Sarilumab for previously treated moderate or severe rheumatoid arthritis: A Single Technology Appraisal

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Date completed	Date completed (19/07/2017)

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 19/04/17.

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 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

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 54.

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 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 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