150mg Q2W + MTX SAR 200mg Q2W + MTX	MTX	52	1,197	MOBILITY B (Genovese 2015[33])
TCZ IV 4mg/kg Q4W + MTX TCZ IV 8mg/kg Q4W + MTX	MTX	24	623	OPTION (Smolen 2008[119])
TCZ IV 8mg/kg Q4W + MTX	MTX	24	132	MEASURE (McInnes 2015,[120] Mirjafari 2013[121])
TCZ IV 4mg/kg Q4W + MTX TCZ IV 8mg/kg Q4W + MTX	MTX	104	1,196	LITHE (Fleischmann 2013,[122] Kremer 2011[123])
TCZ SC 162mg Q2W + cDMARD	cDMARD	24	656	BREVACTA (Kivitz 2014,[124] Kivitz 2013[125])
TCZ IV 8mg/kg Q4W + cDMARD	cDMARD	24	1,220	TOWARD (Genovese 2008[126])
TCZ IV 8mg/kg Q2W + cDMARD	cDMARD	24	619	ROSE (Yazici 2012[127])
JAK inhibitors studies				
TOF oral 1mg BID + MTX TOF oral 3mg BID + MTX TOF oral 5mg BID + MTX TOF oral 10mg BID + MTX TOF oral 15mg BID + MTX TOF oral 20mg BID + MTX	MTX	24	509	TOF efficacy and safety study (Kremer 2012[128])
TOF oral 5mg BID + MTX TOF oral 10mg BID + MTX	MTX	104	797	Oral Scan (van der Heijde 2013[129])
TOF oral 5mg BID + MTX TOF oral 10mg BID + MTX TOF oral 40mg BID + MTX	MTX	52	717	Oral Standard (Van Vollenhoven 2012[130])

Intervention arm(s)	Control arm	Duration of study (weeks)	Number of patients	References
ADA SC 40mg Q2W + MTX				
TOF oral 5mg BID + cDMARD TOF oral 10mg BID + cDMARD	cDMARD	53	636	TOF efficacy and safety study (Kremer 2013[131])
BAR oral 2mg OD + cDMARD BAR oral 10mg OD + cDMARD	cDMARD	24	684	RA-BUILD (Dougados 2017[132])
Biologic vs. same biologic				
Comparisons of different routes of administration				
TCZ SC 162mg QW+ cDMARDs	TCZ IV 162mg Q4W+ cDMARDs	104	1,262	SUMMACTA (Burmester 2014,[133, 134] Burmester 2013[135])
Head-to-head comparisons of bDMARDs				
TNFi vs. non-TNFi				
ADA SC 40mg Q2W + MTX	ABT SC 125mg QW + MTX	104	646	AMPLE (Schiff 2014,[136] Weinblatt 2013[137])
ADA SC 40mg Q2W + MTX	BAR oral 4mg OD + MTX	52	1307	RA-BEAM (Taylor 2017[138])
IL-6 vs. TNFi				
TCZ IV 8mg/kg Q4W	ADA SC 40mg Q2W	32	326	ADACTA (Gabay 2013[73])
SAR SC 200mg Q2W	ADA SC 40mg Q2W	24	396	MONARCH (Burmester 2016[35])

ABT=abatacept; ADA=adalimumab; BAR= baricitinib; BID=Twice a day; BIW=twice weekly; cDMARD= disease-modifying anti-rheumatic drugs; CTZ= certolizumab pegol; CYC= cyclophosphamide; ETN= etanercept; GOL= golimumab; HCQ= hydroxychloroquine; IFX=infliximab; IL-6=interleukin-6; IV=intravenous; MTX=methotrexate; OD=once daily; OLE=open labelled extension; QW=once a week; Q2W=every 2 weeks; Q4W=every 4 weeks; Q8W=every 8 weeks; RTX= rituximab; SAR= sarilumab; SC=subcutaneous; SIR= sirukumab; SSZ= sulfasalazine; TCZ= tocilizumab; TOF= tofacitinib

Table 35: Studies included in the NMA for the TNFi-IR population: Updated review (reproduced from Table 4.28 of the CS)

Intervention	Comparator(s)	Duration of study (weeks)	Number of patients	References
Monotherapy studies vs. placebo				
GOL SC 50mg Q4W +/- cDMARD	cDMARDs	24	461	GO-AFTER (Smolen 2009[139])

GOL SC 100mg Q4W +/- cDMARD					
SIR SC 500mg Q4W +/- cDMARD SIR SC 1000mg Q2W +/- cDMARD		cDMARD	NA	878	SIRROUND-T (Tanaka 2016[140])
Combination studies vs. cDMARD					
Non-TNFi studies					
ABT IV 10mg/kg Q4W + cDMARD		cDMARD	26	258	ATTAIN (Westhovens 2006,[141] Genovese 2005[142])
RTX IV 1,000mg at days 1 and 15 + MTX		MTX	104	520	REFLEX (Keystone 2009,[143] Keystone 2008,[144] Cohen, 2006[145])
TOF oral 5mg BID + MTX TOF oral 10mg BID + MTX		MTX	26	399	Oral Step (Strand 2015,[146] Burmester 2013[147])
IL-6 studies					
TCZ IV 4mg/kg Q4W + MTX TCZ IV 8mg/kg Q4W + MTX		MTX	24	489	RADIATE (Strand 2012,[148] Emery 2008[149])
SAR SC 150mg Q2W + cDMARD SAR SC 200mg Q2W + cDMARD		cDMARD	24	546	TARGET (Fleischmann 2017[34])
JAK inhibitors studies					
BAR oral 2mg OD + cDMARD BAR oral 4mg OD + cDMARD		cDMARD	24	527	RA-BEACON (Genovese 2016[150])
Head-to-head comparisons of bDMARDs					
SAR SC 150mg Q2W + cDMARD SAR SC 200mg Q2W + cDMARD		TCZ IV 4-8mg/kg Q4W + cDMARD	24	202	ASCERTAIN (Sanofi Genzyme[36])
ABT (dose/frequency not stated)	RTX (dose/frequency not stated)	TNFi (dose/frequency not stated)	52	143	Open-label study (Manders 2015[151])

ABT=abatacept; BAR= baricitinib; bDMARD= biological disease-modifying anti-rheumatic drugs; cDMARD=conventional disease-modifying anti-rheumatic drugs; IL-6=interleukin-6; GOL= golimumab; IR=irresponsive; IV=intravenous; MTX=methotrexate; QW=once a week; Q2W=every 2 weeks; Q4W=every 4 weeks; Q8W=every 8 weeks; RTX= rituximab; SAR= sarilumab; SC=subcutaneous; SIR= sirukumab; TNFi=tumour necrosis factor inhibitor; TCZ= tocilizumab; TOF= tofacitinib.

4.4 Critique of the network meta-analysis

NMAs were performed separately for the cDMARD-IR and TNFi-IR populations using a Bayesian approach for efficacy and safety outcome measures at either 24 weeks or 52 weeks (see

Table 36). In the cDMARD-IR population, studies investigating combination therapies and monotherapies were separated into two different networks. The TNFi-IR network only had studies with combination therapy, as no studies were identified investigating bDMARDs as monotherapy in this population.

The ERG agrees with the decision to perform separate analyses for the two populations. In contrast, the ERG does not agree with the use of separate networks for combination therapy and monotherapy in the cDMARD-IR population as three studies had been excluded because of the use of two networks (see critique in Section 4.3).

For continuous outcomes, HAQ-DI and mTSS, a normal likelihood with identity link function model was used in the NMA. For ordered categorical outcomes, ACR and EULAR response, a binomial likelihood with either a logit link function in meta-regression on baseline risk or a risk difference model was used by dichotomising the data. For binary data, the efficacy outcome (DAS28 remission) used either meta-regression on the baseline risk model with a logit link function or a risk difference model; safety outcomes (serious infections and serious adverse events) used either a risk difference model or logit model.

Table 36: **Outcomes and models used in the NMA per population and time point for the combination therapy**

Outcome	cDMARD-IR (combination therapy)		cDMARD-IR (monotherapy)	TNFi-IR
	Model (24 weeks)	Model (52 weeks)	Model (24 weeks)	Model (24 weeks)
ACR20, 50 and 70	Random effects-baseline risk regression		Fixed effect-logit model	Fixed effect-risk difference
HAQ-DI CFB	Random effects-change from baseline		Fixed effects-change from baseline	Fixed effect-change from baseline
EULAR moderate-to-good, good	Fixed effect-risk difference		Fixed effect-risk difference	Fixed effect-risk difference
DAS28 remission	Random effects-baseline risk regression		Fixed effects-risk difference	Fixed effect-risk difference
mTSS CFB	Fixed effect-change from baseline	Fixed effect-change from baseline		
SIs		Random effects-risk difference	Fixed effect-risk difference	Fixed effect-logit model
SAE		Random effects-logit model	Fixed effect-logit model	Fixed effect-logit model

ACR20/50/70=American College of Rheumatology 20%/50%/70% improvement; CFB=change from baseline; DAS28=28-joint disease activity score; HAQ-DI=Health Assessment Questionnaire Disability Index; mTSS=modified Total Sharp Score; NMA=network meta-analysis; SAE=serious adverse event; SI=serious infections

The ERG disagrees with dichotomising ACR and EULAR response. The choice of the likelihood function/link function should be based on the data generating process. A multinomial likelihood with probit/logit link function is preferred to a binomial likelihood for the ordered categorical ACR or EULAR data, because it accounts for natural ordering and correlations between the categories within the outcome measure. This is important to the decision problem when these results are used to populate the economic model.

Meta-regression on the baseline risk is not very useful for decision-making as it does not explain the heterogeneity in terms of prognostic factors. When there were too few studies to perform a meaningful regression, a risk difference scale was used for all the efficacy outcomes rather than the most frequently applied odds ratio scale (a logit model). The company stated that this was because the observed treatment effect was statistically significantly correlated with the observed baseline risk when the effect was measured using an odds ratio scale, but was not statistically significantly correlated when the effect was measured using risk difference scale. The ERG disagrees with the model selection procedure.

Firstly, a *p*-value is not very useful as an estimate of the strength of an association, because it is influenced by the number of observations. Secondly, it is known that the sample estimate of the treatment effect has a negative association with the sample estimate of the baseline on the odds ratio scale, but the true magnitude of the association depends on the between-study variance in the true underlying risk, which is unknown. Finally, the treatment effect needs to be constrained when using a risk difference model in the NMA so that the probability of achieving an event is bounded between 0 and 1. In response to clarification question A11,[31] it is suggested that the constraint used was only to limit the probability not to be less than 0, but it still allowed it to exceed 1.

Random effects models were used to allow for heterogeneity when sufficient data were available, with fixed effect models used when data were sparse. The ERG disagrees with the rationale that too few studies would rule out a random effects analysis. If heterogeneity is expected, then a random effect model should be applied with careful consideration of the prior for the between-study variance. In response to clarification question A12,[31] the company stated that a less vague prior was used for the regression coefficient, the relative treatment effect *d* and the baseline effect *mu*. The ERG argues that the less vague prior should be applied on the between-study variance when data were sparse.

In response to clarification question A9,[31] the company stated that the baseline absolute effect was calculated by averaging all study effects with cDMARD/MTX in both cDMARD-IR and TNFi-IR networks. The code for generating the baseline effect was also provided. The ERG notes that averaging the effects for studies with cDMARD/MTX may not be appropriate, as this does not account for uncertainty in the baseline treatment effect of cDMARD/MTX properly.

In response to clarification question A15,[31] the company stated that "*the goodness-of-fit was estimated by calculating the mean residual deviance of the model (mean residual deviance close to 1 was considered to be a good model fit)*". It was also stated that mean total residual deviance compared to the number of fitted data points was considered in selecting the preferred model. However, no comments regarding the performance of each model fitting were provided by the company.

The I^2 statistic was used to assess the heterogeneity for the pairwise treatment comparisons. Heterogeneity was observed in the cDMARD-IR combination therapy NMAs, but not observed in the cDMARD-IR monotherapy NMAs and TNFi-IR NMAs. The ERG notes that both cDMARD-IR monotherapy and TNFi-IR NMAs had limited data and the I^2 statistic calculation may be biased due to too few studies. Inconsistency was checked using the Bucher method.[152] No inconsistency was found in most of the NMAs, except for ACR50 response (ADA combination, cDMARD and tofacitinib combination loop) in the cDMARD-IR population.

In the base case cDMARD-IR NMA, SAR 200mg combination therapy (in combination with cDMARD) demonstrated statistically superiority to cDMARD for all efficacy outcome measures (Table 4.30 in the CS). SAR 200mg combination therapy was comparable to other bDMARD combination therapies on ACR responses, DAS28 remission and HAQ-DI (TCZ SC combination therapy was not included in the HAQ-DI network) at 24 weeks (Table 4.30 in the CS). SAR 200mg combination therapy showed statistically superiority to ABT combination, IFX combination, TCZ 4mg IV, RTX and SAR 150mg on EULAR good response at 24 weeks, and was comparable with GOL and TCZ 8mg IV, each in combination with cDMARD. SAR 200mg combination therapy was statistically inferior to CTZ combination on EULAR at least moderate response at 24 weeks, but was comparable with GOL, IFX, TCZ 4mg IV and 8mg IV, RTX and SAR 150mg each in combination with cDMARD (Table 4.30 in the CS). For mTSS at 24 weeks, SAR 200mg combination therapy was statistically superior to baricitinib 2mg, tofacitinib and CTZ each in combination with cDMARD, and comparable with baricitinib 4mg, ADA, GOL, TCZ SC 162mg each in combination with cDMARD (Table 4.30 in the CS). For mTSS at 52 weeks, SAR 200mg combination therapy was comparable to ABT, ADA, CTZ and ETN each in combination with cDMARD, and superior to SAR 150mg combination therapy (Table 4.30 in the CS).

In the cDMARD-IR monotherapy NMA, the outcome measures were all assessed at 24 weeks and the results were provided in Table 4.31 of the CS. SAR 200mg monotherapy showed statistically superiority to placebo and cDMARD for all the efficacy outcome measures, except that it was comparable with cDMARD on HAQ-DI, and DAS28 remission was not analysed for placebo. SAR 200mg monotherapy was also statistically superior to ADA on all ACR responses, and sirukumab 50mg on ACR20 and ACR50 response. SAR 200mg was comparable with CTZ, ETN, sirukumab 100mg, TCZ 8mg and tofacitinib on all ACR responses. SAR 200mg was statically superior to ADA and sirukumab 50mg on DAS28 remission, and comparable with sirukumab 100mg and TCZ 8mg. SAR 200mg was statistically superior to ADA on HAQ-DI, and comparable with CTZ, ETN and TCZ 8mg. SAR 200mg was statistically superior to ADA on EULAR responses, and comparable with TCZ 8mg.

In the TNFi-IR population, the outcome measures were all assessed at 24 weeks and the results were provided in Table 4.32 of the CS. SAR 200mg combination therapy showed statistically superiority to cDMARD for all the efficacy outcome measures. SAR 200mg combination was statistically superior to baricitinib 2mg combination, sirukumab 50mg combination on ACR50, and comparable with other bDMARD combination therapies on all ACR responses. SAR 200mg combination was statistically superior to ABT combination, baricitinib 2mg combination, GOL combination, sirukumab 50mg combination, TCZ 4mg combination, and RTX combination on DAS28 remission, and comparable with other bDMARD combination therapies. None of the effect on HAQ-DI was statistically significant. For EULAR good response, SAR 200mg combination was statistically superior to rituximab combination,

and comparable to abatacept combination and SAR 150mg combination. For EULAR at least moderate response, SAR 200mg combination was statistically inferior to TCZ 8mg combination and RTX combination, and comparable with ABT, GOL and SAR 150mg all as combination therapies.

In relation to safety data, SAR 200mg combination therapy was associated with significantly higher odds of SAEs at 52 weeks when compared with cDMARD in the cDMARD-IR population. All other results were not statistically significant (Tables 4.30-4.32 in the CS).

Scenario analyses were conducted assuming TNFis had identical efficacy. These analyses showed that SAR 200mg combination therapy was statistically superior to cDMARD and comparable with all other combination therapies on ACR20 at 24 weeks. SAR 200mg monotherapy was statistically superior to placebo, cDMARD, sirukumab 50mg monotherapy, TNF monotherapy and tofacitinib monotherapy and comparable with sirukumab 100mg monotherapy and TCZ 8mg monotherapy on ACR 20 at 24 weeks (Tables 4.33-4.34 in the CS).

The ERG considers that the base case NMA results in the CS should be interpreted with caution. The statistically significant results of SAR 200mg compared with other bDMARD treatments (both as combination therapy and monotherapy) may be as a result of using a fixed effect model, which underestimates uncertainty in the treatment effects. The ordered categorical ACR response and EULAR response data were dichotomised in the NMA, which ignores the natural ordering and correlations between the categories within the outcome measure. When a risk difference model was used for binary data, the probability was not constrained to be below 1.0. Furthermore, the MOBILITY B and TARGET trial designs allowed patients who did not achieve a ≥20% improvement from baseline in the swollen joint count or tender joint count at two consecutive assessments to switch to open-label SAR 200mg at 16 and 12 weeks, respectively. Non-responder imputation was carried out for the control arm, assuming that none of the non-responders in the cDMARD control group would become responders at 24 weeks, which may overestimate the relative treatment effect of SAR combination therapy versus cDMARD.

The ERG requested that the company perform additional analysis for ACR and EULAR response in both populations (see clarification response[31] --question A7) with the following settings:

- Using a random effects probit model with an informative prior for the between-study variance (log normal with mean -2.56 and variance of 1.74*1.74, which is proposed by Turner *et al* 2012.[153] The log normal is truncated so that the odds ratio in one study would not be ≥50 times than in another, and re-scaled to match the probit scale).
- Keeping all treatments separate.

- Including combination therapy and monotherapy in a single network in order that trials comparing both regimens can provide evidence (including the studies in Appendix 8, Table 8.7 of the CS and HARUKA[154]).
- Including the studies which were excluded due to small sample size (CS Appendix 8 Table 8.1 and Table 8.9)
- Including the previously excluded studies that were included in TA375.
- Including the studies in Table 8.3 of the CS Appendix assuming that ETN 50mg once weekly was equivalent to ETN 25mg twice weekly.
- Incorporate the KAKEHASI[155] study for consistency with the main network, which includes studies in Asian patients.

The ERG also requested a sensitivity analysis for the requested NMA where TNFis were pooled into a 'TNFi-bundle'.

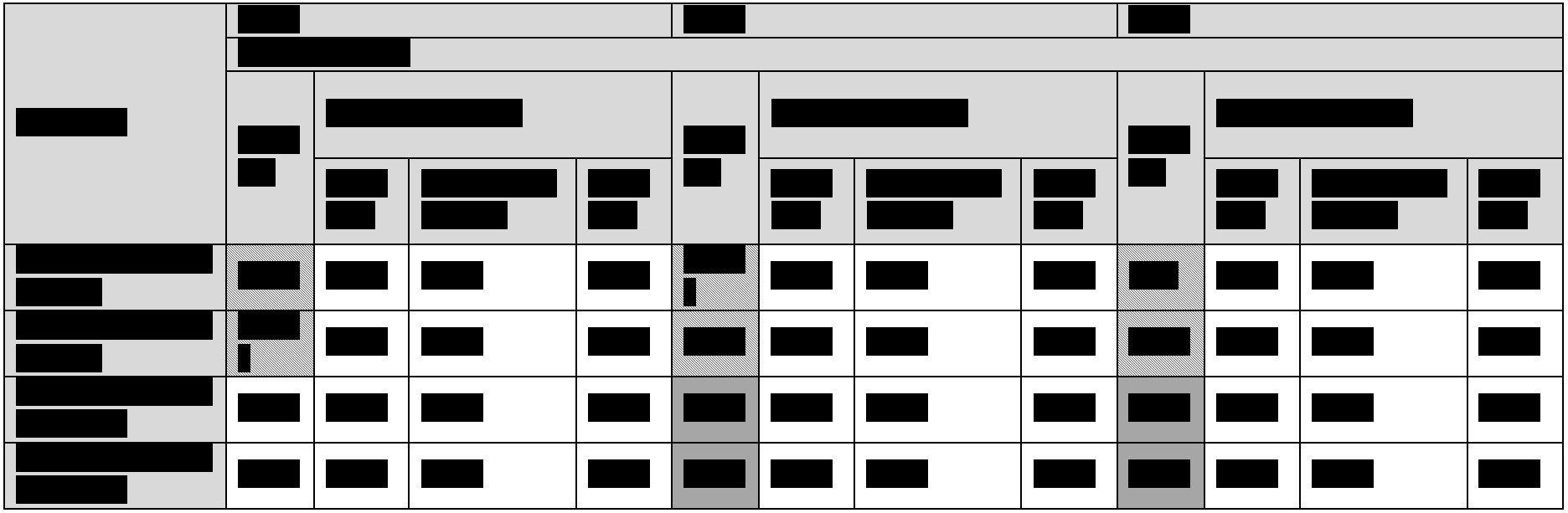
The company only provided the results for the cDMARD-IR population on ACR responses. The company justified not using a random effects probit model for the TNFi-IR population on ACR responses stating that "*this analysis produces results that are inconsistent with the observed head-to-head data from both the RADIATE and TARGET studies. The results from the random effects probit model both significantly under- and over-estimate relative treatment effect compared to trial data*" (clarification response[31] -- question A7). The comparison of ACR responder rate as observed data and the values estimated from the NMA using probit link at 24 weeks are reproduced in

Table 37. The ERG disagrees with the approach that was taken by the company in determining that a random effects probit model was not a suitable model for ACR responses in the TNFi-IR population. This is because the absolute effect (the responder rate) was compared between the observed data and the values estimated from the NMA, and the estimated responder rate from NMA shown in

Table 37 depends on how the baseline effect was estimated. The inconsistency observed in

Table 37 was because the chosen baseline effect was different from the baseline effect in the RADIATE and TARGET studies. The relative effect should be used for comparison not the absolute effect as used by the company. In addition, the findings in the TNFi-IR population may not apply to the cDMARD-IR population.

Table 37: **Comparison ACR20/50/70 responder rate as observed (direct results) and estimated from NMA using probit link approach in a random effects model at 24 weeks in TNF-IR population**



White cells mean NMA predicts well, hatched cells that the NMA over predicts, grey cells that the NMA under predict

ACR: American College of Rheumatology; ACR20/50/70: 20%/50%/70% improvement in the ACR score; combi: combination therapy CrI: credible interval; SAR: sarilumab; TCZ: tocilizumab

In addition, the company did not conduct the requested analysis for EULAR responses. The company justified this omission stating that the data for EULAR outcomes were only available for two categories (EULAR no response and EULAR at least moderate response). The ERG notes that EULAR good response data are available from nine studies in the cDMARD-IR combination therapy network, four studies in the cDMARD-IR monotherapy network and three studies in the TNFi-IR network (Table 8.23, Table 8.32 and Table 8.43 in the CS Appendix). Although not all the studies have reported data in all three EULAR categories, the probit model is able to incorporate such data.

The company concluded that the results for ACR outcomes from the requested NMA were in line with the results in the original CS and the conclusion that SAR in combination with cDMARD showed comparable efficacy to other bDMARDs was unchanged. The ERG notes that the additional analyses performed by the company involved meta-regression on a baseline risk model with a probit link function, rather than the standard probit NMA model. All the results presented were the effects with covariate adjustment. To make the results more interpretable, the analyses used centred covariate values by subtracting the mean covariate value. However, the company did not report what this mean covariate value was. The estimates for the covariate coefficient suggested that there was not enough evidence for an interaction effect between the baseline risk and treatment effects on the probit scale. The ERG agrees with the company that the conclusion has not altered, but notes that the results from the requested NMA may be numerically different from the original NMA in the CS. The comparison of ACR responder rates between the two NMAs is presented in [redacted] to [redacted] for the combination therapies and [redacted] to [redacted] for the monotherapies.

[redacted]2[redacted]

[redacted]3[redacted]

[redacted]4

[redacted]

[redacted]5

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4.5 Additional work on clinical effectiveness undertaken by the ERG

No additional work was undertaken by the ERG as the company performed the analyses requested by the ERG, albeit with some deviations.

4.6 Conclusions of the clinical effectiveness section

The key clinical effectiveness evidence for SAR was based on five RCTs. Additionally one long-term extension study was included. There were three RCTs in MTX-IR RA patients (MOBILITY-A, MOBILITY-B, MONARCH). Two RCTs were undertaken in a TNFi-IR RA population (TARGET and ASCERTAIN). One RCT had a comparator of TCZ (ASCERTAIN), one had a comparator of ADA (MONARCH); the other RCTs included a PBO comparator.

Three RCTs had ACR20 as their primary endpoint (MOBILITY-A, MOBILITY-B and TARGET). In the MTX-IR population, the RCTs showed a significant advantage in ACR responses for licensed doses of SAR+MTX over PBO+MTX ($p \leq 0.05$) (MOBILITY-A, MOBILITY-B), and a significant advantage for SAR monotherapy over ADA monotherapy ($p < 0.01$) (MONARCH). In the TNFi-IR population, TARGET reported a significant advantage for SAR+cDMARD over PBO+cDMARD for ACR20 ($p < 0.0001$), and ACR50 and ACR70 ($p \leq 0.005$).

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

The MOBILITY-A, MOBILITY-B, MONARCH and TARGET trials reported significantly favourable results for licensed doses of SAR over comparators for improvement in HAQ-DI. SAR had a significant advantage over comparator for DAS28-CRP in the MOBILITY-B and TARGET trials, and for DAS28-ESR in the MONARCH trial. MOBILITY-B measured radiographic progression by mTSS, and reported a significantly lower deterioration from baseline for SAR over comparator.

[redacted]

The ERG considers that the base case NMA results in the CS should be interpreted with caution. The statistically significant results of SAR 200mg compared with other bDMARD treatments (both as combination therapy and monotherapy) may be as a result of using a fixed effect model, which underestimates uncertainty in the treatment effects. The ordered categorical ACR response and EULAR response data were dichotomised in the NMA; this ignores the natural ordering and correlations between the categories within the outcome measure. When a risk difference model was used for binary data, the probability was not constrained to be below 1.0. Furthermore, the MOBILITY B and TARGET trial designs allowed patients who did not achieve a ≥20% improvement from baseline in the swollen joint count or tender joint count at two consecutive assessments to switch to open-label SAR 200mg at 16 and 12 weeks, respectively. Non-responder imputation was carried out for the control arm, assuming none of the non-responders in the cDMARD control group would become responders at 24 weeks; this may overestimate the relative treatment effect of SAR combination therapy versus cDMARD.

5 COST EFFECTIVENESS

This chapter presents a review of the cost-effectiveness evidence provided in the CS for SAR, with or without MTX, for treating moderate to severe, or severe RA. For brevity, the moderate to severe RA group is referred to as moderate RA The cost-effectiveness evidence comprised a systematic review of economic analyses that included SAR and the economic analysis based on the company's *de novo* model. Following the clarification round,[31] the company made a number of amendments to the model at the request of the ERG, which resulted in different ICERs to those presented in the CS; the broad conclusions remained unchanged for patients with severe RA, but are different for patients with moderate RA. The ERG report will discuss only the latest version of the model unless there is a clear reason to provide significant detail to the original version.

5.1 ERG's comment on company's review of cost-effectiveness evidence

5.1.1 Objective of cost effectiveness review

The company performed a literature search in order to identify cost-effectiveness evaluations of bDMARDs used to treat people with moderate or severe RA.

5.1.2 Inclusion and exclusion criteria used in the company's review

A full description of the company's search strategy is provided in Appendix 9 of the CS. The company's review was undertaken in two stages. An initial review was conducted in March 2014 searching MEDLINE, Embase, Health Economic Evaluation Database (HEED) and NHS Economic Evaluation Database (NHS EED). An update to this review was performed in December 2016, with the exceptions of HEED and NHS EED, whose coverage expired in December 2014 and March 2015 respectively. Conference proceedings were not included due to "*the limited reporting of methodologies in such publications.*"

The inclusion and exclusion criteria of the company's review are presented in Table 38.

Table 38: Inclusion and exclusion criteria of the company's review (reproduced from Table 5.1 of the CS)

Domain	Inclusion criteria	Exclusion criteria
• **Population**	• Adult patients with moderate-to-severe RA • Refractory to cDMARD or TNFi therapy • Or: • Intolerant to cDMARD or TNFi therapy	• Any patient population other than adult patients with moderate-to-severe RA • Studies that do not report separate results for moderate-to-severe RA patients
• **Intervention / comparators**	• bDMARDs	• Any treatment other than bDMARDs
• **Outcomes**	• Model characteristics • Costs/utilities/disutilities • LYs/QALYs • CERs/ICERs	• Epidemiologic outcomes • Clinical efficacy and safety outcomes • PROs • Other economic outcomes
• **Study designs**	• Economic evaluations: trial-based economic analyses and economic models • Cost-benefit analyses • Cost-effectiveness analyses • Cost-utility analyses	• The following study designs without an economic evaluation component • Cross-sectional studies • RCTs • Longitudinal observational studies • Economic evaluations: trial-based economic analyses and economic models • Cost-minimisation analyses • Cost-consequence analyses • Budget impact analyses
Geography	No limitation in regards to geography	
Time period	No date restrictions were applied	
Language	English language	Non-English language

bDMARD=biologic disease-modifying anti-rheumatic drug; cDMARD= disease-modifying anti-rheumatic drug; CER = cost-effectiveness ratio; DMARD = disease-modifying anti-rheumatic drugs; ICER = incremental cost-effectiveness ratio; LYs = life years; PRO=patient-reported outcomes; RA=rheumatoid arthritis; RCTs=randomised controlled trials; TNFi=tumour necrosis factor inhibitor; QALYs = quality-adjusted life years

The ERG has some concerns about what has been excluded in the company's review (every instance of the word "review" in searchable fields – this would include its use in a figurative sense as well as in reference to a type of evidence synthesis). Additionally, the ERG queries whether it was necessary to exclude all secondary evidence relating to the cost-effectiveness of SAR in this fashion; particularly

given the company's statement in their response to the clarification letter that "the references of any systematic literature review identified in the searches were reviewed for studies matching the inclusion criteria" (clarification response[31] -- Literature searching, Q2).[31]

In response to the ERG's query on the use of limits in its clarification letter,[31] the company justified its decision by citing several other NICE TAs in RA as evidence that it was unlikely that there were any more published cost-effectiveness studies the review had missed. In spite of concerns regarding the method of retrieval, the ERG considers it unlikely that any significant cost-effectiveness studies have been overlooked by this systematic literature review.

5.1.3 Findings of the cost-effectiveness review

A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram is presented by the company in Figure 5.1 of the CS. A total of 76 records were identified, of which 50 were economic evaluations and 26 were health technology assessment reports with economic models. A description of the identified studies are provided in Section 5.1.2 of the CS with further information provided in Appendix 10 and Appendix 11 of the CS. None of the identified studies considered SAR.

5.2 Summary and critique of company's submitted economic evaluation by the ERG

Given that none of the identified records considered SAR, the company constructed a *de novo* model to address the cost-effectiveness of SAR, as monotherapy or in combination with MTX. The company state that the parameters in the *de novo* model "*were largely informed by previous models with special consideration to the independent assessment group model in TA375".* This model has been published in a peer-reviewed journal.[24]

5.2.1 NICE Reference Case checklist

A summary of the key features of the company's *de novo* model relating to the NICE Reference Case[156] is provided in Table 39.

Table 39: Adherence of the company's economic analysis to the NICE Reference Care

Element	Reference case	Satisfactorily addressed within the CS?	ERG Comments
Defining the decision problem	The scope developed by NICE	Yes	-
Comparators	As listed in the scope developed by NICE	Mostly	Some comparators have been excluded from the decision problem including: biosimilars for ADA and RTX; and MTX alone where other bDMARDs have been recommended by NICE.
Perspective on costs	NHS and Personal Social Services (PSS)	Yes	-
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes	Health gains for patients are modelled in terms of QALYs gained.
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	Yes	-
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes	The time horizon of the analysis is 100 years, which is assumed to be representative of patients' remaining lifetimes.
Synthesis of evidence on health effects	Based on systematic review	Mostly	The ERG has concerns with the NMA (see Section 4.4).
Measure and valuation of health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	Yes	Health gains were valued in terms of QALYs. HAQ scores were mapped using three methods: (i) Malottki *et al*.[157] used in TA195;[27] Hernández-Alava *et al*[158] accepted by the Appraisal Committee in TA375;[25] and, (iii) Bansback *et al*.[159]
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes	Resource use estimates associated with HAQ categories were based on data from the Norfolk Arthritis Register (NOAR) database[160] and were inflated to 2016 values.
Discount rate	The same annual rate for both costs and health effects (currently 3.5%)	Yes	-
Equity considerations	An additional QALY has the same weight regardless of the other characteristics	Not applicable	No additional equity weighting is applied to the estimated QALY gains.

Element	Reference case	Satisfactorily addressed within the CS?	ERG Comments
	of the individuals receiving the health benefit		

5.2.2 Population

Patient-level data from three SAR trials (MOBILITY B,[33] TARGET[34] and MONARCH[35]) were used to populate the company's model. Table 5.3 of the CS uses alpha-numeric coding for each patient group. This convention was not intuitive for the ERG who have renamed the population groups for the purposes of this report. Further, the group labelled C4 was not clear, but the ERG has attempted to interpret this based on the sequences evaluated in this group.

The groups as renamed by the ERG are:

- cDMARD-IR patients with severe RA who can tolerate MTX (CS denoted A1);
- cDMARD-IR patients with severe RA who cannot tolerate MTX (CS denoted B);
- TNFi-IR patients with severe RA who can tolerate RTX and MTX (CS denoted C2);
- TNFi-IR patients with severe RA who cannot tolerate RTX (CS denoted C1);
- TNFi-IR patients with severe RA who cannot tolerate MTX (CS denoted C3);
- TNFi-IR patients who have received RTX and MTX (CS denoted C4); and
- cDMARD-IR patients with moderate RA and DAS28 between 4.0 and 5.1 who can tolerate MTX (CS denoted A2).

The data sources for the modelled population differ from the approach used in TA375[25] in which data from the British Society for Rheumatology Biologics Register (BSRBR) were used. The CS states that the baseline characteristics of the MOBILITY-B study (used for cDMARD-IR patients with severe RA who can tolerate MTX and for cDMARD-IR patients with moderate RA who can tolerate MTX), the MONARCH study (used for cDMARD-IR patients with severe RA who cannot tolerate MTX) and the TARGET study (used for all remaining populations) were found to be similar to data from the BSRBR. Data on the baseline patient characteristics are provided in Table 4.12 (p93-94) of the CS. Data used in the model are provided in

Table **40**.

Table 40: Population characteristics used in the model

	MOBILITY B	MONARCH	TARGET
Age (Years) (SD)	50.8 (12.5)	52.2 (12.3)	52.9 (12.3)
Proportion Male	18.3%	16.8%	18.1%
Weight (Kg) (SD)	74.39 (18.52)	72.05 (17.15)	78.8 (21.52)
HAQ score	1.64 (0.64)	1.64 (0.60)	1.78 (0.63)

5.2.3 Interventions and comparators

Descriptions of the intervention and the comparators are provided in Sections 3.2 and 3.3. The company did not include biosimilars for ADA or RTX. The ERG also notes that CTZ used as a monotherapy has not been included in the decision problem.

The model compares sequences of treatments that for simplicity include a 'TNFi bundle' in the base case. This TNFi bundle used the pooled efficacy of TNFis with the price weighted according to the estimated market share of each TNFi. The market share assumed by the company (Table 5.7, p211 of the CS) has been reproduced in Table 41, although the company have marked the data as commercial-in-confidence. These data were estimated from a freedom of information request to all UK hospital trusts asking for the number of RA patients treated with each named bDMARD between September and December 2016. The ERG comment that these data are likely to change as based on clinical advice provided to the ERG, clinicians are advised to start patients requiring bDMARDs on a biosimilar.

Table 41: Assumed market share of TNFis

TNFi	Market share
Etanercept (Enbrel®)	[redacted]
Etanercept biosimilar (Benepali ®)	[redacted]
Adalimumab (Humira®)	[redacted]
Infliximab (Remicade®)	[redacted]
Infliximab biosimilar (Remsima®/Inflectra®)	[redacted]
Golimumab (Simponi ®)	[redacted]
Certolizumab pegol (Cimzia®)	[redacted]
Total	**100%**

Different treatment sequences were evaluated for each of the populations. The sequences evaluated in the CS are reproduced in Appendix 1 of this report (Table 70 to Table 76). The ERG were concerned that these sequences were not consistent with those accepted in TA375 and requested that the company perform analyses using an alternative set of sequences. Following clarification,[31] the company evaluated the set of sequences requested by the ERG, which are provided in Table 42 to

Table 48. The ERG notes that it erroneously included a second line of biologics in some sequences for the TNFi-IR RTX-ineligible population as indicated in Table 45. These sequences have been used in the company's analyses but have been amended in the ERG's exploratory analyses. A particularly significant change is for patients with moderate RA, where a strategy that incorporates patients becoming severe and then receiving bDMARDs has been added.

Table 42: Treatment sequences for a cDMARD-IR population with severe RA who can tolerate MTX

	SAR+MTX	**TCZ IV + MTX**	**TCZ SC + MTX**	**TNFi bundle + MTX**	**ABT SC + MTX**
1	SAR + MTX	TCZ IV + MTX	TCZ SC + MTX	TNFi bundle + MTX	ABT SC + MTX
2	RTX + MTX	RTX + MTX	RTX + MTX	RTX + MTX	RTX + MTX
3	MTX	MTX	MTX	TCZ IV + MTX	TCZ IV + MTX
4	BSC	BSC	BSC	MTX	MTX
5				BSC	BSC

ABT, abatacept; BSC, best supportive care; MTX, methotrexate; RTX, rituximab; SAR, sarilumab; TCZ, tocilizumab; IV, intravenous; SC, subcutaneous; TNFi, tumour necrosis factors inhibitor

Table 43: Treatment sequences for a cDMARD-IR population with severe RA who cannot tolerate MTX

	SAR	**TCZ IV**	**TCZ SC**	**TNFi bundle**
1	SAR	TCZ IV	TCZ SC	TNFi bundle
2	TNFi bundle	TNFi bundle	TNFi bundle	TNFi bundle
3	SSZ	SSZ	SSZ	SSZ
4	BSC	BSC	BSC	BSC

BSC, best supportive care; SAR, sarilumab; SSZ, sulfasalazine; TCZ, tocilizumab; IV, intravenous; SC, subcutaneous; TNFi, tumour necrosis factors inhibitor

Table 44: Treatment sequences for a TNFi-IR population with severe RA who can tolerate RTX and MTX

	SAR	**RTX**	**SAR,TCZ**	**RTX,TCZ**
1	SAR + MTX	RTX + MTX	SAR + MTX	RTX + MTX
2	MTX	MTX	TCZ IV + MTX	TCZ IV + MTX
3	BSC	BSC	MTX	MTX
4			BSC	BSC

BSC, best supportive care; MTX, methotrexate; RTX, rituximab; SAR, sarilumab; TCZ IV, intravenous tocilizumab; TNFi, Tumour necrosis factors inhibitor

Table 45: Treatment sequences for a TNFi-IR population with severe RA for whom RTX is not an option

	SAR + MTX	TCZ IV + MTX	TCZ SC + MTX	TNFi bundle + MTX	ABT SC + MTX
1	SAR + MTX	TCZ IV + MTX	TCZ SC + MTX	TNFi bundle + MTX	ABT SC + MTX
2	MTX	MTX	ABT SC + MTX*	TCZ IV + MTX*	TCZ IV + MTX*
3	BSC	BSC	MTX	MTX	MTX
4			BSC	BSC	BSC

ABT, abatacept ; BSC, best supportive care; MTX, methotrexate; SAR, sarilumab; TCZ, tocilizumab; IV, intravenous; SC, subcutaneous; TNFi, tumour necrosis factors inhibitor
*Erroneously included in the sequences requested by the ERG and in the analyses presented by the company in their clarification response but excluded from the ERG's exploratory analyses.

Table 46: Treatment sequences for a TNFi-IR population with severe RA who cannot tolerate MTX

	SAR	TNFi bundle
1	SAR	TNFi bundle
2	SSZ	SSZ
3	BSC	BSC

BSC, best supportive care; SAR, sarilumab; SSZ, sulfasalazine; TCZ, tocilizumab; TNFi, tumour necrosis factors inhibitor

Table 47: Treatment sequences for a TNFi-IR population with severe RA who have already received RTX + MTX

	SAR + MTX	TCZ IV + MTX	TCZ SC + MTX
1	SAR + MTX	TCZ IV + MTX	TCZ SC + MTX
2	MTX	MTX	MTX
3	BSC	BSC	BSC

BSC, best supportive care; MTX: methotrexate; SAR, sarilumab; TCZ, tocilizumab; IV, intravenous; SC, subcutaneous

Table 48: Treatment sequences for the cDMARD-IR population with moderate RA

	Moderate sequences	
	SAR + MTX	**MTX**
1	SAR + MTX	MTX
2	MTX	BSC
3	BSC	
	Severe sequences	
1	TNFi bundle + MTX	
2	RTX + MTX	
3	TCZ IV + MTX	
4	SSZ*	
5	BSC	

BSC, best supportive care; MTX, methotrexate; RTX, rituximab; SAR, sarilumab; SSZ, sulfasalazine; TCZ IV, intravenous tocilizumab; TNFi, tumour necrosis factors inhibitor

*The ERG notes that MTX could replace SSZ in this position

5.2.4 Perspective, time horizon and discounting

The model takes the perspective of the NHS and PSS. The time horizon is 100 years, which is assumed to be representative of a lifetime horizon. All costs and benefits were discounted at 3.5% per annum in line with the NICE Reference Case.[156]

5.2.5 Model structure

The company used a Markov model approach which differed from the discrete event simulation (DES) method used by the AG in TA375.[25] A Markov model requires the definition of time cycles and half-cycle correction. The company selected cycle lengths of six months to "*mirror the frequent of treatment decisions in the UK as per NICE guidance*". The ERG comments that a DES approach is more appropriate than a Markov approach, as fixed time cycles have limitations when costs are not apportioned equally through the cycle, for instance when 3 months' of intervention may be provided on day 1 of the cycle, and when patients discontinue treatment during a cycle which misaligns all subsequent six-month response periods.

The model structure presented by the company is reproduced in Figure 8 with a flow schematic shown in Figure 9.

Figure 8: Model structure presented by the company (reproduced from Figure 5.4 of the CS)

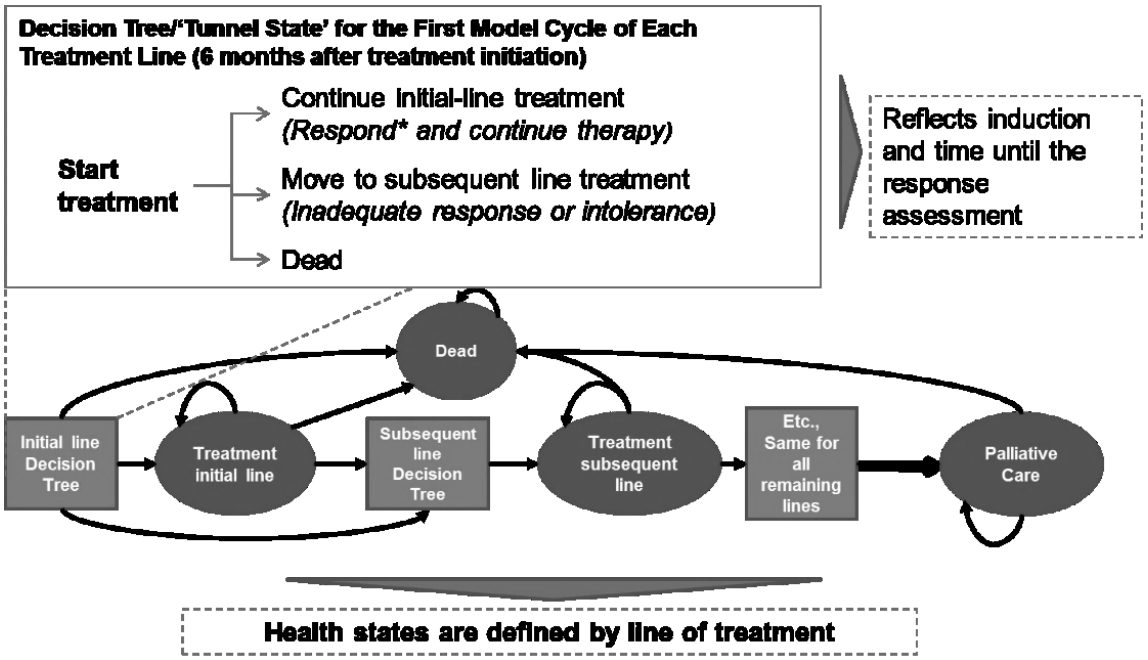
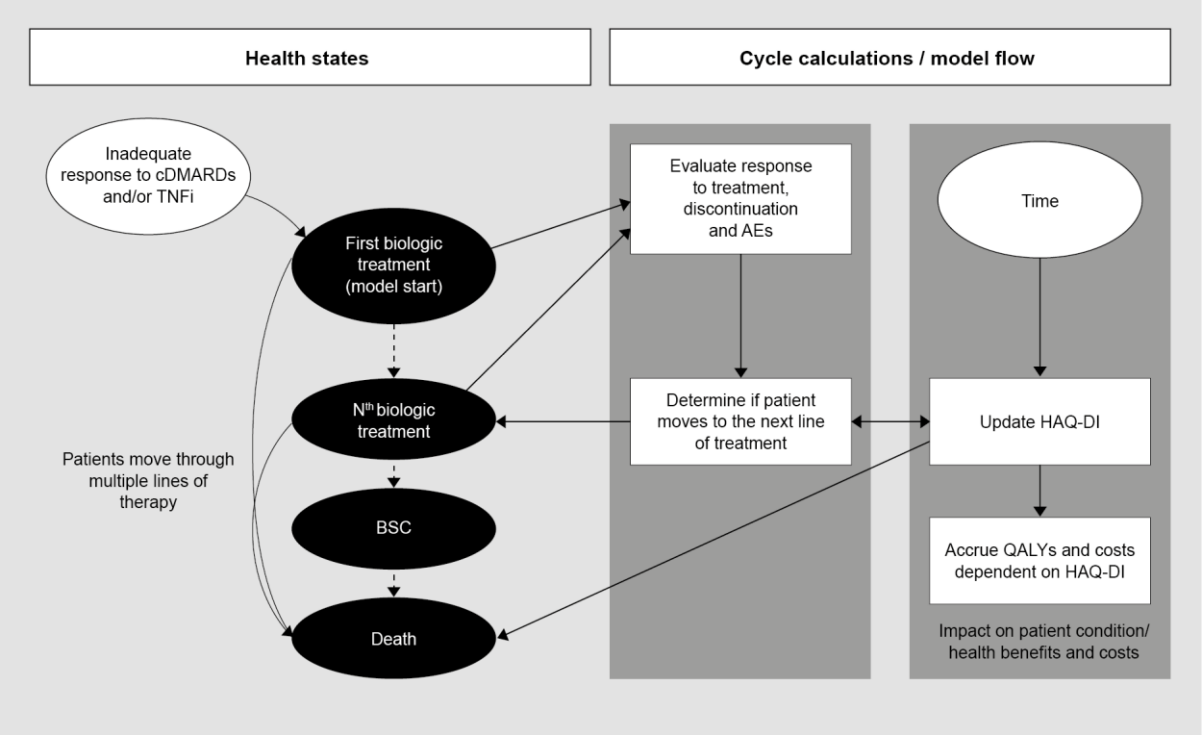


Figure 9: Model flow schematic presented by the company (reproduced from Figure 5.5 of the CS)



BSC=best supportive care; HAQ-DI=Health Assessment Questionnaire Disability Index; TNFi=tumour necrosis factor inhibitor

Within the model a clinical response in terms of EULAR (good, moderate or none) is estimated at six months. Patients who experience either a good or a moderate EULAR response remain on treatment; those who experience no response have their treatment withdrawn and move on to the next treatment in the sequence, unless the patient was already receiving BSC. Throughout the model, the costs incurred and the utility of the patient were assumed to be related to HAQ score.

5.2.6 Treatment effectiveness, extrapolation and discontinuation

The company estimated the probabilities of EULAR responses for SAR and competitors by initially undertaking an NMA of ACR responses, applying odds ratios for each intervention to predicted ACR responses on cDMARD to obtain estimated absolute ACR responses for each intervention. The ACR responses were then transformed to EULAR responses using a simple mapping that was used by the AG in TA375 based on data within the Veteran's Affairs Rheumatoid Arthritis (VARA) registry. The ERG comments that this mapping was not particularly robust due to small sample sizes (for example, only two patients had an ACR70 response in the VARA registry, one of whom had a moderate EULAR response and one who had a good EULAR response). The mapping was used in TA375 with the sole purpose of providing a secondary validation to the ICERs generated when using EULAR data directly. In TA375 the ICERs were fairly consistent regardless of whether the direct EULAR data, or ACR mapped to EULAR data were used.

The absolute EULAR responses estimated by the company are reproduced in

Table **49** for cDMARD-IR patients, in Table 50 for cDMARD-IR patients who cannot receive MTX and in Table 51 for patients who are TNFi-IR. The company acknowledged the lack of evidence for TNFi-IR patients who cannot receive MTX and justified its assumption that the estimates for this population would be equal to those of combination therapies in TNFi-IR patients. The ERG notes that MTX alone, or alternative cDMARDs for those who cannot receive MTX have not been included in these efficacy tables, as cDMARDs not in combination with bDMARDs were excluded from the sequences evaluated.

[redacted]

Table 49: Absolute EULAR responses estimated by the company in cDMARD-IR patients

Intervention	At least moderate EULAR response, % (95% CI)	Good EULAR response, % (95% CI)
SAR + MTX	[redacted]	[redacted]
TNFi bundle + MTX	[redacted]	[redacted]
TCZ (IV) + MTX	[redacted]	[redacted]
TCZ (SC) + MTX	[redacted]	[redacted]
ABT (SC) + MTX	[redacted]	[redacted]

ABT= abatacept; CI=confidence interval; EULAR= European League Against Rheumatism; IV=intravenous; MTX=methotrexate; TNFi=Tumour Necrosis Alpha inhibitor; SAR=sarilumab; SC=subcutaneous; TCZ=tocilizumab;

Table 50: Absolute EULAR responses estimated by the company in cDMARD-IR patients who cannot receive MTX

Intervention	At least moderate EULAR response, % (95% CI)	Good EULAR response, % (95% CI)
SAR	[redacted]	[redacted]
TNFi bundle	[redacted]	[redacted]
TCZ (IV)	[redacted]	[redacted]
TCZ (SC)	[redacted]	[redacted]

CI=confidence interval; EULAR= European League Against Rheumatism; TNFi=Tumour Necrosis Alpha inhibitor; IV=intravenous; SAR=sarilumab; SC=subcutaneous; TCZ=tocilizumab;

Table 51: Absolute EULAR responses estimated by the company in TNFi-IR patients

Intervention	At least moderate EULAR response, % (95% CI)	Good EULAR response, % (95% CI)
SAR	[redacted]	[redacted]
TNFi bundle + MTX	[redacted]	[redacted]
TCZ (IV) + MTX	[redacted]	[redacted]
TCZ (SC) + MTX	[redacted]	[redacted]
ABT (SC) + MTX	[redacted]	[redacted]
RTX (IV) + MTX	[redacted]	[redacted]

ABT= abatacept; CI=confidence interval; EULAR= European League Against Rheumatism; TNFi=Tumour Necrosis Alpha inhibitor; IV=intravenous; MTX=methotrexate; RTX= rituximab; SAR=sarilumab; SC=subcutaneous; TCZ=tocilizumab;

HAQ improvement upon treatment response

After six months, patients are assumed to be assessed for response. Patients who achieved a moderate or good EULAR response were assumed to have an associated reduction in HAQ score which is assumed independent of treatment. This value was taken from MOBILITY-B[33] and is reproduced in Table 52. The ERG notes that these values are percentage reductions, whereas fixed reductions in HAQ score conditional on EULAR response were used by the AG in TA375.[25] Following the clarification

round,[31] the company provided results using the values in TA375: these were reductions of 0.672 for patients who experienced a good EULAR response, and 0.317 for patients who experienced a moderate EULAR response.

Table 52: Changes in HAQ score conditional on EULAR response

	Original company submission	Post clarification
Treatment response	**% change in HAQ score (95% CI)**	**Change in HAQ score**
EULAR— No response	−7.17% (−15.98%, 1.63%)	0
EULAR—Moderate response	−22.63% (−28.27%, −16.99%)	-0.317
EULAR—Good response	−47.28% (−55.70%, −38.86%)	-0.672

CI=confidence interval; EULAR= European League Against Rheumatism

HAQ trajectory following initial response

In the base case, patients on bDMARD treatment are assumed to have zero HAQ progression in line with assumptions made in the AG model for TA375.[25] Supportive data were provided for the assumption for SAR using data from EXTEND,[42] an open-label study which recruited people from the MOBILITY B[33] and TARGET[34] RCTs. The company states that HAQ scores "*remained constant after the initial Week 24 improvement*" which the ERG acknowledges to appear to be correct. Further data from the BSRBR database and RHUMADATA, a large clinical database and registry in Canada, were presented to support the assumption of a constant HAQ score whilst on bDMARDs.

For patients on best supportive care, the company's base case assumes that HAQ scores progress at a rate of 0.06 per year; after clarification response,[31] the company assumed that the HAQ score of patients on cDMARDs would progress at a rate of 0.045 per year. The ERG believes that these analyses are inappropriate as HAQ progression has been proven to be non-linear[30] with the Appraisal Committee in TA375 in favour of a non-linear approach advocated by the AG.[25] This method used a modified version of the latent class approach of Norton *et al*., [161] which identifies four classes of HAQ trajectory: low, moderate, high and severe. Norton *et al*. report a regression model to calculate each patient's probability of belonging to each class based on the patient's baseline characteristics. The ERG comments that the linear method is not likely to significantly affect the conclusions in the comparison of SAR with bDMARDs, due to similar efficacy levels as shown in Section 4.4, but could have a significant effect, favourable to SAR, when the comparator is cDMARDs.

Adjustments to HAQ scores to consider initiation and discontinuation of treatments

In order to take into account the gradual improvement in HAQ score upon treatment initiation and the gradual deterioration in HAQ score prior to discontinuation the company adjust the HAQ score in the first and last cycle of a treatment. In both cases, the HAQ score in the cycle is calculated as the average

of two values: the HAQ score prior to treatment and the HAQ score following response for the initiation cycle; and the HAQ score following response and the HAQ score on treatment discontinuation. As the model assumes that HAQ score remains constant on bDMARDs, this means that the value is equal in both amended time cycles. The ERG believes that this adjustment is reasonable.

After applying changes to HAQ scores, the resulting values were rounded in the original CS to the nearest valid HAQ score (which is a multiple of 0.125). The ERG notes that this approach can lead to inaccurate results and contrasts with the approach used in TA375[25] where scores are rounded to either the higher or the lower valid HAQ score with a probability proportional to their distance to each (e.g. a value twice closer to the upper HAQ score would be twice as likely to be simulated as the upper score than simulated as the lower score). Following the clarification process,[31] the company provided results using the method employed in TA375 rather than the original method.

Treatment duration

Patients who fail to achieve moderate or good EULAR response at 6 months discontinue the current treatment and start the next treatment in the sequence. In contrast, patients who achieve moderate or good EULAR response stay on treatment until loss of efficacy. The company estimate time to treatment discontinuation from RHUMADATA and used the method employed by the AG in TA375 in a sensitivity analysis. The CS states that they have used RHUMADATA because "*it takes into account differences in retention among different classes of therapy*" and can therefore allow a time to discontinuation to be estimated for different types of bDMARDs (TNFi; IL-6; and other modes of action). These data (post amendments for typographical errors) are reproduced in *** [redacted] 10 along with the curve fits.

[redacted]

In the clarification process, the ERG asked the company to use a generalised gamma distribution. The company presented analyses in their clarification response[31] using the generalised gamma where the key conclusions did not change. However, the company's approach does not model discontinuation conditional on EULAR response, which is captured in the AG method used in TA375. The ERG is satisfied that the company have presented results also using the approach proposed by the AG in TA375 in their sensitivity analyses.

[redacted] 10 [redacted]

5.2.7 Mortality

The company applied the mortality ratios per HAQ score at baseline used in TA375[25] to the life tables from the Office for National Statistics (ONS).[162] The company adopted the assumption that only baseline HAQ score, and not changes to the HAQ, affected mortality, as was the case in the AG's model in TA375.[25] This implies that the life expectancy of patients is independent of the treatment option. The CS states that this "*is considered to be a conservative approach because it does not acknowledge mortality benefits for improvements in disease severity*."

5.2.8 Health-related quality of life

The literature review detailed in Section 5.1 was used to inform health-related quality of life (HRQoL) values for patients with RA. The CS reports that the studies identified were contained in Appendix 16. The ERG, however, comments that key papers or reports appear not to have been identified, such as Hernandez *et al.*, which estimates EQ-5D based on patient characteristics (HAQ score, pain on a visual analogue scale, age and sex),[158] and Stevenson *et al*.,[24] which reviewed and critiqued the mapping of HAQ to utility undertaken in the companies' submissions for TA375. The CS comments that "*During early development of the model, the method used in TA375 was considered. However, in the Advisory Board, expert clinical opinion noted that it may double count the effects of pain since the HAQ-DI assessment already includes pain*" which resulted in the mapping of Malottki et al.[157] being used in the base case of the company submission. The ERG does not agree with the views of the company's expert clinical advisors, but notes that the company did use the method proposed by the AG in TA375, and accepted by the appraisal committee in sensitivity analyses, alongside a mapping reported by Bansback *et al*.[159] Following the clarification process, the company have used the mapping of Hernandez *et al.*[158]

In addition to HAQ-related utility, the company considered the impacts of serious infections on HRQoL. The rates of serious infections for SAR and BSC were taken from the pivotal studies: MOBILITY-B[33] for cDMARD-IR patients who could receive MTX (4.0% and 2.3% per cycle respectively); MONARCH[35] for cDMARD-IR patients who could not receive MTX (1.1% and 2.3% per cycle respectively); and TARGET[34] for the remaining patients (1.1% and 1.1% per cycle respectively). The company assumed that the rates for SAR were applicable to other bDMARDs. Within sensitivity analyses, the company employed the rates used in the AG model in TA375 (3.5% per cycle for bDMARDs and 2.6% for cDMARDs in cDMARD-IR patients). TA375 did not consider TNFi-IR patients and the company have assumed this population to have a rate of zero serious infections. The ERG believes that the use of rates equivalent to those for cDMARD-IR patients would have reflected a more reasonable assumption. Further the ERG notes that the method used by the AG in TA375 assumed only one serious infection per intervention and used the difference in incidences reported by Singh *et al.*[163] (35 per 1000 patient years on bDMARDs and 26 per 1000 patient years on cDMARDs) to calculate

the relative effect of bDMARDs. As the level of serious infections was shown not to be a key driver of the ICER in TA375, the impact related to the limitations of the company's approach will be minimal.

QALYs losses due to serious infections were stated to have been estimated based on the method used in the AG model for TA375 whereby serious infections were assumed to be of 28 days' duration and incur a disutility of 0.156, both taken from Oppong *et al*.[164] The company have translated this into a QALY loss of 0.024 per cycle.

5.2.9 Resources and costs

The company used the literature review previously described to identify economic evaluations with that deemed most appropriate selected. The company's model includes costs associated with drug acquisition, drug administration and monitoring, hospitalisation and serious infections. A detailed estimate of the price of each intervention is provided in Table 53.

There is a PAS for CTZ that provides the first 12 weeks of treatment free of charge; this was incorporated into the first year's acquisition costs. The PAS for GOL, where 100mg is provided at the same price of 50mg was also incorporated. The confidential PAS for ABT and TCZ were not excluded, as recommended by NICE, but were assumed to be equal to 15%. The ERG comments that this is not appropriate and such exploratory analyses should not be included in the base case. The ERG notes that biosimilars are available for both RTX and ADA and that these have not been included in the company's analyses.

Table 53: Drug acquisition costs

Drug	Package	Cost	Indicative annual cost (1st year)
SAR	200mg syringe x 1	[redacted]	[redacted]
ABT	125mg syringe x 4	£1,209.40[a]	£15,776
	250mg vial x 1	£302.40[a]	£11,834 (£12,741) ‡
GOL	50mg syringe x 1	£762.97[a]	£9,156*
	100mg syringe x 1	£1,525.94[a]*	
ETN	50mg syringe x 4	£715.00[a]	£9,327
	25mg syringe x 4	£357.50[a]	
ETNb	50mg syringe x 4	£656.00[a]	£8,557
ADA	40mg syringe x 2	£704.28[a]	£9,187
RTX	500mg vial x 1	£873.15[a]	£4,657
	100mg vial x 2	£349.25[a]	
CTZ	200mg syringe x 2	£715.00[a]**	£9,327 (£6,824)
TCZ IV	80mg vial x 1	£102.40[a]	£10,018 ‡

	200mg vial x 1	£256.00[a]	
	400mg vial x 1	£512.00 [a]	
TCZ SC	162mg x 4	£913.12[a]	£11,911
IFX	100mg vial x 1	£419.62[a]	£8,211 (£9,784) ‡
IFXb[165]	100mg vial x 1	£377.66[a]	£7,390 (£8,806) ‡
MTX[†]	2.5mg tablet x 28	£1.79 [a]	£42
	10mg tablet x 100	£37.89 [a]	

[¥]Sanofi Genzyme PASLU Application, [a]http://www.mims.co.uk/, , *PAS makes 100mg dose available at same price as 50mg dose applied in all analysis, **12 weeks free PAS applied in all analysis, [†]Adjuvant therapy added to all bDMARDs in combination analyses. ‡based on a weight of 74.3 Kg
ABT: abatacept; TCZ: tocilizumab; ADA: adalimumab; CTZ: certolizumab pegol; ETN: etanercept; ETNb: etanercept biosimilar; GOL: golimumab; IFX: infliximab; IFXb: infliximab biosimilar; RTX: rituximab; MTX: methotrexate;

The cost of the TNFi bundle was calculated using a weighted average of the individual agents informed by market share provided in Table 41. The retreatment interval for RTX was assumed to be 9 months and the cost of a RTX biosimilar has not been incorporated. BSC was costed at £360 per 6 months, and for the PSA the company put uncertainty on this value with an assumption that the standard error was 20% of the mean value. The company's base case assumes vial wastage with a sensitivity analysis exploring the impact of vial sharing.

Administration costs were based on TA375[166] and were inflated to 2015/16 prices using the hospital & community health services (HCHS) index in the PSSRU report.{Personal Social Services Research Unit, 2015 #31} This resulted in estimated costs of infusion of £170 and costs of a nurse visit (required by 10% of patients receiving a SC injection) of £77. The company states that this may be an overestimation "*since Sanofi Genzyme provides and funds a homecare service for sarilumab patients at no cost to the NHS. This is thought to be similar to comparator product manufacturers with SC bDMARDs therefore minimal impact is expected on the results.*" The ERG notes that in TA375, the time required by a district nurse was 30 minutes rather than the hour assumed by the company, although the ERG agrees that this limitation will have no impact on the conclusions.

Monitoring costs were also based on TA375[166] and included full blood count, erythrocyte sedimentation rate (ESR), biochemical profile, and chest x-ray prior to treatment with the addition of lipid profiles for TCZ and SAR. Full blood counts, biochemical profile and lipid profiles for TCZ and SAR were assumed to occur ten times in the first six months, and monthly thereafter. After the initial six months, monthly monitoring costs were assumed to be low: £7 for SAR and TCZ and £5 for all other bDMARDs although all interventions were associated with a monthly outpatient attendance assumed to cost £143 per visit, based on NHS Reference Costs.[167]

Hospitalisation costs were based on those within the AG's model in TA375,[166] inflated to 2015/2016 prices. In these estimates, hospitalisation costs were dependent on HAQ score band and were calculated

based on data from the NOAR database on inpatient days, joint replacements and NHS Reference Costs. The costs used in the model are provided in Table 54.

Table 54: Annual hospitalisation costs used in the company's model

HAQ-DI score	Annual costs
(0 - 0.5]	£180
(0.5 - 1.0]	£110
(1.0 - 1.5]	£391
(1.5 - 2.0]	£562
(2.0 - 2.5]	£1,338
(2.5 - 3.0]	£2,885

The cost per serious infection was assumed to be that used in the AG model for TA375[166] (£1479); this was uplifted to 2014/15 prices resulting in a cost of £1588 per episode.

5.2.10 Methods of the analysis

The company undertook analyses on the following groups:

- cDMARD-IR patients with severe RA who can tolerate MTX (CS denoted A1);
- cDMARD-IR patients with severe RA who cannot tolerate MTX (CS denoted B);
- TNFi-IR patients with severe RA who can tolerate RTX and MTX (CS denoted C2);
- TNFi-IR patients with severe RA who cannot tolerate RTX (CS denoted C1);
- TNFi-IR patients with severe RA who cannot tolerate MTX (CS denoted C3);
- TNFi-IR patients who have received RTX and MTX (CS denoted C4); and
- cDMARD-IR patients with moderate RA and DAS28 between 4.0 and 5.1 who can tolerate MTX (CS denoted A2).

The company used baseline characteristics of patients from the SAR trials for the patients simulated in the model. Instead of sampling with replacement from the patient pool, the model simulated each patient once in what the company called a replication. The deterministic results in the base case were produced by running enough replications to exceed 5,000 simulations. The company ran the model using a wide range of patient numbers and concluded that 5,000 patients provided the best trade-off between stability of the results and computation time. For sensitivity analyses, the number of replications for each patient was set so that the number of simulations was approximately 1,000. The company stated that this number of simulation provides a level of stability of results that ensures that the effect of changes in model parameters can be properly examined. Graphs and standard errors were presented to support the company's conclusion. The model generated a pool of random numbers that were used across sequences to alleviate differences stemming from Monte Carlo sampling error.

The company presented results of the probabilistic sensitivity analyses (PSA) in the CS for cDMARD-IR patients with severe RA who could tolerate MTX, for cDMARD-IR patients with severe RA for whom MTX was contraindicated or not tolerated, and for TNFi-IR RTX-ineligible patients. In the clarification response,[31] the company only presented results for the PSA for the cDMARD-IR patients with severe RA who could tolerate MTX. The company determined the number of PSA simulations required to obtain stable results analysing the convergence of mean incremental net benefit (INB) of SAR versus TCZ using the population from the TARGET trial. The company concluded that convergence occurs after approximately 200 runs and used 300 simulations in the PSA. Originally, independent draws from distributions were used for the probabilities of ACR response. However, at the ERG's request in the clarification letter,[31] draws from the joint posterior distribution (i.e. CODA) of the NMA were used instead.

5.2.11 Cost effectiveness results

The company presented results for their analyses in the CS, in which SAR+MTX was estimated to either dominate its comparators, result in ICERs lower than £20,000 per QALY gained or in cost savings per QALY lost higher than £60,000 in all populations except in cDMARD-IR patients with moderate RA and a DAS28 score higher than 4.0 and the TNFi-IR patients for whom RTX was an option. The ICER for SAR+MTX compared with BSC was estimated to be £22,275 per QALY gained in cDMARD-IR patients with moderate RA and a DAS28 score higher than 4.0. In TNFi-IR patients SAR+MTX compared with RTX+MTX results in an ICER of £104,012 per QALY gained.

However, the ERG identified as part of its initial assessment a series of issues in the company's analyses, described in Section **Error! Reference source not found.**, and asked the company in the clarification letter to provide analyses which addressed these problems. The ERG believes that these analyses better reflect the revised company's base case even if the company might disagree with some of the assumptions preferred by the ERG, such as the choice of the survival curve for time to treatment discontinuation. Therefore, the results presented below are the ones included in the company's clarification response.[31]

5.2.11.1 cDMARD-IR patients with severe RA who can tolerate MTX

Table **55** and Table 56 present the results for cDMARD-IR patients with severe RA who can tolerate MTX using the deterministic and probabilistic versions of the model respectively. SAR+MTX dominated both indications of TCZ both in the probabilistic and deterministic analyses. The ICERs of

ABT (SC)+MTX and TNFi bundle + MTX compared with SAR+MTX were higher than £69,199 per QALY gained in both analyses.

Table 55: Results for cDMARD-IR patients with severe RA who can tolerate MTX (deterministic)

Sequences*	Total QALYs	Total costs	Incr. QALYs	Incr. costs	ICER (per QALY)	ICER vs SAR (per QALY)
TCZ (SC) + MTX#	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
TCZ (IV) + MTX#	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
SAR + MTX	[redacted]	[redacted]	-	-	-	-
TNFi bundle + MTX	[redacted]	[redacted]	[redacted]	[redacted]	£79,199	£79,199
ABT (SC) + MTX#	[redacted]	[redacted]	[redacted]	[redacted]	£206,188	£126,110†

ABT: abatacept; MTX: methotrexate; TCZ: tocilizumab; TNFi: tumour alpha necrosis inhibitor; SAR: sarilumab; IV: intravenous; SC: subcutaneous
*Sequences as defined in Table 42
#Does not include confidential PAS
†Approximate ICER calculated by the ERG based on incrementals

The results of the PSA (see Table 56) were very similar to those of the deterministic analysis and the ranking of the treatments by effectiveness remained the same. Figure 1 of the company's clarification response[31] showed that the probability of SAR + MTX being cost-effective at willingness-to-pay (WTP) thresholds of £20,000 and £30,000 per QALY was close to 1.0.

Table 56: Results for cDMARD-IR patients with severe RA who can tolerate MTX (probabilistic)

Sequences*	Total QALYs	Total costs	Incr. QALYs	Incr. costs	ICER (per QALY)	ICER vs SAR (per QALY)
TCZ (SC) + MTX#	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
TCZ (IV) + MTX#	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
SAR + MTX	[redacted]	[redacted]	-	-	-	-
TNFi bundle + MTX	[redacted]	[redacted]	[redacted]	[redacted]	£69,884	£69,884
ABT (SC) + MTX#	[redacted]	[redacted]	[redacted]	[redacted]	£203,809	£117,482†

ABT: abatacept; MTX: methotrexate; TCZ: tocilizumab; TNFi: tumour alpha necrosis inhibitor; SAR: sarilumab; IV: intravenous; SC: subcutaneous
*Sequences as defined in Table 42
#Does not include confidential PAS
†Approximate ICER calculated by the ERG based on incrementals

5.2.11.2 cDMARD-IR patients with severe RA for whom MTX is contraindicated or not tolerated

In cDMARD-IR patients with severe RA for whom MTX is contraindicated or not tolerated, SAR monotherapy resulted in an ICER of £17,123 per QALY gained compared with the TNFi bundle and the ICERs for both indications of TCZ monotherapies compared with SAR monotherapy were higher than £1,000,000 per QALY gained (see Table 57).

Table 57: Results for cDMARD-IR patients with severe RA for whom MTX is contraindicated or not tolerated (deterministic)

Sequences*	Total QALYs	Total costs	Incr. QALYs	Incr. costs	ICER (per QALY)	ICER vs SAR (per QALY)
TNFi bundle	[redacted]	[redacted]	[redacted]	[redacted]	-	£17,123‡
SAR	[redacted]	[redacted]	[redacted]	[redacted]	£17,123	-
TCZ (SC) [#]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	£2,596,000†
TCZ (IV) [#]	[redacted]	[redacted]	[redacted]	[redacted]	£1,578,976	£1,578,976

TCZ: tocilizumab; TNFi: tumour alpha necrosis inhibitor; SAR: sarilumab; IV: intravenous; SC: subcutaneous
*Sequences as defined in Table 43
[#]Does not include confidential PAS
†Approximate ICER calculated by the ERG based on incrementals
‡ICER in the south western quadrant representing cost savings per QALY lost

5.2.11.3 TNFi-IR patients with severe RA who can tolerate RTX and MTX

In TNFi-IR patients with severe RA who can tolerate RTX and MTX, the ICER for a sequence of SAR+MTX followed by TCZ+MTX (SAR,TCZ) compared with the currently recommended sequence (RTX,TCZ) was estimated to be £130,691 per QALY gained (see Table 58). A sequence including only SAR+MTX as biologic therapy was extendedly dominated by a sequence having only RTX + MTX and by the currently recommended sequence (RTX,TCZ).

Table 58: Results for TNFi-IR patients with severe RA who can tolerate RTX and MTX (deterministic)

Sequences*	Total QALYs	Total costs	Incr. QALYs	Incr. costs	ICER (per QALY)
RTX	[redacted]	[redacted]	-	-	-
SAR	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated
RTX,TCZ‡#	[redacted]	[redacted]	[redacted]	[redacted]	£39,994
SAR,TCZ#	[redacted]	[redacted]	[redacted]	[redacted]	£130,691

RTX: rituximab; SAR: sarilumab;
*Sequences as defined in Table 44
#Does not include confidential PAS for TCZ
†Approximate ICER calculated by the ERG based on incrementals
‡Currently recommended sequence

5.2.11.4 TNFi-IR patients with severe RA for whom RTX is not an option

As shown in Table 59, in TNFi-IR patients with severe RA for whom RTX is not an option, the ICERs for all comparators versus SAR+MTX were higher than £60,000 per QALY gained.

Table 59: Results for TNFi-IR patients with severe RA for whom RTX is not an option (deterministic)

Sequences*	Total QALYs	Total costs	Incr. QALYs	Incr. costs	ICER (per QALY)	ICER vs SAR (per QALY)
SAR + MTX	[redacted]	[redacted]	-	-	-	
TCZ (IV) + MTX#	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	£141,995†
TNFi Bundle + MTX	[redacted]	[redacted]	[redacted]	[redacted]	£64,602	£64,602
ABT (SC) + MTX#	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	£80,889†
TCZ (SC) + MTX#	[redacted]	[redacted]	[redacted]	[redacted]	£69,306	£69,306

ABT: abatacept; MTX: methotrexate; TCZ: tocilizumab; TNFi: tumour alpha necrosis inhibitor; SAR: sarilumab; IV: intravenous; SC: subcutaneous
*Sequences as defined in Table 45
#Does not include confidential PAS
†Approximate ICER calculated by the ERG based on incrementals

5.2.11.5 TNFi-IR patients with severe RA for whom MTX is contraindicated or not tolerated

In TNFi-IR patients with severe RA for whom MTX is contraindicated or not tolerated, SAR monotherapy compared with the TNFi bundle was estimated to result in an ICER of £17,794 per QALY gained (see Table 60).

Table 60: Results for TNFi-IR patients with severe RA for whom MTX is contraindicated or not tolerated (deterministic)

Sequences*	Total QALYs	Total costs	Incr. QALYs	Incr. costs	ICER (per QALY)
TNFi Bundle	[redacted]	[redacted]	-	-	-
SAR	[redacted]	[redacted]	[redacted]	[redacted]	£17,794

TNFi: tumour alpha necrosis inhibitor; SAR: sarilumab;
*Sequences as defined in Table 46
†Approximate ICER calculated by the ERG based on incrementals

5.2.11.6 TNFi-IR patients who have received RTX + MTX

As shown in Table 61, the ICER for TCZ (IV) + MTX and TCZ (SC) + MTX compared with SAR + MTX was estimated to be £141,995 and £133,548 respectively in TNFi-IR patients after receiving RTX + MTX.

Table 61: Results for TNFi-IR patients who have received RTX + MTX (deterministic)

Sequences*	Total QALYs	Total costs	Incr. QALYs	Incr. costs	ICER (per QALY)	ICER vs SAR +MTX (per QALY)
SAR + MTX	[redacted]	[redacted]	[redacted]	[redacted]	-	
TCZ (IV) + MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	£141,995†
TCZ (SC) + MTX	[redacted]	[redacted]	[redacted]	[redacted]	£133,548	£133,548

ABT: abatacept; MTX: methotrexate; TCZ: tocilizumab; TNFi: tumour alpha necrosis inhibitor; SAR: sarilumab; IV: intravenous; SC: subcutaneous
*Sequences as defined in Table 47
#Does not include confidential PAS
†Approximate ICER calculated by the ERG based on incrementals

5.2.11.7 cDMARD-IR patients with moderate RA (DAS28 between 4.0 and 5.1) who can tolerate MTX

In cDMARD-IR patients with moderate RA (DAS28 between 4.0 and 5.1) who can tolerate MTX, the ICER for SAR+MTX compared with MTX was estimated to be £38,254 per QALY gained (see Table 62).

Table 62: Results for cDMARD-IR patients with moderate RA (DAS28 between 4.0 and 5.1) who can tolerate MTX (deterministic)

Sequences*#	Total QALYs	Total costs	Incr. QALYs	Incr. costs	ICER (£/QALY)
MTX	[redacted]	[redacted]	[redacted]	[redacted]	-
SAR + MTX	[redacted]	[redacted]	[redacted]	[redacted]	£38,254

ABT: abatacept; MTX: methotrexate; TCZ: tocilizumab; TNFi: tumour alpha necrosis inhibitor; SAR: sarilumab; IV: intravenous; SC: subcutaneous
*Sequences as defined in Table 48
#Does not include confidential PAS of TCZ

5.2.12 Model validation and face validity check

The ERG adopted a number of approaches to explore, interrogate and critically appraise the company's submitted economic evaluation and the underlying health economic model upon which this was based. These approaches included:

- Consideration of key items contained within published economic evaluation and health economic modelling checklists to critically appraise the company's model and analysis.[157, 168, 169]
- Scrutiny of the company's model by health economic modellers including:
  - White-box validation: checking of inputs, code and formulae
  - Black-box testing: changing inputs to check whether the output matches expectations
  - Face-validity testing: checking model results match expectations
  - Comparison of deterministic and probabilistic ICERs.
- Replication of the base case results, PSA and scenario analysis presented within the CS.[170]
- Where possible, checking parameter values used in the company's model against the original data sources.
- Examination of concordance between the description of the model reported within the CS[170] and the company's executable model.
- The use of expert clinical input to judge the clinical robustness of the company's economic evaluation and of the assumptions underpinning the model.

5.3 Summary of key limitations identified within the critical appraisal

The main limitations identified within the ERG's initial critical appraisal of the company's economic analysis that were corrected by the company are the following:

1. Inadequate treatment sequences
2. Omission of the possibility of patients with moderate RA to progress to the severe state
3. Use of Malottki *et al.*[157] instead of Hernandez *et al.*[158] for the mapping of HAQ to EQ-5D
4. Limitations in the company's NMA

5.	Using percentages of improvement of HAQ instead of absolute mean changes
6.	Omission of rounding to the nearest valid HAQ score
7.	Use of an inappropriate time to treatment discontinuation
8.	Using independent samples from beta distributions for the probabilities of ACR responses in the PSA instead of correlated samples from the CODA of the NMA
9.	Using 9 free doses of CTZ instead of 10.
10.	Inclusion of a speculative PAS of 15% applied to TCZ and ABT.

Based on the new analyses presented by the company following the clarification round, the key remaining limitations are as follows:

1.	Linear progression of HAQ score for patients on cDMARDs and BSC
2.	Incorrect implementation of transition from moderate to severe RA
3.	Assuming same efficacy for monotherapies as for combination therapies in TNFi-IR patients
4.	Assuming same efficacy for second and third lines of bDMARDs

The issues identified by the ERG and corrected by the company in the revised model presented along the clarification responses are further explained below:

1. Inadequate treatment sequences

The sequences used by the company suffer mainly from two issues:

- The omission of one cDMARD treatment (MTX or SSZ) after biologics and before BSC.
- The inclusion of ABT+MTX after RTX+MTX in cDMARD-IR patients or after SAR+MTX in TNFi-IR patients who are RTX-eligible.

After clarification, the company provided analyses using the sequences requested by the ERG, which addressed these limitations.

2. Omission of the possibility of patients with moderate RA to progress to the severe state

The company's model assumed that patients with moderate RA and a DAS28 score higher than 4.0 would never progress to severe RA. The ERG acknowledges that the independent analysis by the AG in TA375[24] also omitted this possibility. However, the ERG believes that including the possible transition of these patients to the severe RA state and subsequently to the recommended treatment sequences for severe patients provides a more accurate representation of clinical practice. In their clarification response,[31] the company presented analyses where patients with moderate RA could progress to the severe state.

3. Use of Malottki et al.[157]*. instead of Hernandez et al.*[158] *for the mapping of HAQ to EQ-5D*

For their base case analysis, the company adopted the approach taken by Malottki *et al.*[157] to mapping HAQ scores to EQ-5D and used the approach proposed by Hernandez *et al.*[158] in a scenario analysis.

The company justified their choice referring to expert clinical opinion obtained during an advisory board, which noted that Hernandez *et al.*'s approach may double count the effects of pain since the HAQ-DI assessment already includes pain. The ERG disagrees with this view and notes that double counting is avoided by taking HAQ-DI and pain jointly into account. Most analyses previous to Hernandez *et al.*[158] had excluded pain. However, a substantially better estimate of EQ-5D is obtained by the inclusion of pain alongside HAQ than via HAQ alone, because HAQ and pain are not perfectly correlated.[158] It is therefore important to include pain as an explanatory variable in estimating EQ-5D.

4. Limitations with the company's NMA

The ERG identified a number of limitations in the NMA presented in the CS, such as the use of a fixed effect model, which have been described in Section 4.4. As requested by the ERG in its clarification letter, the company undertook an NMA addressing some of these limitations and presented economic analyses using its results.

5. Using percentages of improvement of HAQ instead of absolute mean changes

In the CS, the company applied improvements in the HAQ score upon response in terms of percentage of improvement instead of applying a fixed reduction. The ERG notes that this approach differs from that accepted by the AC in TA375 and that percentage improvement is prone to vary depending on the patient mix. The company adopted absolute HAQ score improvements upon response in the analyses presented in the clarification response.[31]

6. Omission of rounding to the nearest valid HAQ score

HAQ scores range from 0 to 3, with higher scores indicating greater disability. HAQ scores lie on a discrete scale with step values of 0.125, resulting in 25 points. In the model, patients start with a baseline HAQ score and the HAQ progression of patients is modified reflecting treatment response, loss of treatment efficacy or disease progression over time. Changes applied to the HAQ score are usually estimates based on average changes observed in trials or registries and therefore are rarely exact multiples of 0.125. Thus, after applying such a change, the resulting HAQ score of a patient has to be assigned to a valid HAQ score. However, the company did not round the values to the nearest valid HAQ score. The ERG requested that the company implement a stochastic rounding of HAQ scores analogous to that used by the AG in TA375[25] i.e. rounding up values a probability inversely proportional to the distance of the value to the closest valid HAQ score, and rounding down otherwise. For example, a change of 0.4 would have a 0.8 probability of being rounded down to 0.375 and a probability of 0.2 of being rounded up to 0.5. The company correctly implemented this stochastic HAQ rounding after clarification.

7. Use of an inappropriate time to treatment discontinuation

Patients who achieve moderate or good EULAR response stay on treatment until loss of efficacy. The company estimated time to treatment discontinuation by fitting different survival curves to time to treatment discontinuation data from RHUMADATA. The company chose the Gompertz distribution for their base case because it provided a good statistical fit (both Akaike Information Criterion [AIC] and Bayesian Information Criterion [BIC]) and a good visual fit. The ERG notes that the generalised gamma resulted in better AIC and BIC scores than the Gompertz in most of the curves. Following a request for clarification from the ERG, the company justified their preference for the Gompertz curve stating that towards the tail of the Kaplan-Meier curve, the generalised gamma under-predicted the proportion of patients still on treatment for the IL-6 class and the class grouping other mechanisms of action whilst the Gompertz provided a good visual fit for all treatment classes (see clarification response [31] -- question B4). The ERG notes that the estimates at the tail of the Kaplan-Meier are most uncertain [redacted]

Therefore, the ERG believes that the generalised gamma provides a more plausible extrapolation for time to treatment discontinuation. The company presented analyses using the generalised gamma curve for time to treatment discontinuation in their clarification responses.

8. Using independent samples from beta distributions for the probabilities of ACR responses in the PSA instead of correlated samples from the CODA of the NMA

Within the PSA, the company used independent samples from beta distributions to model the uncertainty around the ACR response rates. The ERG notes that this approach ignores the existing correlations. The ERG asked the company to provide analyses where samples from the CODA of the NMA were used instead, which the company did in their revised version of the model.

9. Using 9 free doses of CTZ instead of 10.

The company assumed that the PAS for CTZ comprised 9 free doses, instead of the 10 free doses established in the NICE guidance produced in TA375 and TA415. The company also varied the number of free doses for CTZ in the PSA, as if it were an uncertain value. The company adopted 10 free doses of CTZ and fixed the value in the PSA in the analyses presented in the clarification response.

10. Inclusion of a speculative PAS of 15% applied to TCZ and ABT.

The ERG notes that including a speculative PAS discount for TCZ and ABT is misleading and that NICE recommends the use of the list price in such cases. The ERG provides a confidential appendix which presents a set of analyses where the confidential PAS for TCZ and ABT have been included. The company removed the speculative PAS of 15% from the analyses presented in the clarification response.[31]

The company implemented these changes in their model and produced the results summarised in Section 5.2.11. The issues remaining in the revised version of the model and therefore in the analyses presented by the company in their clarification response[31] are further explained below:

1. Linear progression of HAQ score for patients on cDMARDs and BSC

The company applied a linear annual increase of 0.06 in HAQ score to BSC in the analyses presented in the CS. The ERG believes that these analyses are inappropriate as HAQ progression has been proven to be non-linear[30] with the Appraisal Committee in TA375 favouring the non-linear approach advocated by the AG.[25] The ERG comments that the linear method is not likely to significantly affect the conclusions in the comparison of SAR with bDMARDs, due to similar efficacy levels, but could have a significant favourable effect for SAR when the comparator is cDMARDs. The company acknowledged this issue (see clarification response[31] -- question B2) but was unable to implement the latent class approach in the revised model due to time constraints, and instead used the linear HAQ increment also for patients on cDMARDs.

2. Incorrect implementation of transition from moderate to severe RA

The ERG requested from the company to implement the possibility for moderate patients to progress to the severe state and consequently to transition to the treatment sequences recommended for patients with severe RA. In their implementation, the company assumed patients would go through the moderate sequence and only once they would start on best supportive care they would transition to the sequences recommended for patients with severe RA, only if their HAQ was above a certain threshold that was calculated through a regression as being related to a DAS28 score of 5.1. The ERG believes there are two main issues with the company's implementation. First, the relationship between changes in HAQ and DAS28 scores should have been calculated instead of the absolute scores. The relationship between these scores is far from being linear and by applying it to the changes in these scores instead of the absolute values, the error in the extrapolation is minimised. The company acknowledged that their regression resulted in a DAS28 score of 5.1 being predictive of an implausibly low HAQ score of 0.375. Second, patients should progress to the severe sequences at the point when their DAS28 score increases above 5.1, without waiting until they have reached the ebd of the moderate sequence.

3. Assuming same efficacy for monotherapies as for combination therapies in TNFi-IR patients

In light of the absence of evidence of the efficacy of monotherapies in TNFi-IR patients, the company assumed that the effectiveness of SAR monotherapy and its comparators would be the same as for the respective combination therapies. The company did not identify any RCTs that reported the efficacy of bDMARDs in this population and assumed that the effectiveness of monotherapies would be equal to that of combination therapies in TNFi-IR patients. The ERG notes that even though such an assumption is reasonable in light of the lack of evidence, the true effectiveness of bDMARD monotherapies is in TNFi-IR patients is still uncertain.

4. Assuming same efficacy for different lines of bDMARDs

The company assumed that the effectiveness of interventions in terms of ACR response rates and HAQ score improvements upon response would be the same, whether it was first-line or in subsequent therapy lines. In practice, as can be seen by comparing ACR rates in cDMARD-IR and TNFi-IR patients, the efficacy of treatment is reduced for subsequent treatment lines. This issue is mostly cancelled out when comparing sequences of equal length but might produce inaccurate results when comparing sequences of different lengths.

5.4 Additional exploratory analyses undertaken by the ERG

The ERG undertook exploratory analyses based on the company's revised model after applying the following two changes:

- The implementation of the non-linear HAQ progression based on the latent classes' approach described by Norton *et al.*[161] as implemented in the model developed by the AG in TA375.
- The amendment of the mechanism by which patients with moderate RA transition to the severe state and consequently to the treatment sequence recommended for patients with severe RA:
    - Calculating the DAS28 score of the patient at each cycle based on their DAS28 score at baseline, the change in HAQ score from baseline and the coefficient for HAQ score calculated by the company in their regression and used in their amended model.
    - Assuming that patients would transition to the sequence recommended for patients the moment their estimated DAS28 score is above 5.1.

Due to the time constraints and the running times of the company's model, the ERG only presents results of deterministic analyses. The ERG believes the probabilistic results would be very similar to the deterministic ones based on the similarity of the deterministic and probabilistic results presented for the cDMARD-IR population with severe RA presented in Table 55 and Table 56 respectively.

5.4.1 cDMARD-IR patients with severe RA who can tolerate MTX

In cDMARD-IR patients with severe RA who can tolerate MTX, SAR + MTX was estimated to dominate both indications of TCZ with concomitant MTX and the ICERs for TNFi bundle + MTX and ABT (SC) + MTX compared with SAR + MTX were estimated to be in excess of £150,000 per QALY gained – see Table 63.

Table 63: Results for cDMARD-IR patients with severe RA who can tolerate MTX (deterministic)

Sequences*	Total QALYs	Total costs	Incr. QALYs	Incr. costs	ICER (per QALY)	ICER vs SAR (per QALY)
TCZ (SC) + MTX#	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
TCZ (IV) + MTX#	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
SAR + MTX	[redacted]	[redacted]	[redacted]	[redacted]	-	
TNFi bundle + MTX	[redacted]	[redacted]	[redacted]	[redacted]	£151,563	£151,563
ABT (SC) + MTX#	[redacted]	[redacted]	[redacted]	[redacted]	£311,453	£214,071

ABT: abatacept; MTX: methotrexate; TCZ: tocilizumab; TNFi: tumour alpha necrosis inhibitor; SAR: sarilumab; IV: intravenous; SC: subcutaneous
*Sequences as defined in Table 42
#Does not include confidential PAS

5.4.2 cDMARD-IR patients with severe RA for whom MTX is contraindicated or not tolerated

As shown in Table 64, the ICER for SAR monotherapy compared with TNFi bundle monotherapy in cDMARD-IR patients with severe RA for whom MTX was contraindicated or not tolerated was estimated to be £34,422 per QALY gained, whilst the ICERs for both indications of TCZ compared with SAR monotherapy were estimated to be in excess of £1,500,000 per QALY gained. The ERG notes that the effectiveness of TCZ SC and TCZ IV is assumed to be the same and therefore the differences in the estimated total QALYs are the result of Monte Carlo sampling error.

Table 64: Results for cDMARD-IR patients with severe RA for whom MTX is contraindicated or not tolerated (deterministic)

Sequences*	Total QALYs	Total costs	Incr. QALYs	Incr. costs	ICER (per QALY)	ICER vs SAR (per QALY)
TNFi bundle	[redacted]	[redacted]	[redacted]	[redacted]	-	£34,422‡
SAR	[redacted]	[redacted]	[redacted]	[redacted]	£34,422	-
TCZ (SC)#	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	£2,541,618
TCZ (IV)#	[redacted]	[redacted]	[redacted]	[redacted]	£1,676,280	£1,676,280

TCZ: tocilizumab; TNFi: tumour alpha necrosis inhibitor; SAR: sarilumab; IV: intravenous; SC: subcutaneous
*Sequences as defined in Table 43
#Does not include confidential PAS
‡ICER in the south western quadrant representing cost savings per QALY lost

5.4.3 TNFi-IR patients with severe RA who can tolerate RTX and MTX

Table 65 shows the results of the analysis in patients with severe RA who can tolerate RTX and MTX: a sequence where SAR+MTX replaced RTX+MTX was estimated to result in an ICER of £171,466 per QALY gained.

Table 65: Results for TNFi-IR patients with severe RA who can tolerate RTX and MTX (deterministic)

Sequences*	Total QALYs	Total costs	Incr. QALYs	Incr. costs	ICER (per QALY)
RTX	[redacted]	[redacted]	[redacted]	[redacted]	
SAR	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated
RTX,TCZ‡#	[redacted]	[redacted]	[redacted]	[redacted]	£69,947
SAR,TCZ#	[redacted]	[redacted]	[redacted]	[redacted]	£171,466

RTX: rituximab; SAR: sarilumab;
*Sequences as defined in Table 44
#Does not include confidential PAS for TCZ
‡Currently recommended sequence

5.4.4 TNFi-IR patients with severe RA for whom RTX is not an option

In TNFi-IR patients with severe RA for whom RTX is not an option, SAR + MTX was estimated to result in an ICER of £34,979 per QALY gained compared with TNFi bundle whilst the ICER for both TCZ indications with concomitant MTX compared with SAR + MTX was estimated to be in excess of £195,000 – see Table 66. The ERG notes that the sequences evaluated in the company's analyses and the ERG's exploratory analyses differ as explained in Table 45.

Table 66: Results for TNFi-IR patients with severe RA for whom RTX is not an option (deterministic)

Sequences*	Total QALYs	Total costs	Incr. QALYs	Incr. costs	ICER (per QALY)	ICER vs SAR (per QALY)
TNFi bundle+ MTX	[redacted]	[redacted]	[redacted]	[redacted]	-	£34,979
ABT (SC) + MTX#	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
SAR + MTX	[redacted]	[redacted]	[redacted]	[redacted]	£34,979	-
TCZ (IV) + MTX#	[redacted]	[redacted]	[redacted]	[redacted]	£198,863	£198,863
TCZ (SC)+MTX#	[redacted]	[redacted]	[redacted]	[redacted]	£777,770	£205,638

ABT: abatacept; MTX: methotrexate; TCZ: tocilizumab; TNFi: tumour alpha necrosis inhibitor; SAR: sarilumab; IV: intravenous; SC: subcutaneous
*Sequences as defined in Table 45
#Does not include confidential PAS

5.4.5 TNFi-IR patients with severe RA for whom MTX is contraindicated or not tolerated

In TNFi-IR patients with severe RA for whom MTX is contraindicated or not tolerated, the ICER for SAR monotherapy compared with TNFi bundle was estimated to be £31,433 per QALY gained – see Table 67. The ERG notes that this analysis is subject to considerable uncertainty given that the effectiveness estimates for the monotherapies were assumed to be equal to those in combination with

MTX due to lack of evidence. The ERG also notes that TCZ, the only IL-6 recommended by NICE for severe RA, is not recommended in this population.

Table 67: Results for TNFi-IR patients with severe RA for whom MTX is contraindicated or not tolerated (deterministic)

Sequences*	Total QALYs	Total costs	Incr. QALYs	Incr. costs	ICER (per QALY)
TNFi bundle	[redacted]	[redacted]			
SAR	[redacted]	[redacted]	[redacted]	[redacted]	£31,433

TNFi: tumour alpha necrosis inhibitor; SAR: sarilumab;
*Sequences as defined in Table 46

5.4.6 TNFi-IR patients who have received RTX + MTX

As shown in Table 68, in TNFi-IR patients who have already received RTX+MTX, the ICERs for both indications of TCZ with concomitant MTX compared with SAR+MTX were estimated to be in excess of £200,000 per QALY gained.

Table 68: Results for TNFi-IR patients who have received RTX + MTX (deterministic)

Sequences*	Total QALYs	Total costs	Incr. QALYs	Incr. costs	ICER (per QALY)	ICER vs SAR +MTX (per QALY)
SAR + MTX	[redacted]	[redacted]	[redacted]	[redacted]	-	-
TCZ (IV) + MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	£245,465
TCZ (SC) + MTX	[redacted]	[redacted]	[redacted]	[redacted]	£219,153	£219,153

ABT: abatacept; MTX: methotrexate; TCZ: tocilizumab; TNFi: tumour alpha necrosis inhibitor; SAR: sarilumab; IV: intravenous; SC: subcutaneous
*Sequences as defined in Table 47
#Does not include confidential PAS

5.4.7 cDMARD-IR patients with moderate RA (DAS28 between 4.0 and 5.1) who can tolerate MTX

In cDMARD-IR patients moderate RA and a DAS28 higher than 4.0, a sequence starting with SAR+MTX compared with MTX was estimated to result in an ICER of £63,438 per QALY gained – see Table 69.

Table 69: Results for cDMARD-IR patients with moderate RA (DAS28 between 4.0 and 5.1) who can tolerate MTX (deterministic)

Sequences*#	Total QALYs	Total costs	Incr. QALYs	Incr. costs	ICER (£/QALY)
MTX	[redacted]	[redacted]			
SAR + MTX	[redacted]	[redacted]	[redacted]	[redacted]	£63,438

ABT: abatacept; MTX: methotrexate; TCZ: tocilizumab; TNFi: tumour alpha necrosis inhibitor; SAR: sarilumab; IV: intravenous; SC: subcutaneous
*Sequences as defined in Table 48
#Does not include confidential PAS of TCZ

5.5 Discussion

The CS includes a systematic review of economic evaluations of treatments for moderate and severe RA together with a *de novo* model-based economic evaluation of SAR + MTX versus currently recommended treatments in adult moderate and severe RA, cDMARD-IR and TNFi-IR patients. The company's systematic review of existing economic evaluations did not identify any studies that estimated the cost effectiveness of SAR + MTX.

The company's *de novo* economic model was largely based on the model developed by the AG in TA375.[25] Costs and health outcomes for SAR + MTX and its comparators were estimated from the perspective of the NHS and PSS over a lifetime horizon. The analyses presented in the CS relate to seven different populations of RA patients: (1) cDMARD-IR patients with severe RA who can tolerate MTX; (2) cDMARD-IR patients with severe RA for whom MTX is contraindicated or not tolerated; (3) TNFi-IR patients with severe RA for whom RTX is an option; (4) TNFi-IR patients with severe RA for whom RTX is not an option; (5) TNFi-IR patients with severe RA for whom MTX is contraindicated or not tolerated; (6) TNFi-IR patients with severe RA after treatment with RTX+MTX; and, (7) a subgroup of cDMARD-IR patients with moderate RA whose DAS28 scores are between 4.0 and 5.1. The definition of severe RA was a DAS28 score higher than 5.1, whilst moderate RA was defined as a DAS28 > 3.2 and ≤ 5.1. Baseline characteristics of patients are based on the relevant clinical SAR trials.

The company presented analyses in the CS and in the clarification response as per the ERG's request. The ERG believes that the analyses presented by the company in the clarification responses are closer to the company's intended base case than those in the CS. According to the company's revised probabilistic analysis, in cDMARD-IR patients with severe RA who could tolerate MTX, SAR+MTX dominated both indications of TCZ with concomitant MTX and the ICERs for SAR+MTX versus the TNFi bundle and ABT(SC) + MTX were £69,884 and £117,482 per QALY gained respectively. In the cDMARD-IR population with severe RA who could not tolerate MTX, the estimated ICER for SAR monotherapy versus the TNFi bundle was £17,123 per QALY gained, whilst the ICER for both TCZ indications compared with SAR was higher than £1,000,000 per QALY gained. In TNFi-IR patients for

whom RTX+MTX was an option, the ICER for SAR+MTX compared with RTX+MTX was estimated to be £130,691 per QALY gained. If RTX was not an option, the ICER for the considered comparators versus SAR+MTX in TNFi-IR patients was higher than £60,000 per QALY gained. For TNFi-IR patients who could not tolerate MTX, the ICER for SAR monotherapy compared with a TNFi bundle was estimated to be £17,794 per QALY gained. In patients who have received RTX+MTX, the ICER for both indications of TCZ compared with SAR+MTX were estimated to be greater than £130,000 per QALY gained. Finally, in cDMARD-IR patients with moderate RA and a DAS28 score higher than 4.0, the ICER for SAR+MTX was estimated to be £38,254 per QALY gained.

The ERG undertook exploratory analyses after amending the transition from moderate to severe RA and implementing the non-linear HAQ trajectory based on the latent class approach for patients on cDMARDs and BSC. According to the ERG's exploratory analyses, in cDMARD-IR patients with severe RA who can tolerate MTX, SAR + MTX was estimated to dominate both indications of TCZ with concomitant MTX and the ICERs for TNFi bundle + MTX and ABT (SC) + MTX compared with SAR + MTX are estimated to be in excess of £150,000 per QALY gained. In cDMARD-IR patients with severe RA for whom MTX was contraindicated or not tolerated, the ICER for SAR monotherapy compared with TNFi bundle monotherapy was estimated to be £34,422 per QALY gained, whilst the ICERs for both indications of TCZ compared with SAR monotherapy where estimated to be in excess of £1,500,000 per QALY gained. In TNFi-IR patients with severe RA who can tolerate RTX and MTX the ICER for SAR+MTX compared with RTX+MTX was estimated to be £171,466 per QALY gained. In TNFi-IR patients with severe RA for whom RTX is not an option, SAR + MTX was estimated to result in an ICER of £34,979 per QALY gained compared with TNFi bundle whilst the ICER for both TCZ indications with concomitant MTX compared with SAR + MTX was estimated to be in excess of £195,000. In TNFi-IR patients with severe RA for whom MTX is contraindicated or not tolerated, the ICER for SAR monotherapy compared with TNFi bundle was estimated to be £31,433 per QALY gained. In TNFi-IR patients who have already received RTX+MTX, the ICERs for both indications of TCZ with concomitant MTX compared with SAR+MTX were estimated to be in excess of £200,000 per QALY gained. In cDMARD-IR patients moderate RA and a DAS28 higher than 4.0, a sequence starting with SAR+MTX compared with MTX was estimated to result in an ICER of £63,438 per QALY gained.

The ERG presents the results of the analyses using the company's model whilst incorporating the confidential PAS currently in place for TCZ and ABT in a confidential appendix.

There remain two potentially important areas of uncertainty:

- *The effectiveness of SAR monotherapy and its comparators in TNFi-IR patients*. The company did not identify any RCTs that reported the efficacy of bDMARDs in this population and

assumed that the efficacy of monotherapies would be equal to that of combination therapies in TNFi-IR patients. The ERG notes that even though such an assumption is reasonable in light of the lack of evidence, the true effectiveness of bDMARD monotherapies is in TNFi-IR patients is still uncertain.

- *The effectiveness of SAR + MTX as third line biologic*. The company assumed that the same efficacy estimate for SAR + MTX in TNFi-IR patients would apply before and after RTX + MTX. However, only 23.2% of patients enrolled in the TARGET trial, from which the effectiveness of SAR + MTX was estimated, had more than one previous TNFi and the company did not provide a subgroup analysis of the efficacy of SAR + MTX in these patients. The ERG notes that considering that the efficacy of SAR + MTX is reduced in TNFi-IR patients compared with cDMARD-IR patients, it is reasonable to believe that its efficacy will be further reduced in subsequent treatment lines. However, the ERG acknowledges that this issue is unlikely to have an important impact in the cost-effectiveness of SAR + MTX because it also applies to the comparators and any potential reduction in the efficacy of SAR + MTX would probably be cancelled out by similar reductions in its comparators.

6 END OF LIFE

NICE end of life supplementary advice should be applied in the following circumstances and when both the criteria referred to below are satisfied:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months and;
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment, and;

The company did not include any claim or justification in the CS for SAR to be considered as an end of life treatment. The ERG believe that neither criterion would be met as patients receiving treatment would be expected to have a life expectancy considerably longer than 24 months and there is little robust evidence to suggest that SAR would provide an additional 3 months of life compared with its comparators.

7 OVERALL CONCLUSIONS

The key clinical effectiveness evidence for SAR was based on five RCTs and one long-term extension study. Three RCTs had ACR20 as their primary endpoint (MOBILITY-A, MOBILITY-B and TARGET). In the MTX-IR population, the RCTs showed a significant advantage in ACR responses for licensed doses of SAR+MTX over PBO+MTX, and a significant advantage for SAR monotherapy over ADA monotherapy. In the TNFi-IR population, there was a significant advantage for SAR+cDMARD over PBO+cDMARD. The MOBILITY-A, MOBILITY-B, MONARCH and TARGET trials reported significantly favourable results for licensed doses of SAR over comparators for improvement in HAQ-DI. SAR had a significant advantage over comparator for DAS28-CRP in the MOBILITY-B and TARGET trials, and for DAS28-ESR in the MONARCH trial. MOBILITY-B measured radiographic progression by mTSS, and reported a significantly lower deterioration from baseline for SAR over PBO+MTX.

SAEs were [redacted]. The most common AEs [redacted] The ASCERTAIN trial reported a similar safety profile for SAR to that of TCZ.

The company presented results of analyses based on a *de novo* economic model that was largely based on the model developed by the AG in TA375. In their clarification response the company presented a new set of analyses after addressing a multitude of issues identified by the ERG. The ERG considers these to be closer to the company's intended base case than those presented in the CS. The ERG undertook exploratory analyses after addressing two remaining issues: the HAQ trajectories of patients on cDMARDs and BSC; and the timing of the transition of patients with moderate RA to severe RA.

In cDMARD-IR patients with severe RA who could tolerate MTX, according to the analyses presented by the company in their clarification response and the ERG's exploratory analyses, SAR + MTX dominates both indications of TCZ in combination with MTX and the estimated ICER of the other comparators versus SAR +MTX is in excess of £75,000 per QALY gained.

In cDMARD-IR patients with severe RA for whom MTX was contraindicated or not tolerated, the ICER of SAR monotherapy compared with the TNFi bundle monotherapy is estimated to be £17,123 and £34,422 per QALY gained based on the company's analyses and the ERG's analyses respectively. The difference between the ICERs can be explained by the comparatively lower long-term HAQ progression whilst on cDMARDs based on the non-linear HAQ progression. In both analyses, the ICER of TCZ monotherapies (SC and IV) is estimated to be in excess of £1,500,000 per QALY gained.

In TNFi-IR patients who can tolerate MTX and for whom RTX is an option, a sequence of SAR + MTX followed by TCZ + MTX results in ICERs ranging from £130,691 to £171,466 per QALY gained compared with a sequence of RTX + MTX followed by TCZ + MTX.

In TNFi-IR patients who can tolerate MTX but for whom RTX is not an option, according to the company's analyses the ICERs of all comparators versus SAR + MTX are in excess of £64,602 per QALY gained. Contrastingly, according to the ERG's analyses the ICER of SAR+MTX compared with TNFi bundle + MTX is £34,979 but SAR + MTX dominates ABT + MTX and the ICERs of both indications of TCZ in combination with MTX versus SAR + MTX are in excess of £195,000. The difference in the results is partly explained by differences in the sequences used by the ERG and the company: the company's include bDMARDs in the second line of the sequence that are not recommended by NICE.

In TNFi-IR patients for whom MTX is contraindicated or not tolerated, the ICER for SAR monotherapy compared with TNFi bundle monotherapy is estimated to be £17,794 per QALY gained according to the company's analyses and £31,433 according to the ERG's analyses. The ERG notes that the difference between the ICERs is likely to be due to the lower benefit estimated from bDMARDs compared with cDMARDs/BSC when assuming a non-linear HAQ progression.

In TNFi-IR patients who have had RTX + MTX, the ICERs of both indications of TCZ are estimated to be in excess of £130,000 per QALY gained according to both the company's and the ERG's analyses.

In cDMARD-IR patients with moderate RA, a sequence starting with SAR + MTX compared with the currently recommended sequence starting with MTX is estimated to result in an ICER of £38,254 per QALY gained according to the company's analyses and £63,438 per QALY gained according to the ERG's analyses.

The ERG notes that the confidential PASs in place for ABT and TCZ were not included in these analyses. The ERG presents the analyses including the confidential PASs in a confidential appendix.

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9 APPENDICES

Appendix 1: The sequences evaluated in the original company submission.

Table 70: Treatment Sequences compared for cDMARD-IR patients with severe RA who can receive MTX

Line 1	Line 2	Line 3	Line 4
Sarilumab + MTX	> Rituximab + MTX	> Abatacept IV + MTX	> BSC
Tocilizumab IV + MTX	> Rituximab + MTX	> Abatacept IV + MTX	> BSC
Tocilizumab SC + MTX	> Rituximab + MTX	> Abatacept IV + MTX	> BSC
TNFi Bundle + MTX	> Rituximab + MTX	> Abatacept IV + MTX	> BSC
Abatacept SC + MTX	> Rituximab + MTX	> Tocilizumab IV + MTX	> BSC

BSC=best supportive care; IV=intravenous; MTX=methotrexate; SC=subcutaneous; TNFi=tumour necrosis factor inhibitor

Table 71: Treatment Sequences compared for cDMARD-IR patients with severe RA who cannot receive MTX

Line 1	Line 2	Line 3
Sarilumab	> TNFi Bundle	> BSC
Tocilizumab IV	> TNFi Bundle	> BSC
Tocilizumab SC	> TNFi Bundle	> BSC
TNFi Bundle	> TNFi Bundle	> BSC

BSC=best supportive care; IV=intravenous; SC=subcutaneous; TNFi=tumour necrosis factor inhibitor

Table 72: Treatment Sequences compared for TNFi-IR patients with severe RA who can receive RTX and MTX

Line 1	Line 2	Line 3
Sarilumab + MTX	> Abatacept IV + MTX	> BSC
Rituximab + MTX	> Abatacept IV + MTX	> BSC

BSC=best supportive care; MTX=methotrexate; TNFi=tumour necrosis factor inhibitor

Table 73: Treatment Sequences compared for TNFi-IR patients with severe RA who cannot receive but can receive MTX

Line 1	Line 2	Line 3
Sarilumab + MTX	> Abatacept IV + MTX	> BSC
Tocilizumab IV + MTX	> Abatacept IV + MTX	> BSC
Tocilizumab SC + MTX	> Abatacept IV + MTX	> BSC
TNFi Bundle + MTX	> Abatacept IV + MTX	> BSC
Abatacept SC + MTX	> Tocilizumab IV + MTX	> BSC

BSC=best supportive care; IV=intravenous; SC=subcutaneous; TNFi=tumour necrosis factor inhibitor

Table 74: Treatment Sequences compared for TNFi-IR patients with severe RA who cannot receive MTX

Line 1	Line 2
Sarilumab	> BSC
TNFi Bundle	> BSC

BSC=best supportive care; MTX=methotrexate; TNFi=tumour necrosis factor inhibitor

Table 75: Treatment Sequences compared for TNFi-IR patients with severe RA who have received RTX + MTX

Line 1	Line 2
Sarilumab + MTX	> BSC
Tocilizumab IV + MTX	> BSC
Tocilizumab SC + MTX	> BSC
BSC	-

BSC=best supportive care; IV=intravenous; SC=subcutaneous

Table 76: Treatment Sequences compared for cDMARD-IR patients with moderate RA (DAS28 > 4.0) who can receive MTX

Line 1	Line 2
Sarilumab + MTX	> BSC
BSC	

BSC=best supportive care

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Sarilumab for previously treated moderate to severe active rheumatoid arthritis [ID994]

You are asked to check the ERG report from School of Health and Related Research (ScHARR) to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on Tuesday 1 August 2017** using the below proforma 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 Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 p17

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Typographical error in the cost-effectiveness results for the cDMARD-IR population of patients with severe RA who could tolerate MTX.	The text should state: "... the incremental cost-effectiveness ratios (ICERs) of the weighted average of TNFi-s (TNFi bundle) and ABT (SC) + MTX compared with SAR+MTX were £69,884 and £117,482	This error leads to a false conclusion of the results.	Agreed. Apologies, text amended.

Line 3 states: "...the incremental cost-effectiveness ratios (ICERs) for SAR+MTX compared with a weighted average of TNFi-s (TNFi bundle) and ABT (SC) + MTX were £69,884 and £117,482 per QALY gained respectively."	per QALY gained respectively."		

Issue 2 p43

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Typographical error in table 8. The number of patients in the analysis for the ADA arm in MONARCH is reported as: "(n=185)".	The number of patients should state: "(n=184)"	To report the trial data accurately.	Changed to 184 Added footnote to explain that this is the safety population

Issue 3 p43

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Typographical error in table 8. The number of AEs leading to discontinuation for ADA in MONARCH is reported as: "15 (8.1)".	This cell should state: "13 (7.1)"	To report the trial data accurately.	Changed

Issue 4 p56

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Typographical error in table 29. The number of AEs leading to discontinuation for ADA in MONARCH is reported as: "15 (8.1)".	This cell should state: "13 (7.1)"	To report the trial data accurately.	Changed

Issue 5 p60

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Missing information on RACAT and Machado 2014 studies. Paragraph 2 states: "The company justified the exclusion of RACAT and Machado 2014 stating that it was unable to link them in the network. The ERG disagrees with the decision because both trials had ETN 50mg every week plus MTX, which can be linked to the network"	The text should be amended as follows: "The company justified the exclusion of RACAT and Machado 2014 stating that it was unable to link them in **the base case** network. The base case network considered separate dosages of etanercept 25 mg (noted as ETA combi) and 50 mg (noted as ETA 50 combi). Only RACAT and Machado 2014 studies had 50 mg dosage but due to 1/2csDMARD + MTX as comparator, it could not be linked in the network. However, RACAT and Machado 2014 studies were included in the pooled dose sensitivity analyses. RACAT and Machado 2014 studies were also included in the combined combination and monotherapy ACR analysis using probit model."	To fully describe the NMA methodology.	Not factual errors. The CS only stated that various other scenarios were also tested, but no further details were given. In addition, Table 8.3 in the appendix stated that the experiment treatment for both RACAT and Machado 2014 was Etanercept 50 mg every week + MTX.

Issue 6 p66

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Typographical error in table 34 under IL-6 vs TNFi. The number of patients in the MONARCH study is reported as; "396".	This cell should state: "369"	To report the trial data accurately. This error originated from the CS.	Number amended.

Issue 7 p68

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Incomplete statement on models used for the outcomes of interest. Paragraph 5 states: "For continuous outcomes, HAQ-DI and mTSS, a normal likelihood with identity link function model was used in the NMA. For ordered categorical outcomes, ACR and EULAR response, a binomial likelihood with either a logit link function in meta-regression on baseline risk or a risk difference model was used by dichotomising the data. For binary data, the efficacy outcome (DAS28 remission) used either meta-regression on the baseline risk model with a logit link	The text should be amended as follows: "Normal likelihood models with identity link function were run for all the outcomes. However, in case of convergence or study effect issues, meta-regression on baseline risk or risk difference models were used. For continuous outcomes, HAQ-DI and mTSS, a normal likelihood with identity link function model was selected in the NMA. For ordered categorical outcomes, ACR and EULAR response, a binomial likelihood with logit link function with and without meta-regression on baseline risk or a risk difference model by dichotomising the data was selected. For binary data, the efficacy outcome (DAS28 remission) used either meta-regression on the baseline risk model with a logit link function or a risk difference model; safety outcomes (serious	To fully describe the NMA methodology.	Not factual errors. The suggested text was inaccurate. Only continuous data NMAs used normal likelihood models with identity link function.

function or a risk difference model; safety outcomes (serious infections and serious adverse events) used either a risk difference model or logit model."	infections and serious adverse events) used either a risk difference model or logit model."		

Issue 8 p69

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Incomplete description of table 36. The title sates: "Outcomes and models used in the NMA per population and time point for the combination therapy"	The title should be amended to: "Outcomes and final base case models used in the NMA per population and time point for the combination therapy"	To accurately describe the NMA models shown in the report.	Amended.

Issue 9 p69

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Typographical error in table 36 for the NMA model for EULAR moderate-to-good in the cDMARD-IR population. The table states: "EULAR moderate-to-good, good: Fixed effect risk difference"	This cell should be split and state: "EULAR good: Fixed effect risk difference" "EULAR moderate to good: Random effect risk difference"	To accurately describe the NMA methodology.	Amended for cDMARD-IR (combination therapy). The fixed effect risk difference model was used for cDMARD-IR (monotherapy) (see CS appendix section 8.11.1.6).

Issue 10 p69

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Typographical error in table 36 for the NMA model for SAE in the cDMARD-IR monotherapy population. The model is reported as: "Fixed effect logit model"	This cell should state: "Fixed effect risk difference"	To accurately describe the NMA methodology.	Amended.

Issue 11 p70

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Incomplete statement on random effect and fixed effect model selection. Paragraph 2 states: "Random effects models were used to allow for heterogeneity when sufficient data were available, with fixed effect models used when data were sparse."	The paragraph should be amended as follows: "Random effects models were used to allow for heterogeneity when sufficient data were available, with fixed effect models used when data were sparse. However, for ACR and DAS28 remission outcomes in monotherapy population, a random effects model with informative priors as suggested by NICE was also run and no changes were observed in the results as compared to FEM (DIC values are similar between FEM and the informative priors REM model)."	To fully describe the NMA model selection.	Not factual errors. The CS didn't state that DIC was used for selection between a fixed effect and random effects model.

Issue 12 p70

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Addition to heterogeneity assessment. Paragraph 2 states: "In response to clarification question A12, 31 the company stated that a less vague prior was used for the regression coefficient, the relative treatment effect d and the baseline effect mu. The ERG argues that the less vague prior should be applied on the between-study variance when data were sparse"	The following text should be added: "Less vague priors for regression coefficient were used only as sensitivity analysis where data were sparse. For all the base case results present in the report, NICE recommended vague priors (as discussed in TSD 3) were used."	To fully describe the NMA methodology.	Not factual errors. NICE TSD 3 suggested a half-normal prior for the between-study standard deviation. However, the CS didn't state that this prior was used for all base case NMAs.

Issue 13 p70

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Addition to heterogeneity assessment. Paragraph 5 states: "…NMAs had limited data and the I2 statistic calculation may be biased due to too few studies. Inconsistency was checked using the Bucher method.152 No inconsistency was found in most of the NMAs, except for ACR50 response (ADA combination,	The following text should be added: "Qualitative assessment was carried out to check the heterogeneity in between the studies where I2 statistic calculation was not possible due to limited data."	To fully describe the NMA methodology.	Not factual errors. It was not mentioned in the CS that qualitative assessment was carried out in such situation.

cDMARD and tofacitinib combination loop) in the cDMARD-IR population.”			

Issue 14 p98

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Typographical error in the year the cost of serious infection was inflated to. The text states: “The cost per serious infection was assumed to be that used in the AG model for TA375 (£1479); this was uplifted to 2014/15 prices resulting in a cost of £1588 per episode.”	The text should state: “The cost per serious infection was assumed to be that used in the AG model for TA375 (£1479); this was uplifted to 2015/16 prices resulting in a cost of £1588 per episode.”	To accurately describe the adjustment to costs that was made.	Text amended.

Issue 15 p113

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Typographical error in the cost-effectiveness results for the cDMARD-IR population of patients with severe RA who could tolerate MTX. Paragraph 3 states: “...the ICERs for SAR+MTX versus the TNFi bundle and ABT	The text should state: “...the ICERs for the TNFi bundle and ABT (SC) + MTX versus SAR+MTX were £69,884 and £117,482 per QALY gained respectively.”	This error leads to a false conclusion of the results.	Agreed. Apologies, text amended.

(SC) + MTX were £69,884 and £117,482 per QALY gained respectively.”			

Sarilumab for previously treated moderate or severe rheumatoid arthritis: A Single Technology Appraisal

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
Authors	Iñigo Bermejo, Research Associate, ScHARR, University of Sheffield, Sheffield, UK Shijie Ren, Research Fellow, ScHARR, University of Sheffield, Sheffield, UK Emma Simpson, Research Fellow, ScHARR, University of Sheffield, Sheffield, UK Mark Clowes, Information Specialist, ScHARR, University of Sheffield, Sheffield, UK David L Scott, Department of Rheumatology, King's College Hospital NHS Foundation Trust, London, UK Adam Young, Department of Rheumatology, West Hertfordshire Hospital NHS Trust, Hertfordshire, UK Matt Stevenson, Professor of Health Technology Assessment, ScHARR, University of Sheffield, Sheffield, UK
Corresponding Author	Iñigo Bermejo, Research Associate, ScHARR, University of Sheffield, Sheffield, UK
Date completed	Date completed (19/07/2017)

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revised probabilistic analysis, in the cDMARD-IR population of patients with severe RA who could tolerate MTX, SAR with concomitant MTX (SAR+MTX) dominated both indications of TCZ with concomitant MTX and the incremental cost-effectiveness ratios (ICERs) for a weighted average of TNFi-s (TNFi bundle) and ABT (SC) + MTX were £69,884 and £117,482 per QALY gained respectively compared with SAR+MTX. In cDMARD-IR patients with severe RA who could not tolerate MTX, the deterministic ICER for SAR monotherapy compared with the TNFi bundle was estimated to be £17,123 per QALY gained, whilst the ICER for both TCZ indications compared with SAR was in excess of £1,000,000 per QALY gained. In TNFi-IR patients for whom RTX+MTX was an option, the ICER for SAR+MTX compared with RTX+MTX was estimated to be £130,691 per QALY gained. In patients for whom RTX is not an option, the ICER for the comparators versus SAR+MTX in TNFi-IR patients was greater than £60,000 per QALY. For TNFi-IR patients who cannot tolerate MTX, the ICER for SAR monotherapy compared with a TNFi bundle was estimated to be £17,794 per QALY gained. In patients who have received RTX+MTX, the ICER for both indications of TCZ compared with SAR+MTX were estimated to be greater than £130,000 per QALY gained. Finally, in cDMARD-IR patients with moderate RA and a DAS28 score higher than 4.0, the ICER for SAR+MTX was estimated to be £38,254 per QALY gained.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The company's model was based on the model developed by the Assessment Group (AG) in NICE Technology Appraisal 375 (TA375) but was an individual patient level Markov model rather than a discrete event simulation (DES). The ERG believes that the conceptual model was broadly appropriate.

After an initial evaluation of the company's analyses, the ERG requested that the company perform new analyses after addressing a number of issues. The company presented new analysis after addressing the following issues: (i) inadequate treatment sequences that did not reflect NICE recommendations; (ii) omission of the possibility of patients with moderate RA to progress to the severe state; (iii) use of Malottki *et al.* instead of Hernandez *et al.* for the mapping of HAQ scores to EQ-5D; (iv) limitations in the company's NMA explained in Section **Error! Reference source not found.**; (v) using percentages of improvement of HAQ instead of absolute mean changes; (vi) omission of rounding to the nearest valid HAQ score; (vii) use of an implausible extrapolation of time to treatment discontinuation; (viii) using independent samples for the probabilities of ACR responses in the PSA instead of correlated samples from the CODA of the NMA; (ix) assuming 9 free doses of CTZ instead of 10; and, (x) the inclusion of the speculative Patient Access Scheme (PAS) discount of 15% applied to TCZ and ABT.

The main issue remaining in the company's analyses after these amendments is the assumption that the HAQ score of patients on cDMARDs and BSC follow a linear trajectory. The ERG notes that there is extensive evidence that shows that the HAQ trajectory for these patients is not linear and that

Table 1: Discontinuation during cDMARD-IR trials[38, 39, 41 32 33 35]

	MOBILITY-A 12weeks			MOBILITY-B 52 weeks			MONARCH 24 weeks	
	PBO + MTX (n=52)	SAR 150mg Q2W + MTX (n=51)	SAR 200mg Q2W + MTX (n=52)	Placebo + MTX (n=428)	SAR 150mg Q2W + MTX (n=430)	SAR 200mg Q2W + MTX (n=427)	ADA 40mg Q2W (n=184)*	SAR 200mg Q2W (n=184)
Discontinuation during double blind period, n (%)	3 (5.8)	3 (5.9)	6 (11.5)	62 (14.5)	78 (18.1)	88 (20.6)	28 (15.1)	19 (10.3)
Any AE leading to treatment discontinuation, n (%)	1 (1.9)	2 (3.8)	4 (7.8)	20 (4.7)	54 (12.5)	59 (13.9)	13 (7.1)	11 (6.0)

AE: adverse events; PBO: placebo: MTX: methotrexate; SAR: salirumab; ADA: adalimumab; Q2W: every other week. *safety population (1 patient randomised but not treated so excluded from safety analysis)

Table 2: Discontinuation during TNFi-IR trials at week 24 [34 36 40]

	TARGET			ASCERTAIN		
	PBO + cDMARD (n=181)	SAR 150mg Q2W + cDMARD (n=181)	SAR 200mg Q2W + cDMARD (n=181)	TCZ IV 4–8mg/kg Q4W + cDMARD (n=102)	SAR 150mg Q2W + cDMARD (n=49)	SAR 200mg Q2W + cDMARD (n=51)
Discontinuation, n (%)	17 (9.4)	31 (17.1)	25 (13.6)	[redacted]	[redacted]	[redacted]
Any AE leading to treatment discontinuation, n (%)	8 (4.4)*	14 (7.7)	17 (9.2)	[redacted]	[redacted]	[redacted]

*additionally 1 PBO and 4 SAR 150mg, abnormal laboratory values at baseline [34]

AE: adverse events; PBO: placebo: SAR: salirumab; TCZ: tocilizumab; IV: intravenous; Q2W: every 2 weeks; Q4W: every 4 weeks; cDMARD: conventional disease-modifying antirheumatic drug

Table 3: AEs in cDMARD-IR trials (adapted from CS Tables 4.41, 4.42 and 4.45)[32 33 35 38, 39, 41]

	MOBILITY-A 12weeks			MOBILITY-B 52 weeks			MONARCH 24 weeks	
	PBO + MTX (n=52)	SAR 150mg Q2W + MTX (n=51)	SAR 200mg Q2W + MTX (n=52)	PBO + MTX (n=427)	SAR 150mg Q2W + MTX (n=431)	SAR 200mg Q2W + MTX (n=424)	ADA 40mg Q2W (n=184)*	SAR 200mg Q2W (n=184)
Any AE, n (%)	24 (47.1)	28 (53.8)	33 (64.7)	263 (61.6)	321 (74.5)	331 (78.1)	117 (63.6)	118 (64.1)
Any SAE, n (%)	2 (3.9)	0	0	23 (5.4)	38 (8.8)	48 (11.3)	12 (6.5)	9 (4.9)
Any AE leading to treatment discontinuation, n (%)	1 (1.9)	2 (3.8)	4 (7.8)	20 (4.7)	54 (12.5)	59 (13.9)	13 (7.1)	11 (6.0)
Deaths, n	0	0	0	2 (0.5)	2 (0.5)	1 (0.2)	0	1 (0.5)

AE: adverse events; SAE: serious AE; PBO: placebo: MTX: methotrexate; SAR: salirumab; ADA: adalimumab; Q2W: every other week *safety population

Table 4: AEs in TNFi-IR trials[34 40 36]

	TARGET 24 weeks			ASCERTAIN 24 weeks		
	PBO + cDMARD (n=181)	SAR 150mg Q2W + cDMARD (n=181)	SAR 200mg Q2W + cDMARD (n=184)	TCZ IV 4–8mg/kg Q4W + cDMARD (n=102)	SAR 150mg Q2W + cDMARD (n=49)	SAR 200mg Q2W + cDMARD (n=51)
Any AE, n (%)	90 (49.7)	119 (65.7)	120 (65.2)	[redacted]	[redacted]	[redacted]
Any SAE, n (%)	6 (3.3)	6 (3.3)	10 (5.4)	[redacted]	[redacted]	[redacted]
Any AE leading to treatment discontinuation, n (%)	8 (4.4)	14 (7.7)	17 (9.2)	[redacted]	[redacted]	[redacted]
Deaths, n (%)	1 (0.6)	0	0	[redacted]	[redacted]	[redacted]

AE: adverse events; SAE: serious AE; PBO: placebo: SAR: salirumab; TCZ: tocilizumab; IV: intravenous; Q2W: every 2 weeks; Q4W: every 4 weeks; cDMARD: conventional disease-modifying antirheumatic drug

BAR oral 2mg OD + cDMARD BAR oral 10mg OD + cDMARD	**cDMARD**	**24**	**684**	**RA-BUILD (Dougados 2017[132])**
Biologic vs. same biologic				
Comparisons of different routes of administration				
TCZ SC 162mg QW+ cDMARDs	TCZ IV 162mg Q4W+ cDMARDs	104	1,262	SUMMACTA (Burmester 2014,[133, 134] Burmester 2013[135])
Head-to-head comparisons of bDMARDs				
TNFi vs. non-TNFi				
ADA SC 40mg Q2W + MTX	ABT SC 125mg QW + MTX	104	646	AMPLE (Schiff 2014,[136] Weinblatt 2013[137])
ADA SC 40mg Q2W + MTX	BAR oral 4mg OD + MTX	52	1307	RA-BEAM (Taylor 2017[138])
IL-6 vs. TNFi				
TCZ IV 8mg/kg Q4W	ADA SC 40mg Q2W	32	326	ADACTA (Gabay 2013[73])
SAR SC 200mg Q2W	ADA SC 40mg Q2W	24	369	MONARCH (Burmester 2016[35])

ABT=abatacept; ADA=adalimumab; BAR= baricitinib; BID=Twice a day; BIW=twice weekly; cDMARD= disease-modifying anti-rheumatic drugs; CTZ= certolizumab pegol; CYC= cyclophosphamide; ETN= etanercept; GOL= golimumab; HCQ= hydroxychloroquine; IFX=infliximab; IL-6=interleukin-6; IV=intravenous; MTX=methotrexate; OD=once daily; OLE=open labelled extension; QW=once a week; Q2W=every 2 weeks; Q4W=every 4 weeks; Q8W=every 8 weeks; RTX= rituximab; SAR= sarilumab; SC=subcutaneous; SIR= sirukumab; SSZ= sulfasalazine; TCZ= tocilizumab; TOF= tofacitinib

Table 5: Studies included in the NMA for the TNFi-IR population: Updated review (reproduced from Table 4.28 of the CS)

Intervention	Comparator(s)	Duration of study (weeks)	Number of patients	References
Monotherapy studies vs. placebo				
GOL SC 50mg Q4W +/- cDMARD GOL SC 100mg Q4W +/- cDMARD	cDMARDs	24	461	GO-AFTER (Smolen 2009[139])
SIR SC 500mg Q4W +/- cDMARD SIR SC 1000mg Q2W +/- cDMARD	cDMARD	NA	878	SIRROUND-T (Tanaka 2016[140])
Combination studies vs. cDMARD				

Table 6: **Outcomes and final base case models used in the NMA per population and time point for the combination therapy**

Outcome	cDMARD-IR (combination therapy)		cDMARD-IR (monotherapy)	TNFi-IR
	Model (24 weeks)	Model (52 weeks)	Model (24 weeks)	Model (24 weeks)
ACR20, 50 and 70	Random effects-baseline risk regression		Fixed effect-logit model	Fixed effect-risk difference
HAQ-DI CFB	Random effects-change from baseline		Fixed effects-change from baseline	Fixed effect-change from baseline
EULAR moderate-to-good	Fixed effect-risk difference		Fixed effect-risk difference	Fixed effect-risk difference
EULAR good	Random effect-risk difference		Fixed effect-risk difference	Fixed effect-risk difference
DAS28 remission	Random effects-baseline risk regression		Fixed effects-risk difference	Fixed effect-risk difference
mTSS CFB	Fixed effect-change from baseline	Fixed effect-change from baseline		
SIs		Random effects-risk difference	Fixed effect-risk difference	Fixed effect-logit model
SAE		Random effects-logit model	Fixed effect-risk difference	Fixed effect-logit model

ACR20/50/70=American College of Rheumatology 20%/50%/70% improvement; CFB=change from baseline; DAS28=28-joint disease activity score; HAQ-DI=Health Assessment Questionnaire Disability Index; mTSS=modified Total Sharp Score; NMA=network meta-analysis; SAE=serious adverse event; SI=serious infections

The ERG disagrees with dichotomising ACR and EULAR response. The choice of the likelihood function/link function should be based on the data generating process. A multinomial likelihood with probit/logit link function is preferred to a binomial likelihood for the ordered categorical ACR or EULAR data, because it accounts for natural ordering and correlations between the categories within the outcome measure. This is important to the decision problem when these results are used to populate the economic model.

Meta-regression on the baseline risk is not very useful for decision-making as it does not explain the heterogeneity in terms of prognostic factors. When there were too few studies to perform a meaningful regression, a risk difference scale was used for all the efficacy outcomes rather than the most frequently applied odds ratio scale (a logit model). The company stated that this was because the observed treatment effect was statistically significantly correlated with the observed baseline risk when the effect was measured using an odds ratio scale, but was not statistically significantly

bDMARDs therefore minimal impact is expected on the results." The ERG notes that in TA375, the time required by a district nurse was 30 minutes rather than the hour assumed by the company, although the ERG agrees that this limitation will have no impact on the conclusions.

Monitoring costs were also based on TA375[166] and included full blood count, erythrocyte sedimentation rate (ESR), biochemical profile, and chest x-ray prior to treatment with the addition of lipid profiles for TCZ and SAR. Full blood counts, biochemical profile and lipid profiles for TCZ and SAR were assumed to occur ten times in the first six months, and monthly thereafter. After the initial six months, monthly monitoring costs were assumed to be low: £7 for SAR and TCZ and £5 for all other bDMARDs although all interventions were associated with a monthly outpatient attendance assumed to cost £143 per visit, based on NHS Reference Costs.[167]

Hospitalisation costs were based on those within the AG's model in TA375,[166] inflated to 2015/2016 prices. In these estimates, hospitalisation costs were dependent on HAQ score band and were calculated based on data from the NOAR database on inpatient days, joint replacements and NHS Reference Costs. The costs used in the model are provided in Table 7.

Table 7: Annual hospitalisation costs used in the company's model

HAQ-DI score	Annual costs
(0 - 0.5]	£180
(0.5 - 1.0]	£110
(1.0 - 1.5]	£391
(1.5 - 2.0]	£562
(2.0 - 2.5]	£1,338
(2.5 - 3.0]	£2,885

The cost per serious infection was assumed to be that used in the AG model for TA375[166] (£1479); this was uplifted to 2015/16 prices resulting in a cost of £1588 per episode.

5.2.10 Methods of the analysis

The company undertook analyses on the following groups:

- cDMARD-IR patients with severe RA who can tolerate MTX (CS denoted A1);
- cDMARD-IR patients with severe RA who cannot tolerate MTX (CS denoted B);
- TNFi-IR patients with severe RA who can tolerate RTX and MTX (CS denoted C2);
- TNFi-IR patients with severe RA who cannot tolerate RTX (CS denoted C1);
- TNFi-IR patients with severe RA who cannot tolerate MTX (CS denoted C3);
- TNFi-IR patients who have received RTX and MTX (CS denoted C4); and

Sequences*#	Total QALYs	Total costs	Incr. QALYs	Incr. costs	ICER (£/QALY)
MTX	[redacted]	[redacted]			
SAR + MTX	[redacted]	[redacted]	[redacted]	[redacted]	£63,438

ABT: abatacept; MTX: methotrexate; TCZ: tocilizumab; TNFi: tumour alpha necrosis inhibitor; SAR: sarilumab; IV: intravenous; SC: subcutaneous
*Sequences as defined in **Error! Reference source not found.**
#Does not include confidential PAS of TCZ

5.5 Discussion

The CS includes a systematic review of economic evaluations of treatments for moderate and severe RA together with a *de novo* model-based economic evaluation of SAR + MTX versus currently recommended treatments in adult moderate and severe RA, cDMARD-IR and TNFi-IR patients. The company's systematic review of existing economic evaluations did not identify any studies that estimated the cost effectiveness of SAR + MTX.

The company's *de novo* economic model was largely based on the model developed by the AG in TA375.[25] Costs and health outcomes for SAR + MTX and its comparators were estimated from the perspective of the NHS and PSS over a lifetime horizon. The analyses presented in the CS relate to seven different populations of RA patients: (1) cDMARD-IR patients with severe RA who can tolerate MTX; (2) cDMARD-IR patients with severe RA for whom MTX is contraindicated or not tolerated; (3) TNFi-IR patients with severe RA for whom RTX is an option; (4) TNFi-IR patients with severe RA for whom RTX is not an option; (5) TNFi-IR patients with severe RA for whom MTX is contraindicated or not tolerated; (6) TNFi-IR patients with severe RA after treatment with RTX+MTX; and, (7) a subgroup of cDMARD-IR patients with moderate RA whose DAS28 scores are between 4.0 and 5.1. The definition of severe RA was a DAS28 score higher than 5.1, whilst moderate RA was defined as a DAS28 > 3.2 and ≤ 5.1. Baseline characteristics of patients are based on the relevant clinical SAR trials.

The company presented analyses in the CS and in the clarification response as per the ERG's request. The ERG believes that the analyses presented by the company in the clarification responses are closer to the company's intended base case than those in the CS. According to the company's revised probabilistic analysis, in cDMARD-IR patients with severe RA who could tolerate MTX, SAR+MTX dominated both indications of TCZ with concomitant MTX and the ICERs for a weighted average of TNFi-s (TNFi bundle) and ABT (SC) + MTX were £69,884 and £117,482 per QALY gained respectively compared with SAR+MTX. In the cDMARD-IR population with severe RA who could not tolerate MTX, the estimated ICER for SAR monotherapy versus the TNFi bundle was £17,123 per QALY gained, whilst the ICER for both TCZ indications compared with SAR was higher than £1,000,000 per QALY gained. In TNFi-IR patients for whom RTX+MTX was an option, the ICER