Sarilumab for previously-treated moderate or severe rheumatoid arthritis: An Evidence Review Group perspective of a NICE Single Technology Appraisal

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Short running title: "Sarilumab for previously-treated moderate or severe RA: An ERG perspective"

Abstract

As part of its single technology appraisal (STA) process, the National Institute for Health and Care Excellence (NICE) invited the manufacturer (Sanofi Genzyme) of sarilumab (SAR; Kevzara®) to submit evidence of its clinical and cost-effectiveness for previously-treated moderate or severe rheumatoid arthritis (RA). The School of Health and Related Research Technology Appraisal Group at the University of Sheffield was commissioned to act as the independent Evidence Review Group (ERG). The ERG produced a detailed review of the evidence for the clinical and cost-effectiveness of the technology, based upon the company's submission to NICE. The clinical effectiveness evidence in the company's submission for SAR was based predominantly on five randomised controlled trials (RCTs) comparing the efficacy of SAR against adalimumab, tocilizumab or placebo. The clinical-effectiveness review identified no head to head evidence on the efficacy of SAR against all the comparators within the scope. Therefore, the company performed three network meta-analyses (NMAs) in two different populations: two in patients who had had an inadequate response to conventional disease-modifying antirheumatic drugs (cDMARDs) (one for combination therapies and one for monotherapies), and the other one in patients who had had an inadequate response to tumour necrosis factor inhibitors (TNFi). The company's NMAs concluded that SAR in combination with cDMARDs or as monotherapy has a statistically superior efficacy to cDMARDs and a comparable efficacy to most biologic disease-modifying antirheumatic drugs (bDMARDs) in both populations. The company submitted a Markov model that assessed the cost effectiveness of SAR from the perspective of the National Health Service (NHS) and Personal Social Services in seven different populations: (1) patients with severe RA who have had an inadequate response to cDMARDs (cDMARD-IR); (2) cDMARD-IR patients with severe RA for whom methotrexate (MTX) is contraindicated or not tolerated; (3) patients with severe RA who have had an inadequate response to a TNFi (TNFi-IR); (4) TNFi-IR patients with severe RA for whom rituximab (RTX) is not an option; (5) TNFi-IR patients with severe RA for whom

MTX is contraindicated or not tolerated; (6) TNFi-IR patients after RTX; and, (7) cDMARD-IR patients with moderate RA whose 28-joint Disease Activity Score (DAS28) is between 4.0 and 5.1. The company's economic evaluation results in incremental cost-effectiveness ratios (ICERs) lower than £20,000 per quality-adjusted life year (QALY) for SAR in combination with MTX or as monotherapy when the comparators were less effective and in ICERs higher than £60,000 per QALY for the comparators versus SAR when SAR was less effective, except: in TNFi-IR patients who are RTX eligible, the ICER for SAR + MTX compared with RTX + MTX is £130,691 per QALY; and in patients with moderate RA and a DAS28 > 4.0 the ICER of SAR + MTX compared with MTX is £38,254 per QALY gained. Following a critique of the model, the ERG undertook exploratory analyses after applying two changes to the company's model: (1) using a latent class approach to model Health Assessment Questionnaire Disability Index (HAQ-DI) progression for patients on cDMARDs; and, (2) amending the company's modelling of patient progression from moderate to severe RA. The ICERs estimated by the ERG's exploratory analyses for SAR + MTX increased to £171,466 per QALY when compared with RTX + MTX in TNFi-IR patients who are RTX eligible and to £63,438 per QALY when compared with MTX in patients with moderate RA and a DAS28 > 4.0. The Appraisal Committee concluded that SAR in combination with MTX or as monotherapy is a cost-effective use of NHS resources in the considered populations except in TNFi-IR patients who are RTX eligible and in patients with moderate RA and DAS28 > 4.0.

Word count: 597

Key points for decision makers

- Sarilumab (SAR) has shown similar clinical efficacy to other recommended biologic disease-modifying antirheumatic drugs (bDMARDs) or Janus kinase (JAK) inhibitors in previously-treated moderate or severe rheumatoid arthritis (RA).
- A confidential patient access scheme (PAS) has been agreed with the Department of Health under which SAR will be available to the National Health Service (NHS) at a reduced cost.
- Estimated incremental cost-effectiveness ratios (ICERs) for SAR, in combination with MTX or as monotherapy, versus its comparators are within the range usually considered as a cost-effective use of NHS resources in patients with severe RA where other bDMARDs have been recommended, except in patients who have had an inadequate response to a tumour necrosis factor inhibitor and who are eligible for rituximab (RTX). RTX is of similar clinical efficacy to SAR but has a significantly lower cost and therefore, RTX in combination with MTX should be preferred to SAR with MTX.
- In patients with moderate RA and a 28-joint Disease Activity Score (DAS28) between 4.0 and 5.1, the estimated ICER for SAR in combination with MTX versus MTX ranges from £38,254 to £63,438 per quality-adjusted life year (QALY).

1. Introduction

The National Institute for Health and Care Excellence (NICE) is an independent organisation responsible for providing national guidance on promoting good health and preventing and treating ill health in priority areas with significant impact. Health technologies must be shown to be clinically effective and to represent a cost-effective use of National Health Service (NHS) resources in order for NICE to recommend their use within the NHS in England. The NICE Single Technology Appraisal (STA) process usually covers new single health technologies within a single indication, soon after their UK market authorisation.[1] Within the STA process, the company provides NICE with a written submission, alongside a mathematical model that summarises the company's estimates of the clinical and cost effectiveness of the technology. This submission is reviewed by an external organisation independent of NICE (the Evidence Review Group [ERG]), which consults with clinical specialists and produces a report. After consideration of the company's submission, the ERG report and testimony from experts and other stakeholders, the NICE Appraisal Committee (AC) formulates preliminary guidance, the Appraisal Consultation Document (ACD), which indicates the initial decision of the AC regarding the recommendation (or not) of the technology. Stakeholders are then invited to comment on the submitted evidence and the ACD, after which a further ACD may be produced or a Final Appraisal Determination (FAD) issued, which is open to appeal. An ACD is not produced when the technology is recommended within its full marketing authorisation; in this case, a FAD is produced directly.

This paper presents a summary of the ERG report[2] for the STA of sarilumab (SAR), an anti-interleukin-6 (IL-6) agent, for previously-treated moderate or severe rheumatoid arthritis (RA) and a summary of the subsequent development of the NICE guidance for the use of this technology in England. Full details of all relevant appraisal documents (including the appraisal scope, ERG report, company and consultee submissions, FAD and comments from consultees) can be found on the NICE website.[3]

2. The Decision Problem

RA is an autoimmune disease that causes chronic inflammation, progressive, irreversible joint damage, impaired joint function, pain and tenderness caused by swelling of the synovial lining of joints. 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, fatigue, and redness of the peripheral joints.[5, 6] RA is associated with substantial costs both directly (due to treatment acquisition and hospitalisation) and indirectly (due to reduced productivity).[7] The condition has long been reported as being associated with increased mortality,[8, 9] particularly due to cardiovascular events.[10] NICE estimates that there are 400,000 people in the United Kingdom (UK) with RA,[11] with approximately 26,000 incident cases per year.[12] RA is more prevalent 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]

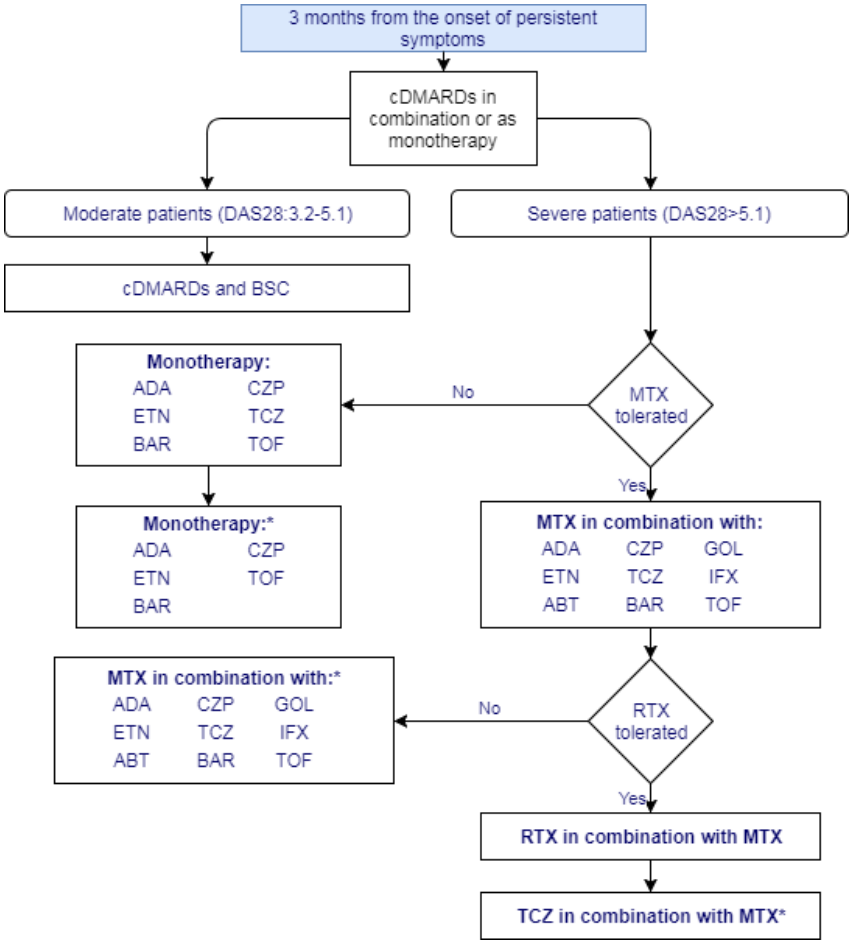
The measurement of improvement in RA symptoms has been assessed using two main classifications: American College of Rheumatology (ACR) responses[14] and European League Against Rheumatism (EULAR) responses.[15] In the UK, progression of RA is often monitored using the 28-joint disease activity score of 28 joints (DAS28). The EULAR response criteria use both the change in DAS28 and the absolute DAS28 score to classify a response as good, moderate or none.[15] Whilst EULAR response has been reported less frequently in RCTs than ACR responses,[16] it is much more closely aligned to the treatment continuation rules stipulated by NICE, which require at least a moderate EULAR response or a DAS28 improvement of more than 1.2 points to continue treatment with biologic disease-modifying antirheumatic drugs (bDMARDs).

2.1 Current Treatment

NICE recommends a combination of conventional disease-modifying antirheumatic drugs (cDMARDs) as first-line treatment for people with newly diagnosed RA, including methotrexate (MTX) and at least one other cDMARD plus short-term glucocorticoids, ideally beginning within 3 months of the onset of

persistent symptoms.[17] For patients who have severe active RA (defined as a DAS28 score greater than 5.1), NICE guidance recommends the use of the following bDMARDs and janus kinase (JAK) inhibitors: abatacept (ABT); adalimumab (ADA); certolizumab pegol (CZP); etanercept (ETN); golimumab (GOL); infliximab (IFX); tocilizumab (TCZ); baricitinib (BAR); and tofacitinib (TOF), each in combination with MTX after the failure to respond to cDMARD treatment.[18-21] For people with severe RA for whom MTX is contraindicated or has been withdrawn, NICE recommends the use of ADA, CZP, ETN, TCZ, TOF and BAR as monotherapy.[18-21] After the failure of the first TNFi, NICE recommends rituximab (RTX) in combination with MTX for the treatment of severe active RA.[22] If RTX is contraindicated or withdrawn because of an adverse event (AE), NICE recommends one of ABT, ADA, ETN, GOL, IFX, TCZ, CZP, TOF and BAR in combination with MTX [19-25]; if MTX is contraindicated or withdrawn because of an AE, NICE recommends ADA, ETN, CZP, TOF or BAR [19, 20, 22] as monotherapy. NICE also recommends TCZ in combination with MTX as a third line bDMARD after inadequate response to RTX in combination with MTX.[23] The treatment pathway is summarised in Figure 1.

Figure 1: Treatment pathway recommended by NICE



*followed by a treatment with a cDMARD (MTX unless not tolerated, SSZ otherwise) and BSC.

cDMARD: conventional disease-modifying antirheumatic drug; DAS28: 28-joint Disease Activity Score; BSC: best supportive care; MTX: methotrexate; ABT: abatacept; ADA: adalimumab; CZP: certolizumab pegol; ETN: etanercept; GOL: golimumab; IFX: infliximab; TCZ: tocilizumab; BAR: baricitinib; TOF: tofacitinib; RTX: rituximab; SSZ: sulfasalazine.

NICE guidance recommends discontinuing treatment with bDMARDs or JAK inhibitors unless a moderate EULAR response is achieved at six months or if the response is not maintained [19, 20, 22-25]. After treatment discontinuation, the next treatment in the sequence initiated.

3. The Independent ERG Review

In accordance with the process for STAs, the ERG and NICE had the opportunity to seek clarification on specific points in the company's submission (CS),[26] in response to which the company provided additional information.[27] The ERG also modified the company's decision analytic model to produce an ERG base case and to assess the impact of alternative parameter values and assumptions on the model results. The evidence presented in the company's submission and the ERG's review of that evidence is summarised here.

3.1 Clinical Evidence Provided by the Company

Evidence was presented in the CS[26] for the efficacy of SAR in combination with MTX or as monotherapy in previously-treated moderate to severe RA. The key clinical effectiveness and safety evidence was based on five randomised controlled trials (RCTs). There were three RCTs in methotrexate (MTX) intolerant or inadequate response (MTX-IR) patients with RA (MOBILITY-A,[28] MOBILITY-B,[29] and MONARCH[30]). Two RCTs (TARGET[31] and ASCERTAIN[32]) were in patients with RA who had had an inadequate response to bDMARDs (bDMARD-IR). One RCT (ASCERTAIN) compared SAR with tocilizumab (TCZ), another study (MONARCH) compared it against adalimumab (ADA), and the rest (MOBILITY-A, MOBILITY-B and TARGET) compared SAR against placebo (PBO). Additionally, one long-term extension study (EXTEND) was included.

Three RCTs had 20% improvement in the American College of Rheumatology (ACR) score (ACR20) as their primary endpoint (MOBILITY-A, MOBILITY-B and 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 cDMARD over PBO+cDMARD on ACR20 ($p < 0.0001$), ACR50 ($p \leq 0.005$) and ACR70 ($p \leq 0.005$).

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 included in the NMA, which were assessed at 24 weeks (unless otherwise stated), were ACR responses, EULAR responses, the Health Assessment Questionnaire Disability Index (HAQ-DI),

DAS28 remission and modified Total Sharp Score (mTSS)). The outcome measures included in the safety NMA were serious infections and serious adverse events (SAEs). In the cDMARD-IR population, separate networks were used for the combination therapies and monotherapies.

Results of the NMA showed that SAR in combination with cDMARDs or as monotherapy had similar or superior efficacy to its comparators. In the NMA for the cDMARD-IR population, SAR 200mg in combination with cDMARDs demonstrated statistical superiority to ABT combination, IFX combination and intravenous (IV) TCZ 4mg/kg on good EULAR response, and was comparable to GOL, TCZ IV 8mg/kg, rituximab (RTX) and SAR 150mg all in combination with cDMARDs. SAR 200mg combination therapy was statistically inferior to CZP combination therapy on at least moderate EULAR response, but comparable to GOL, IFX, TCZ IV 4mg/kg and 8mg/kg, RTX and SAR 150mg all in combination with cDMARDs. In the NMA evaluating monotherapies in the cDMARD-IR population, SAR 200mg monotherapy showed statistically superiority to cDMARDs and ADA on EULAR responses, and was comparable to TCZ 8mg/kg. In the NMA for the TNFi-IR population, SAR 200mg combination therapy showed statistically superiority to cDMARDs for all EULAR responses. 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. Results for ACR responses were similar to those of EULAR responses. 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.

3.1.1 Critique of the Clinical Evidence and Interpretation

The eligibility criteria applied in the selection of evidence for the clinical effectiveness review were considered by the ERG to be reasonable and generally consistent with the decision problem as outlined in the final NICE scope. The quality of the included RCTs was assessed using well-established and recognised criteria. 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 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 TARGET and MOBILITY B 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 12 and 16 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.

3.2 Cost-Effectiveness Evidence Provided 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 excluding best supportive care (BSC), patients may achieve good, moderate or no EULAR response, which 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 HAQ-DI 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-DI whilst on treatment is assumed to remain constant on bDMARDs and SAR; conversely, whilst on cDMARDs and BSC, HAQ-DI is assumed to increasing at a constant annual rate of 0.045 and 0.06 respectively. 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-DI 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-DI score of a patient at baseline. 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-DI and patient characteristics. Serious infection were the only AE included in the analyses. Hospitalisation costs and resource use estimates were based on HAQ-DI bands as in previous NICE technology appraisals.[18] Unit costs were taken from the British National Formulary and NHS Reference Costs. A confidential patient access scheme (PAS) has been agreed with the Department of Health under which SAR will be available to the NHS at a reduced cost.

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 comparators included in the analyses are ABT (SC), TCZ (IV), TCZ (SC) and a blended comparator comprising a weighted average of all the TNFi-s termed 'TNFi bundle' for patients with severe RA and MTX for patients with moderate RA. The intervention as well as the comparators include further lines of treatment to replicate the treatment sequences recommended by NICE.

The company presented their original analyses in the CS[26] and, upon the ERG's request, they presented revised analyses in the clarification responses[27] after addressing several issues identified by the ERG as detailed in Section 3.2.1. The revised analyses are presented here, as we believe that they are closer to the company's intended base case than those reported in the CS. According to the company's revised analysis, in the cDMARD-IR patients with severe RA who could tolerate MTX, SAR+MTX dominated both indications of TCZ with concomitant MTX and the incremental cost-effectiveness ratios (ICERs) for the TNFi bundle+MTX and ABT (SC)+MTX compared with SAR+MTX were £69,884 and £117,482 per QALY gained respectively. In cDMARD-IR patients with severe RA who could not tolerate MTX, the ICER for SAR monotherapy versus 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 TNFi-IR patients for whom RTX is not an option, the ICER for all the comparators versus SAR+MTX 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 already 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 confidential PASs in place for TCZ and ABT were not included in these analyses.

3.2.1 Critique of the Cost-Effectiveness Evidence and Interpretation

The company's model was based on the model developed by the Assessment Group (AG) in NICE Technology Appraisal 375 (TA375) [18] but was an individual patient level Markov model rather than a discrete event simulation (DES). After an initial evaluation of the company's analyses, the ERG requested that the company perform new analyses after addressing a number of limitations. The company presented new analysis after addressing the following issues: (i) inadequate treatment sequences that did not reflect NICE recommendations or current practice: sequences did not include one cDMARD treatment after bDMARDs and included bDMARD treatments outside of the points in the pathway where they are recommended by NICE; (ii) patients with moderate RA were assumed to remain moderate and never progress to the severe state. The ERG requested the company to estimate

when the patients would progress to severe RA by establishing a relationship between changes in HAQ-DI and DAS28; (iii) using Malottki et al.[33] instead of the more accurate Hernandez et al.[34] for the mapping of HAQ-DI to EQ-5D; (iv) the limitations in the company's NMA explained in Section 3.1.1; (v) using percentages of improvement of HAQ-DI instead of absolute changes; (vi) omission of rounding to the nearest valid HAQ-DI value; (vii) using a clinically implausible extrapolation curve for 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 CZP instead of 10; and, (x) the inclusion of the speculative PAS discount of 15% applied to TCZ and ABT.

Two main issues remain in the company's revised analyses are two. First, the assumption that the HAQ-DI of patients on cDMARDs and BSC follow a linear trajectory is at odds with recent evidence[35, 36] that shows that the HAQ-DI progression in these patients is not linear. Additionally, the appraisal committee (AC) for TA375 accepted the non-linear trajectory of HAQ-DI using the latent class approach used by the AG.[16] The ERG notes that the company's assumption of linear HAQ-DI increase is likely to lead to underestimating the ICER for SAR+MTX versus MTX in the moderate RA population with a DAS28 score between 4.0 and 5.1. The second remaining issue in the company's amended model is the inadequate implementation of the transition from moderate to severe RA. In the company's amended model, patients go through the treatment sequence for moderate patients and only once they reach BSC they might transition to the severe RA, if their estimated DAS28 is above 5.1. However, patients should progress to the severe sequences the moment their estimated DAS28 score increases above 5.1, without waiting until they have reached the end of the moderate sequence.

3.3 Additional Work Undertaken by the ERG

The ERG undertook exploratory analyses after implementing two changes in the company's amended model to address the perceived two remaining limitations. First, implementing the latent class approach of non-linear HAQ-DI trajectories used in TA375[16] and applying it to patients on cDMARDs or BSC. And second, amending the transition of moderate RA patients to the severe state by: (1) calculating the patient's DAS28 at each cycle by applying the estimated change in DAS28 based on change in HAQ-DI from baseline using the company's linear regression to the patient's baseline DAS28; and, (2) moving patients to the treatment sequences recommended for severe RA once their estimated DAS28 increased above 5.1.

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. Table 1 shows a summary of the results presented by the company and the ERG.

Table 1: ICERs versus SAR + MTX or SAR monotherapy (depending on population)

[Insert Table 1 here]

The confidential PASs in place for ABT and TCZ were not included in these analyses but the ERG provided NICE with analyses including the confidential PASs in a confidential appendix.

3.4 Conclusions of the ERG Report

The key clinical effectiveness evidence for SAR was based on five RCTs and one long-term extension study in two different populations: MTX-IR and bDMARD-IR. In the MTX-IR population, the RCTs showed a significant advantage in ACR20 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 in ACR20 responses and the trials reported significantly favourable results for licensed doses of SAR over comparators for improvement in HAQ-DI. According to the results of the NMAs undertaken by the company, in the SAR in combination with cDMARDs or as monotherapy demonstrated statistically superiority to cDMARDs in the relevant efficacy outcome measures and showed comparable or statistically superior efficacy to most of its bDMARD comparators.

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 several issues identified by the ERG. The ERG undertook exploratory analyses after addressing two remaining issues: the HAQ-DI trajectories of patients on cDMARDs and BSC and the transition of patients from moderate to severe RA. In cDMARD-IR

patients with severe RA who could tolerate MTX, both the company's and the ERG's analyses concluded that SAR + MTX dominates both indications of TCZ in combination with MTX and that the ICER of all other comparators versus SAR +MTX is in excess of £75,000 per QALY. In cDMARD-IR MTX-intolerant patients with severe RA, the ICER for SAR monotherapy versus TNFi bundle monotherapy is estimated to be £17,123 and £34,422 per QALY based on the company's analyses and the ERG's analyses respectively whilst the ICER of TCZ monotherapies (SC and IV) is estimated to be in excess of £1,500,000 per QALY. In TNFi-IR RTX-eligible patients, both the company's and the ERG's analysis coincide that the ICER for SAR + MTX versus RTX + MTX is in excess of £130,000 per QALY compared with. In TNFi-IR patients for whom RTX is not an option, the ERG and the company used different treatment sequences, which led to different results: according to the company's analyses the ICERs of all comparators versus SAR + MTX are in excess of £64,602 per QALY gained whilst 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. In TNFi-IR MTX-intolerant patients, the ICER for SAR monotherapy versus TNFi bundle monotherapy is estimated to be £17,794 and £31,433 per QALY according to the company's and the ERG's analyses respectively. The difference between the ICERs is due to the ERG applying a different HAQ-DI progression whilst on cDMARDs. In TNFi-IR patients who have had RTX + MTX, the ICERs for both indications of TCZ + MTX versus SAR + MTX are estimated to be in excess of £130,000 per QALY according to the company's and the ERG's analyses. In cDMARD-IR patients with moderate RA, SAR + MTX versus MTX is estimated to result in ICERs of £38,254 and £63,438 per QALY gained according to the company's and the ERG's analyses respectively. The confidential PASs in place for TCZ and ABT have not been included in these analyses.

4. Key Methodological Issues

The company used fixed effect models used when data were sparse. However, too few studies should not 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. The statistically significant results of SAR compared with other bDMARD treatments may be as a result of using a fixed effect model, which underestimates uncertainty in the treatment effects. A limitation remaining in the revised NMA is that the company dichotomised the ordered categorical ACR and EULAR response data, which ignores the natural ordering and correlations between the categories within the outcome measure.

The company's original economic analysis contained several issues, the most important being: (1) inadequate sequences that did not reflect NICE recommendations; (2) patients with moderate RA were

assumed never to transition to severe RA; and, (3) assuming a constant HAQ-DI increase rate for patients on cDMARDs or BSC instead of using long-term HAQ-DI progression data.

Finally, including the TNFi-s independently would have been more informative than using a blended comparator, given the differences in cost and efficacy of different TNFi-s and the fact that their market shares may be changing.

5. National Institute for Health and Care Excellence Guidance

In August 2017, on the basis of the evidence available (including verbal testimony of invited clinical experts and patient representatives), the NICE AC produced guidance that SAR in combination with MTX was recommended as an option for treating active RA in: (1) adults whose disease is severe (DAS28 > 5.1) and has responded inadequately to intensive therapy with a combination of cDMARDs; (2) adults whose disease is severe and has responded inadequately to at least one bDMARD if they cannot have rituximab; (3) adults whose disease has responded inadequately to RTX and at least 1 bDMARD. The NICE AC also recommended SAR as monotherapy for people who cannot tolerate MTX who met the criteria in (1) and (2). All the recommendations where subject to the company providing SAR with the discount agreed in the PAS.

5.1 Consideration of Clinical and Cost-Effectiveness Issues Included in the Final Appraisal Determination (FAD)

This section summarises the key issues considered by the AC. The full list can be found in the FAD.[3]

5.1.1 Current Clinical Management

The AC considered the evidence submitted by Sanofi and the current clinical management of previously-treated moderate or severe RA in England. The AC noted that SAR can be used in five different points in the treatment pathway and that the NICE technology appraisal guidance already exists for these points in the pathway. The AC heard from clinical and patient experts that it would be helpful to have new treatments that can be used at various points in the treatment pathway.

5.1.2 Uncertainties in the Clinical evidence

The AC considered the clinical evidence presented by the company from five randomised controlled trials and concluded that the trials were relevant and adequate for its decision-making. The AC accepted that the results showed that SAR plus MTX is more clinically effective than placebo plus MTX and SAR monotherapy is more clinically effective than ADA monotherapy in cDMARD-IR patients. It also acknowledged that SAR is more clinically effective than cDMARDs in TNFi-IR patients but that SAR has an increased rate of AEs compared with MTX. The AC noted that because the only direct evidence available on the comparative effectiveness of SAR and bDMARDs was with ADA, the company did NMAs for different populations. The committee considered the company's original NMAs as well as

the NMAs requested by the ERG and concluded that the methods used by the company were in line with previous NICE technology appraisals and that the NMAs were therefore suitable for decision-making.

5.1.3 Uncertainties in the Economic Modelling

The AC considered the company's model structure to be appropriate for decision-making, as well as the methods for calculating utilities and costs. However, the AC considered that the treatment sequences used in the analyses were appropriate only after the ERG's corrections. The AC was concerned with the implementation of HAQ-DI progression in response to treatment but concluded that the non-linear approach used by the ERG was appropriate and that the ERG's additional analyses were suitable for decision making. Finally, the committee considered that the ERG's changes to how patients progress from treatment for moderate disease to treatment for severe disease were appropriate.

6. Conclusions

The evidence suggests that SAR in combination with MTX or as monotherapy has a similar efficacy for treating moderate to severe RA to that of other bDMARDs, especially TCZ, another IL-6 already recommended by NICE. The economic analyses conducted by the company and the ERG estimated ICERs within the range usually considered by NICE as a cost-effective use of NHS resources for SAR in combination with MTX or as monotherapy versus some or all of its comparators in the considered populations, excluding TNFi-IR RTX-eligible patients and patients with moderate RA. Consequently, NICE recommended SAR in combination with MTX as an option for patients with severe RA who can tolerate MTX if: they are cDMARD-IR; they are TNFi-IR and RTX is not an option; or, they are TNFi-IR and have already been treated with RTX + MTX. NICE recommended SAR monotherapy for cDMARD-IR and TNFi-IR patients with severe RA who cannot tolerate MTX.

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Author contributions

Iñigo Bermejo and Matt Stevenson critiqued the mathematical model provided and the cost-effectiveness analyses submitted by the company. Emma Simpson critiqued the clinical effectiveness data reported by the company. Shijie Ren critiqued the NMA performed by the company. Mark Clowes critiqued the literature searches undertaken by the company. David L Scott and Adam Young provided clinical advice to the ERG throughout the project. All authors were involved in drafting and

commenting on the final document. Iñigo Bermejo acts as the guarantor of the manuscript. This summary has not been externally reviewed by PharmacoEconomics.

Compliance with Ethical Standards

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Conflicts of Interest

IB, SR, ES, MC, DS, AY and MS have no conflicts of interest to declare.

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