Common Drug Review
Clinical Review Report

May 2017

Drug	sarilumab (Kevzara)
Indication	Treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to one or more biologic or non-biologic disease-modifying antirheumatic drugs
Listing request	As per indication
Dosage form(s)	Pre-filled syringe (150 mg/1.14 mL or 200 mg/1.14 mL)
NOC Date	January 12, 2017
Manufacturer	Sanofi Genzyme

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in rheumatology who provided input on the conduct of the review and the interpretation of findings.

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ABBREVIATIONS

ACR	American College of Rheumatology response
BRM	biologic response modifier
CDAI	Clinical Disease Activity Index
CDR	CADTH Common Drug Review
CI	confidence interval
CRP	C-reactive protein (used with DAS)
DAS 28	Disease Activity Score 28
DMARD	disease-modifying antirheumatic drug
ESR	erythrocyte sedimentation rate
EQ-5D	EuroQol 5-Dimensions questionnaire
FACIT	Functional Assessment of Chronic Illness Therapy
HAQ-DI	Health Assessment Questionnaire–Disability Index
LOCF	last observation carried forward
LSMD	least squares mean difference
MCS	mental component summary
mTSS	modified Total Sharp Score
MTX	methotrexate
OR	odds ratio
PCS	physical component summary
RA	rheumatoid arthritis
SF-36	Short Form (36) Health Survey
TNF	tumour necrosis factor

EXECUTIVE SUMMARY

Introduction

Rheumatoid arthritis (RA) is the most common inflammatory joint disease and is characterized by joint swelling, joint tenderness, and the destruction of synovial joints, leading to severe disability and premature mortality.[1,2] Sarilumab is an interleukin-6 receptor antagonist indicated for the treatment of adults with moderately to severely active RA who have had an inadequate response or intolerance to one or more biologic or non-biologic disease-modifying antirheumatic drugs (DMARDs). Sarilumab may be used as monotherapy or in combination with methotrexate (MTX) or other non-biologic DMARDs.

The objective of this report is to provide a systematic review of the beneficial and harmful effects of sarilumab for the treatment of adults with moderately to severely active RA who have had an inadequate response or intolerance to one or more biologic or non-biologic DMARDs.

Included Studies

The CADTH Common Drug Review (CDR) systematic review included four double-blind randomized controlled trials that investigated the safety and efficacy of sarilumab for the treatment of patients with moderately to severely active RA. These included one 24-week placebo-controlled trial (TARGET, N = 546), one 52-week placebo-controlled trial (MOBILITY, N = 1,197), and two 24-week active-controlled trials that compared sarilumab against adalimumab (MONARCH, N = 369) or tocilizumab (ASCERTAIN, N = 202). The MOBILITY and MONARCH studies required patients to have been previously treated with MTX; the TARGET and ASCERTAIN trials were conducted in patients who were treatment-experienced with one or more tumour necrosis factor alpha antagonists. The studies investigated the use of sarilumab as monotherapy (MONARCH), in combination with MTX (MOBILITY), and in combination with various non-biologic DMARDs (ASCERTAIN and TARGET). Multiple primary efficacy end points were used within and across the studies, including American College of Rheumatology response 20 (20), Health Assessment Questionnaire–Disability Index (HAQ-DI), Disease Activity Score 28 (DAS 28) erythrocyte sedimentation rate (ESR), and modified Total Sharp Score (mTSS). Safety and tolerability were the primary end points of the ASCERTAIN trial; however, no statistical comparisons were made between sarilumab and tocilizumab for any outcome. Consequently, no conclusions can be drawn from the ASCERTAIN trial data.

Three of the included studies (MOBILITY, TARGET, and ASCERTAIN) randomized patients to two different dosages of sarilumab (i.e., 150 mg or 200 mg once every two weeks). The recommended dosage of sarilumab is 200 mg once every two weeks, with a 150 mg dosage recommended for patients with neutropenia, thrombocytopenia, or elevated liver enzymes. The CDR review focused primarily on the Health Canada–approved dosage regimen; since the 150 mg dosage regimens were not restricted to people with the adverse events noted above, the emphasis is placed on the efficacy and safety data for the 200-mg-once-every-two-weeks regimen.

The protocols for the two placebo-controlled trials included early escape criteria for patients who demonstrated a lack of efficacy beginning at week 16 in MOBILITY and at week 12 in TARGET if they failed to demonstrate at least a 20% improvement from baseline in either swollen joint count or tender joint count for two consecutive study visits or demonstrated any other clear lack of efficacy based on the judgment of the investigator. These patients were eligible to receive rescue therapy with open-label sarilumab. Rescue therapy was more commonly initiated in the placebo groups (39.3% to 34.8%) than in the sarilumab groups (12.9% to 14.1%).

Efficacy

Clinical Response

In both MOBILITY and TARGET, sarilumab was associated with statistically significant improvements in the proportion of patients with 20, 50, and 70 responses compared with placebo at 24 weeks (all $P < 0.0001$). In the MONARCH study, sarilumab was associated with a statistically significant increase in the proportion of patients who achieved a 20 response (odds ratio [OR] 1.800; 95% confidence interval [CI], 1.168 to 2.773), 50 response (OR 1.976; 95% CI, 1.289 to 3.028), or 70 response (OR 2.286; 95% CI, 1.300 to 4.020) compared with adalimumab. [redacted]. The clinical expert consulted by CADTH suggested that the differences between sarilumab and placebo or adalimumab were clinically significant. The superiority of sarilumab over adalimumab was established only in the clinical trial where both products were used as a monotherapy. A previous clinical study (PREMIER) has demonstrated that adalimumab is more effective when used in combination with MTX than as monotherapy.[3]

Radiographic Progression

After 52 weeks of treatment in MOBILITY, sarilumab was associated with a statistically significant difference in mTSS compared with placebo (0.25 versus 2.78; $P < 0.0001$) and a statistically significantly greater proportion of sarilumab-treated patients had no evidence of radiographic disease progression compared with placebo (55.6% versus 38.7%; OR 2.001; 95% CI, 1.506 to 2.660). Although sarilumab was associated with a statistically significantly smaller change in mTSS compared with placebo after 52 weeks of treatment, the difference did not exceed the published estimates of the minimal clinically important difference of 3.0 to 4.6 units for this scale.

Disease Activity and Remission

In both the MOBILITY and TARGET studies, treatment with sarilumab was associated with statistically significant improvements in DAS 28 with C-reactive protein (CRP) at 24 weeks (least squares mean difference [LSMD] [redacted] and −1.444 [95% CI, −1.752 to −1.135], respectively) compared with placebo. In MONARCH, sarilumab was associated with a statistically significantly greater improvement in DAS 28-ESR (LSMD −1.077; 95% CI, −1.361 to −0.793) and DAS 28-CRP (LSMD −0.884; 95% CI, −1.138 to −0.629) compared with adalimumab. Sarilumab-treated patients were also statistically significantly more likely to achieve DAS 28-CRP remission (i.e., a score < 2.6) than those treated with placebo (OR 5.801 [95% CI, 2.948 to 11.413] and OR 4.690 [95% CI, 3.176 to 6.926] in TARGET and MOBILITY, respectively) or adalimumab (OR 3.314 [95% CI, 1.973 to 5.566] in MONARCH). [redacted]

Sarilumab was associated with a statistically significant improvement in the Clinical Disease Activity Index (CDAI) scale [redacted] and compared with adalimumab at 24 weeks in MONARCH (LSMD −3.741; 95% CI, −6.016 to −1.466). There was no statistically significance difference between sarilumab and adalimumab for the proportion of patients with a CDAI response at week 12 (OR 1.935; 95% CI, 0.695 to 5.382); however, there was a statistically significant difference at week 24 (OR 2.869; 95% CI, 0.981 to 8.389).

Physical Function

Treatment with sarilumab was associated with a statistically significant improvement in HAQ-DI compared with placebo (LSMD −0.210 [95% CI, −0.325 to −0.095] in TARGET and LSMD −0.258 [95% CI, −0.336 to −0.181] in MOBILITY) and compared with adalimumab (LSMD −0.182 [95% CI, −0.305 to −0.059] in MONARCH). [redacted] The minimal clinically important difference for the HAQ-DI scale is estimated to be a change of 0.22. A statistically significantly greater proportion of sarilumab-treated patients achieved an HAQ-DI unit difference greater than 0.22 at week 24 compared with placebo at week 12 in TARGET (OR 1.613; 95% CI, 1.058 to 2.461) and week 16 in MOBILITY (OR 1.758; 95% CI, 1.323 to 2.337) and compared with adalimumab at 24 weeks in MONARCH (OR 1.747; 95% CI, 1.147 to 2.663).

Health-Related Quality of Life and Fatigue

Compared with placebo, treatment with sarilumab was associated with a statistically significant improvement in the Short Form (36) Health Survey (SF-36) physical component summary (PCS) at 24 weeks in both TARGET (LSMD 4.075; 95% CI, 2.305 to 5.846) and MOBILITY (LSMD 3.201; 95% CI, 1.978 to 4.423). There was a statistically significant difference favouring sarilumab over placebo for change from baseline in SF-36 mental component summary (MCS) at 24 weeks in MOBILITY (LSMD 4.271; 95% CI, 2.761 to 5.781); however, there was no statistically significant difference in TARGET (LSMD 2.013; 95% CI, −0.282 to 4.309). Compared with placebo, sarilumab resulted in greater improvements in SF-36 PCS (LSMD 3.530; 95% CI, 2.164 to 4.897) and SF-36 MCS (LSMD 2.896; 95% CI, 1.199 to 4.593) in MOBILITY at 52 weeks. In the MONARCH study, treatment with sarilumab was associated with a statically significant difference in SF-36 PCS compared with adalimumab at 24 weeks (LSMD 2.650; 95% CI, 1.147 to 4.153); however, there was no difference between sarilumab and adalimumab in SF-36 MCS at 24 weeks (LSMD 1.036; 95% CI, −1.061 to 3.132). The differences between sarilumab and placebo or adalimumab for the SF-36 PCS exceed the lower end of the 2.5-to-5-unit range of the commonly cited minimal clinically important difference.

[redacted] Treatment with sarilumab was associated with greater improvements in the Functional Assessment of Chronic Illness Therapy (FACIT)–Fatigue scale at 24 weeks in TARGET (LSMD 3.246; 95% CI, 1.037 to 5.456) and at 24 weeks and 52 weeks in MOBILITY (LSMD 3.351 [95% CI, 2.092 to 4.611] and LSMD 3.148 [95% CI, 1.746 to 4.551], respectively). There was no statistically significant difference between sarilumab and adalimumab for change from baseline in FACIT-Fatigue at 24 weeks in MONARCH.

Harms

Adverse Events

The proportion of patients who experienced at least one adverse event was greater in the sarilumab groups than in the placebo groups of both MOBILITY (78.1% versus 61.6%) and TARGET (65.2% versus 49.7%). In the active-controlled trials, the proportion of patients with at least one adverse event was similar between the sarilumab and adalimumab groups in MONARCH (64.1% versus 63.6%) and was slightly greater with sarilumab compared with tocilizumab in ASCERTAIN (70.6% versus 66.7%). Compared with placebo, a greater proportion of sarilumab-treated patients experienced at least one adverse event that was classified as an infection or infestation (39.6 versus 31.1% in MOBILITY and 30.4% versus 26.5% in TARGET). Infections and infestations were reported for a similar proportion of

patients in both the sarilumab and adalimumab groups in MONARCH (28.8% versus 27.7%) and [redacted]. Gastrointestinal adverse events were more common with sarilumab compared with placebo (15.1% versus 10.8% in MOBILITY and [redacted]) and [redacted]. [redacted], worsening of RA was cited as an adverse event less frequently in the sarilumab groups compared with [redacted], adalimumab (0.5% versus 3.8%), and tocilizumab (0% versus 5.9%).

In consultation with a clinical expert, the CDR review included serious infections, neutropenia, malignancies, major adverse cardiovascular events, anaphylaxis, gastrointestinal perforations, liver toxicity, and dyslipidemia as adverse events of special interest for this review. A summary of these events is provided below:

- In the 24-week studies, the proportion of patients with at least one serious infection was the same with sarilumab and placebo in TARGET (1.1% in both), adalimumab in MONARCH (1.1% in both), and tocilizumab in ASCERTAIN (2.0% in both); however, the proportion was greater with sarilumab compared with placebo in the 52-week MOBILITY study (4.0% versus 2.3%).
- Neutropenia (i.e., absolute neutrophil count below the lower limit of normal) was more commonly reported with sarilumab than with placebo (14.4% versus 0.2% in MOBILITY and 12.5% versus 1.1% in TARGET), adalimumab (13.6% versus 0.5%), and tocilizumab (15.7% versus 3.9%).
- There were few malignancies reported in the included studies ranging from 0% to 0.7% with sarilumab and 0.2% to 0.6% with placebo. There were no malignancies reported in the ASCERTAIN trial and a single adalimumab-treated patient developed a malignancy in MONARCH.
- [redacted]
- [redacted]
- The manufacturer's safety evaluation grouped adverse events related to diverticulitis, gastrointestinal ulceration, and gastrointestinal perforations into a single end point. [redacted]
- Lipid elevation (i.e., adverse events recorded as hypertriglyceridemia, hypercholesterolemia, triglycerides increased, dyslipidemia, cholesterol increased, high density lipoprotein increased, or low density lipoprotein increased) [redacted]. In the two active-controlled trials, sarilumab was associated with a lower proportion of patients with elevated lipids compared with adalimumab (1.6% versus 4.3%) [redacted].
- There were no events of anaphylaxis reported in any of the included studies.

Serious Adverse Events

Serious adverse events were more commonly reported with sarilumab compared with placebo (11.3% versus 5.4% in MOBILITY and 5.4% versus 3.3% in TARGET). The proportion of patients with at least one serious adverse event was similar between sarilumab and adalimumab (4.9% versus 6.5%) and sarilumab and tocilizumab (5.9% versus 6.9%). Serious adverse events categorized as infections and infestations were more commonly reported with sarilumab compared with placebo in MOBILITY (4.0% versus 2.3%); however, the proportions were the same in the sarilumab and placebo groups of TARGET (1.1% in both). There were no differences between the treatment groups for the proportion of patients

who experienced at least one serious infection in MONARCH (1.1% in each group) and ASCERTAIN (2.0% in each group).

Withdrawals Due to Adverse Events

Withdrawals due to adverse events were more commonly reported in the sarilumab groups compared with the placebo groups (13.9% versus 4.7% in MOBILITY and 9.2% versus 4.4% in TARGET). The proportion of patients who withdrew as a result of adverse events was similar between the sarilumab and adalimumab groups in MONARCH (6.0% versus 7.1%) and was greater with sarilumab compared with tocilizumab in ASCERTAIN (15.7% versus 3.9%).

Potential Place in Therapy[1]

The Canadian Rheumatology Association guidelines for the management of RA support a treat-to-target strategy, where the target is attainment of remission or, when that is not possible, low disease activity.[4] Despite vast improvements in the understanding of the pathogenesis of the disease and available therapeutic options for RA there are many important unmet needs in the management of this disease. Broadly, these include lack of adequate response to current therapies, lack of data regarding best practices for switching biologic therapies, lack of predictive clinical characteristics and biomarkers for response to therapies, safety profiles of current drugs, and persistence and adherence with current therapies.[5]

Traditionally, the primary outcomes in clinical trials for therapies in RA are response rates (20, 50, or 70), which represent a measure of relative incremental improvement in defined signs and symptoms of RA. These outcomes do not speak to the practice of rheumatology in 2016, where clinicians no longer look for incremental improvement, but remission. Importantly, sarilumab has demonstrated not only clinically significant response rates in populations of biologic-naive and biologic-experienced patients but also clinically significant rates of disease remission, which are a better reflection of real-world clinical practice. As monotherapy, sarilumab has shown statistically significant improvement in response rates when compared with adalimumab monotherapy. While some may argue that this trial is biased toward sarilumab given that adalimumab has been shown to more efficacious when used in combination with MTX rather than as monotherapy,[3] it is important to note that many patients are not adherent to MTX.[6] The fact that sarilumab has demonstrated superiority compared with one of the most commonly used first-line biologic therapies in RA supports the conclusion that sarilumab will be an important addition to the armamentarium for appropriate management of RA in a real-world setting where many patients are nonadherent to MTX. In addition, sarilumab has shown clinically significant response rates in patients who have failed prior biologic therapy. This is a difficult population of patients to treat because response rates to therapy tend to diminish after the first biologic therapy has been used. For this reason, sarilumab could fill an important role not only in biologic-naive patients but also in patients who have failed prior biologic therapy.

There is a lack of predictors for evaluating which patients are more likely to respond to any particular RA medication; therefore, it is difficult to specify criteria to determine which patients should receive sarilumab, aside from patients who have active RA (i.e., those whose disease is not in remission or not in a low disease activity state) and who have failed treatment with MTX or biologic therapies or both. Based on the results of the TARGET trial,[7] the RA clinical community is likely to consider sarilumab to be

[1] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

one of the preferred drugs of choice when switching medications after failure with a biologic; however, more data comparing switches to other therapies are required to definitively support this approach.

Conclusions

The CDR systematic review included four double-blind randomized controlled trials that investigated the safety and efficacy of sarilumab for the treatment of patients with moderately to severely active RA. Three double-blind randomized controlled studies demonstrated that treatment with sarilumab resulted in statistically significant and clinically meaningful clinical response (20, 50, or 70), clinical remission (DAS 28 < 2.6), and improvement in physical functioning (HAQ-DI) compared with placebo (MOBILITY and TARGET) and compared with adalimumab (MONARCH). The placebo-controlled trials investigated the efficacy and safety of sarilumab when used in combination with MTX or other DMARDs; the adalimumab-controlled study was conducted using monotherapy regimens. Radiographic progression was evaluated using mTSS, and sarilumab was associated with a statistically significantly smaller increase in mTSS compared with placebo after 52 weeks of treatment; however, the MOBILITY trial was likely too short to accurately observe and conclude that treatment with sarilumab results in clinically meaningful improvements in radiographic progression of disease. Sarilumab was associated with statistically significant and clinically relevant improvements in the physical component score of the SF-36 compared with placebo and adalimumab.

Treatment with sarilumab is associated with an increased risk of neutropenia, thrombocytopenia, elevated liver enzymes, and increased lipid levels; therefore, routine monitoring of neutrophils, platelets, and liver enzymes is recommended. Serious adverse events were more common with sarilumab compared with placebo (11.3% versus 5.4% in MOBILITY and 5.4% versus 3.3% in TARGET). The proportion of patients with at least one serious adverse event was similar between sarilumab and adalimumab (4.9% versus 6.5%) and sarilumab and tocilizumab (5.9% versus 6.9%). Withdrawals due to adverse events were more commonly reported with sarilumab compared with placebo (9.2% to 13.9% versus 4.4% to 4.7%) and tocilizumab (15.7% versus 3.9%), but were similar between sarilumab and adalimumab (6.0% versus 7.1%). The included studies were short-term trials, and many of the adverse events of special interest were rare oss the studies.

[redacted].

TABLE 1: SUMMARY OF EFFICACY RESULTS FROM PLACEBO-CONTROLLED TRIALS

End Point	Time (weeks)	Parameter	TARGET		MOBILITY	
			PLC + DMARD	SARI + DMARD	PLC + MTX	SARI + MTX
20	24	n (%)	61 (33.7)	112 (60.9)	133 (33.4)	265 (66.4)
		OR (95% CI)	3.284 (2.108 to 5.115)		3.975 (2.957 to 5.344)	
		P value	< 0.0001		< 0.0001	
50	24	n (%)	33 (18.2)	75 (40.8)	66 (16.6)	182 (45.6)
		OR (95% CI)	3.374 (2.045 to 5.566)		4.269 (3.064 to 5.948)	
		P value	< 0.0001		< 0.0001	
70	24	n (%)	13 (7.2)	30 (16.3)	29 (7.3)	99 (24.8)
		OR (95% CI)	2.653 (1.308 to 5.383)		4.280 (2.743 to 6.678)	
		P value	0.0056		< 0.0001	
HAQ-DI	12 16[a]	BL mean (SD)	1.78 (0.64)	1.82 (0.62)	1.61 (0.65)	1.69 (0.63)
		LSMD (95% CI)	−0.210 (−0.325 to −0.095)		−0.258 (−0.336 to −0.181)	
		P value	0.0004		< 0.0001	
DAS 28-CRP < 2.6	24	n (%)	13 (7.2)	53 (28.8)	40 (10.1)	136 (34.1)
		OR (95% CI)	[redacted]		[redacted]	
		P value	< 0.0001		< 0.0001	
mTSS	52	BL mean (SD)	Not evaluated		48.01 (65.23)	46.34 (57.43)
		Mean change (SD)			2.78 (7.73)	0.25 (4.61)
		P value			< 0.0001	
mTSS (no progression)	52	N (%)	Not evaluated		154 (38.7%)	222 (55.6%)
		OR (95% CI)			[redacted]	
					< 0.0001	
CDAI	24	BL mean (SD)	[redacted]		[redacted]	
		LSMD (95% CI)	[redacted]		[redacted]	
		P value	[redacted]		[redacted]	
SF-36 PCS	24	BL mean (SD)	29.73 (7.76)	29.36 (6.71)	32.15 (7.01)	31.24 (6.90)
		LSMD (95% CI)	4.075 (2.305 to 5.846)		3.201 (1.978 to 4.423)	
		P value	< 0.0001		< 0.0001	
SF-36 MCS	24	BL mean (SD)	38.52 (12.62)	39.08 (11.40)	37.82 (10.55)	38.92 (11.75)
		LSMD (95% CI)	2.013 (−0.282 to 4.309)		4.271 (2.761 to 5.781)	
		P value	0.0854		< 0.0001	
EQ-5D VAS	24	BL mean (SD)	[redacted]		Not evaluated	
		LSMD (95% CI)	[redacted]			
		P value	[redacted]			
EQ-5D–Utility	24	BL mean (SD)	[redacted]		Not evaluated	
		LSMD (95% CI)	[redacted]			
		P value	[redacted]			
FACIT-Fatigue	24	BL mean (SD)	24.00 (10.42)	23.71 (10.17)	27.24 (9.99)	26.16 (10.46)
		LSMD (95% CI)	3.246 (1.037 to 5.456)		3.351 (2.092 to 4.611)	
		P value	0.0040		< 0.0001	

= American College of Rheumatology; BL = baseline; CDAI = Clinical Disease Activity Index; CI = confidence interval; DAS 28-CRP = Disease Activity Score 28 using C-reactive protein; DMARD = disease-modifying antirheumatic drug; EQ-5D = EuroQol 5-Dimensions questionnaire; FACIT = Functional Assessment of Chronic Illness Therapy; HAQ-DI = Health Assessment Questionnaire–Disability Index; LSMD = least squares mean difference; MCS = mental component summary; mTSS = modified Total Sharp Score; MTX = methotrexate; n = number of patients; OR = odds ratio; PCS = physical component summary; PLC = placebo; SARI = sarilumab; SD = standard deviation; SF-36 = Short Form (36) Health Survey; VAS = visual analogue scale.

[a] Changes in HAQ-DI were evaluated at 12 weeks in TARGET and 16 weeks in MOBILITY.

TABLE 2: SUMMARY OF EFFICACY RESULTS FROM ACTIVE-CONTROLLED TRIALS

End Point	Time (Weeks)	Parameter	MONARCH		ASCERTAIN	
			Adalimumab	SARI	TOC + DMARD	SARI + DMARD
20	24	n (%)	108 (58.4)	132 (71.7)	[redacted]	[redacted]
		OR (95% CI)	1.800 (1.168 to 2.773)		NR	
		P value	0.0074		NR	
50	24	n (%)	55 (29.7)	84 (45.7)	[redacted]	[redacted]
		OR (95% CI)	1.976 (1.289 to 3.028)		NR	
		P value	0.0017		NR	
70	24	n (%)	22 (11.9)	43 (23.4)	[redacted]	[redacted]
		OR (95% CI)	2.286 (1.300 to 4.020)		NR	
		P value	0.0036		NR	
HAQ-DI	24	BL mean (SD)	1.62 (0.64)	1.64 (0.54)	[redacted]	[redacted]
		LSMD (95% CI)	−0.182 (−0.305 to −0.059)		NR	
		P value	0.0037		NR	
DAS 28-CRP < 2.6	24	n (%)	[redacted]	[redacted]	[redacted]	[redacted]
		OR (95% CI)	[redacted]		NR	
		P value	[redacted]		NR	
CDAI	24	BL mean (SD)	42.00 (11.76)	43.52 (11.94)	Not evaluated	
		LSMD (95% CI)	−3.741 (−6.016 to −1.466)			
		P value	0.0013			
SF-36 PCS	24	BL mean (SD)	31.53 (6.48)	30.77 (6.09)	Not evaluated	
		LSMD (95% CI)	2.650 (1.147 to 4.153)			
		P value	0.0006			
SF-36 MCS	24	BL mean (SD)	36.93 (11.59)	36.43 (10.43)	Not evaluated	
		LSMD (95% CI)	1.036 (−1.061 to 3.132)			
		P value	0.3319			
EQ-5D VAS	24	BL mean (SD)	[redacted]	[redacted]	Not evaluated	
		LSMD (95% CI)	[redacted]			
		P value	[redacted]			
EQ-5D-Utility	24	BL mean (SD)	[redacted]	[redacted]	Not evaluated	
		LSMD (95% CI)	[redacted]			
		P value	[redacted]			
FACIT-Fatigue	24	BL mean (SD)	24.43 (10.26)	23.59 (8.92)	Not evaluated	
		LSMD (95% CI)	1.768 (−0.137 to 3.674)			
		P value	0.0689			

AMR = American College of Rheumatology; BL = baseline; CDAI = Clinical Disease Activity Index; CI = confidence interval; DAS 28-CRP = Disease Activity Score 28 using C-reactive protein; DMARD = disease-modifying antirheumatic drug; EQ-5D = EuroQol 5-Dimensions questionnaire; FACIT = Functional Assessment of Chronic Illness Therapy; HAQ-DI = Health Assessment Questionnaire–Disability Index; LSMD = least squares mean difference; MCS = mental component summary; n = number of patients; NR = not reported; OR = odds ratio; PCS = physical component summary; SARI = sarilumab; SD = standard deviation; SF-36 = Short Form (36) Health Survey; TOC = tocilizumab; VAS = visual analogue scale.
Source: Clinical Study Reports for ASCERTAIN[8] and MONARCH.[9]

TABLE 3: SUMMARY OF ADVERSE EVENTS

AEs n (%)	MOBILITY		TARGET		MONARCH		ASCERTAIN	
	Treatment + MTX		Treatment + DMARD		Monotherapy		Treatment + DMARD	
	Placebo (N = 427)	SARI (N = 424)	Placebo (N = 181)	SARI (N = 184)	ADA (N = 184)	SARI (N = 184)	TOC (N = 102)	SARI (N = 51)
Any TEAE	263 (61.6)	331 (78.1)	90 (49.7)	120 (65.2)	117 (63.6)	118 (64.1)	68 (66.7)	36 (70.6)
SAE	23 (5.4)	48 (11.3)	6 (3.3)	10 (5.4)	12 (6.5)	9 (4.9)	7 (6.9)	3 (5.9)
WDAE	20 (4.7)	59 (13.9)	8 (4.4)	17 (9.2)	13 (7.1)	11 (6.0)	4 (3.9)	8 (15.7)

ADA = adalimumab; AE = adverse event; DMARD = disease-modifying antirheumatic drug; MTX = methotrexate; n = number of patients with event; N = number of patients in the safety analysis; SAE = serious adverse event; SARI = sarilumab; TEAE = treatment-emergent adverse event; TOC = tocilizumab; WDAE = withdrawal due to adverse event.
Source: Clinical Study Reports for TARGET,[7] MOBILITY,[10] ASCERTAIN,[8] and MONARCH.[9]

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by joint swelling, joint tenderness, and destruction of synovial joints, leading to severe disability and premature mortality.[1] According to a report by the Arthritis Alliance of Canada, RA is the most common inflammatory joint disease, with a prevalence of 0.9% in 2010 (272,299 patients), which is expected to increase to an estimated 1.3% (549,218 patients) of the Canadian population by 2040. More than half of all new RA cases occur between the ages of 40 years and 70 years, though all age groups are affected, and the prevalence is approximately two times higher among women than among men.[2]

1.2 Standards of Therapy

1.2.1 Non-Pharmacological Management

Guidelines for the management of RA emphasize the use of non-drug interventions in addition to pharmacological therapy.[4,11] Some modalities included in non-drug care are exercise therapy, electro-physical modalities, orthoses and assistive devices, and self-management interventions. There is evidence to support the utility of non-drug care to achieve symptomatic relief including pain control and muscle stimulation, relief of strain or load on a joint, improved patterns of motion and function, and prevention of deformity, without detrimental effects on disease activity.[11] Education on self-management strategies such as joint protection and energy conservation, exercises, or the use of assistive devices may provide support for those living with RA.[11]

1.2.2 Pharmacological Management

The goal of pharmacologic RA treatment is to achieve remission or, when that is not possible, to minimize disease activity while controlling symptoms, halting damage, preventing disability, and improving quality of life.[4] Beginning treatment early and aggressively with non-biologic disease-modifying antirheumatic drugs (DMARD) have been shown to alter the clinical course of RA and slow or halt radiographic progression.[4]

Unless contraindicated, methotrexate (MTX) is the preferred DMARD with respect to efficacy and safety and is usually the first-line DMARD.[4] Therapy with MTX is individualized with doses rapidly titrated to a usual maximum dosage of 25 mg per week for subcutaneous administration, and 20 mg per week for oral use.[4] The Canadian Rheumatology Association recommends parenteral administration of MTX in patients with an inadequate response or intolerance to oral MTX.[4] The initial treatment strategy with DMARDs can also include nonsteroidal anti-inflammatory drugs or corticosteroids (in the lowest effective dose possible) or both as bridging therapies while waiting for DMARDs to take effect, to manage flares, or for symptom control if no other options exist.[4]

Biologic response modifiers (BRMs) are another class of medications to treat RA, and are recommended for patients who are intolerant to, or who have an inadequate response with DMARDS.[7] Currently, all Canadian provincial formularies require failure of at least two DMARDs before accessing a BRM, and many also require failure of an adequate trial of combination DMARD therapy.[4] MTX is the preferred anchor drug in combination therapy with conventional DMARDs, unless contraindicated.[4] The Canadian Rheumatology Association defines inadequate response to DMARD therapy as a moderate to high level of disease activity despite treatment with at least two DMARDs (including MTX unless the patient has contraindication) in monotherapy or as combination therapy after three months at target dosages.[4]

As shown in Table 4, the majority of BRMs that are currently approved for use in Canada are classified as tumour necrosis factor (TNF) alpha antagonists. These include etanercept, infliximab, adalimumab, golimumab, and certolizumab pegol. In addition to the TNF alpha antagonists, the following BRMs are also available in Canada: abatacept (T-cell stimulation inhibitor), rituximab (B lymphocyte–depleting drug), tocilizumab (interleukin-6 antagonist), tofacitinib (janus kinase inhibitor), and anakinra (interleukin-1 antagonist).[4] All of the BRMs are approved for use in combination with one or more DMARDs (typically MTX), and all but infliximab, golimumab, and rituximab are approved for use as monotherapy.[12-24] Not all patients are able to tolerate treatment with MTX; therefore, indications for use as monotherapy or with DMARDs other than MTX can add to the clinical utility of a BRM. Based on the Canadian Rheumatology Association guidelines, patients who have failed treatment with one or two TNF alpha antagonists due to a lack of efficacy or toxicity could be switched to another TNF alpha antagonist or to another BRM with a different mechanism of action.[4] Among the BRMs available in Canada, tocilizumab, abatacept, rituximab, and sarilumab are approved for use in patients who failed treatment with one or more TNF alpha antagonists.[12,13,22,23]

According to the Canadian Rheumatology Association recommendations, patients with active RA should be monitored every one to three months, and non-biologic and biologic DMARD therapy should be adjusted every three to six months if treatment targets have not been achieved.[4]

1.3 Drug

Sarilumab is an interleukin-6 receptor antagonist indicated in the treatment of adult patients with moderately to severely active RA who have had an inadequate response or intolerance to one or more biologic or non-biologic DMARDs. The product monograph states that sarilumab should be used in combination with MTX or other traditional DMARDs but may be given as monotherapy in cases of intolerance or contraindication to MTX or DMARDs. The recommended dosage of sarilumab is 200 mg once every two weeks given as a subcutaneous injection. A reduced dosage of 150 mg once every two weeks is recommended for patients with neutropenia, thrombocytopenia, or elevated liver enzymes (see Appendix 3). No dosage adjustment is required for patients with mild to moderate renal impairment.[12] Sarilumab is available as a solution for subcutaneous injection in 150 mg/1.14 mL or 200 mg/1.14 mL single-dose pre-filled syringes.[12]

Indication under review
Treatment of adult patients with moderately to severely active RA who have had an inadequate response or intolerance to one or more biologic or non-biologic DMARDs
Listing criteria requested by sponsor
As per indication

DMARD = disease-modifying antirheumatic drug; RA = rheumatoid arthritis.

TABLE 4: KEY CHARACTERISTICS OF BIOLOGIC AGENTS AND TOFACITINIB FOR RHEUMATOID ARTHRITIS

Drug Class	Drug	Approved Indications for Rheumatoid Arthritis[a]			Administration and Recommended Dosage
		Inadequate Response	Monotherapy	Combinations	
IL-6 inhibitor	Sarilumab[12]	• ≥ 1 DMARD • ≥ 1 BRM	Yes	• MTX • Other DMARDs	**SC:** 200 mg Q2W
	Tocilizumab[13]	• ≥ 1 DMARD • ≥ 1 TNF inhibitor	Yes	• MTX	**IV:** 4 to 8 mg/kg Q4W **SC:** 162 mg Q2W or QW
TNF inhibitors	Adalimumab[14]	• Not specified	Yes[b]	• MTX[c] • Other DMARDs	**SC:** 40 mg Q2W or QW
	Etanercept[15,16]	• Not specified	Yes	• MTX	**SC:** 50 mg QW
	Golimumab[17]	• Not specified	No	• MTX	**IV:** 2 mg/kg at weeks 0, 4, then Q8W **SC:** 50 mg QM
	Certolizumab[18]	• Not specified	Yes[b]	• MTX	**SC:** 400 mg at weeks 0, 2, 4 then 200 mg Q2W or 400 mg Q4W
	Infliximab[19,20]	• Not specified	No	• MTX	**IV:** 3 mg/kg at weeks 0, 2, 6, then Q8W or up to 10 mg/kg Q4W
JAK inhibitor	Tofacitinib[21]	• MTX	Yes[b]	• MTX	**Oral:** 5 mg b.i.d.
T-cell stimulation inhibitor	Abatacept[22]	• ≥ 1 DMARD • ≥ 1 TNF inhibitor	Yes	• MTX[c] • Other DMARDs	**IV:** 0.5 to 1 g at weeks 0, 2, then Q4W[d] **SC:** 125 mg QW
CD20 inhibitor	Rituximab[23]	• ≥ 1 TNF inhibitor	No	• MTX	**IV:** 1,000 mg at weeks 0, 2
IL-1 inhibitor	Anakinra[24]	• Not required	Yes	• MTX • Other DMARDs	**SC:** 100 mg q.d.

b.i.d. = twice daily; BRM = biologic response modifier; DMARD = disease-modifying antirheumatic drug; JAK = janus kinase; IL = interleukin; IV = intravenous; MTX = methotrexate; Q4W = once every four weeks; Q8W = once every eight weeks; q.d. = once daily; QM = once per month; QW = once per week; SC = subcutaneous; TNF = tumour necrosis factor.

[a] Health Canada–approved indication (all are approved for adults with moderately to severely active rheumatoid arthritis except anakinra, which is approved for active rheumatoid arthritis).

[b] If methotrexate is not tolerated or is contraindicated.

[c] If used as a first-line treatment, should be given in combination with methotrexate.

[d] Weight-based dosing: 500 mg for less than 60 kg; 750 mg for 60 to 100 kg; 1,000 mg for more than 100 kg.

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of sarilumab for the treatment of adults with moderately to severely active RA who have had an inadequate response or intolerance to one or more biologic or non-biologic DMARDs.

2.2 Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase III studies were selected for inclusion based on the selection criteria presented in Table 5.

TABLE 5: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adults with moderately to severely active RA who have had an inadequate response or intolerance to one or more biologic or non-biologic DMARDs Subgroups of interest based on: • Concomitant use of DMARD versus no DMARD • Treatment-experienced with BRMs versus BRM treatment-naive • Disease severity at baseline • Baseline body weight • Rheumatoid factor
Intervention	Sarilumab administered SC at recommended dosages alone or in combination with non-biologic DMARDs
Comparators	Individual or combination therapy with: • TNF alpha antagonists (infliximab, adalimumab, certolizumab, golimumab, etanercept) • T-cell stimulation inhibitor (abatacept) • CD20 inhibitor (rituximab) • Other IL-6 inhibitors (tocilizumab) • JAK inhibitor (tofacitinib) • Non-biologic DMARDs
Outcomes	**Key efficacy outcomes:** • Radiographic changes • response • Health-related quality of life[a] • Functional and disability outcomes[a] • Disease activity[a] • Health care resource utilization **Harms outcomes:** • Adverse events,[a] serious adverse events, withdrawals due to adverse events • Mortality • Adverse events of special interest: ▪ Serious infections, neutropenia, thrombocytopenia, malignancies, major cardiovascular events, anaphylaxis, gastrointestinal perforations, liver toxicity, dyslipidemia
Study Design	Published and unpublished phase III RCTs

AMC = American College of Rheumatology; BRM = biologic response modifier; DMARD = disease-modifying antirheumatic drug; IL = interleukin; JAK = janus kinase; RA = rheumatoid arthritis; RCT = randomized controlled trial; SC = subcutaneous; TNF = tumour necrosis factor.
[a] Outcomes identified as being important to patients during the patient input process.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates via Ovid, Embase (1974–) via Ovid, and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was sarilumab (Kevzara).

No methodological filters were applied to limit retrieval by study type. Retrieval was neither limited by publication year nor by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on November 14, 2016. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee on March 15, 2017. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters checklist (https://www.cadth.ca/grey-matters): Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, Advisories and Warnings, Drug Class Reviews, Clinical Trials, and Databases (free). Google and other Internet search engines were used to search for additional web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information about unpublished studies.

Two CADTH clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 6. There were no excluded studies from the selection process.

3. RESULTS

3.1 Findings From the Literature

A total of four studies were identified from the literature and the manufacturer's submission for inclusion in the systematic review (Figure 1). Key characteristics of the included studies are summarized in Table 6 for the placebo-controlled studies and Table 7 for the active-controlled studies.

FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

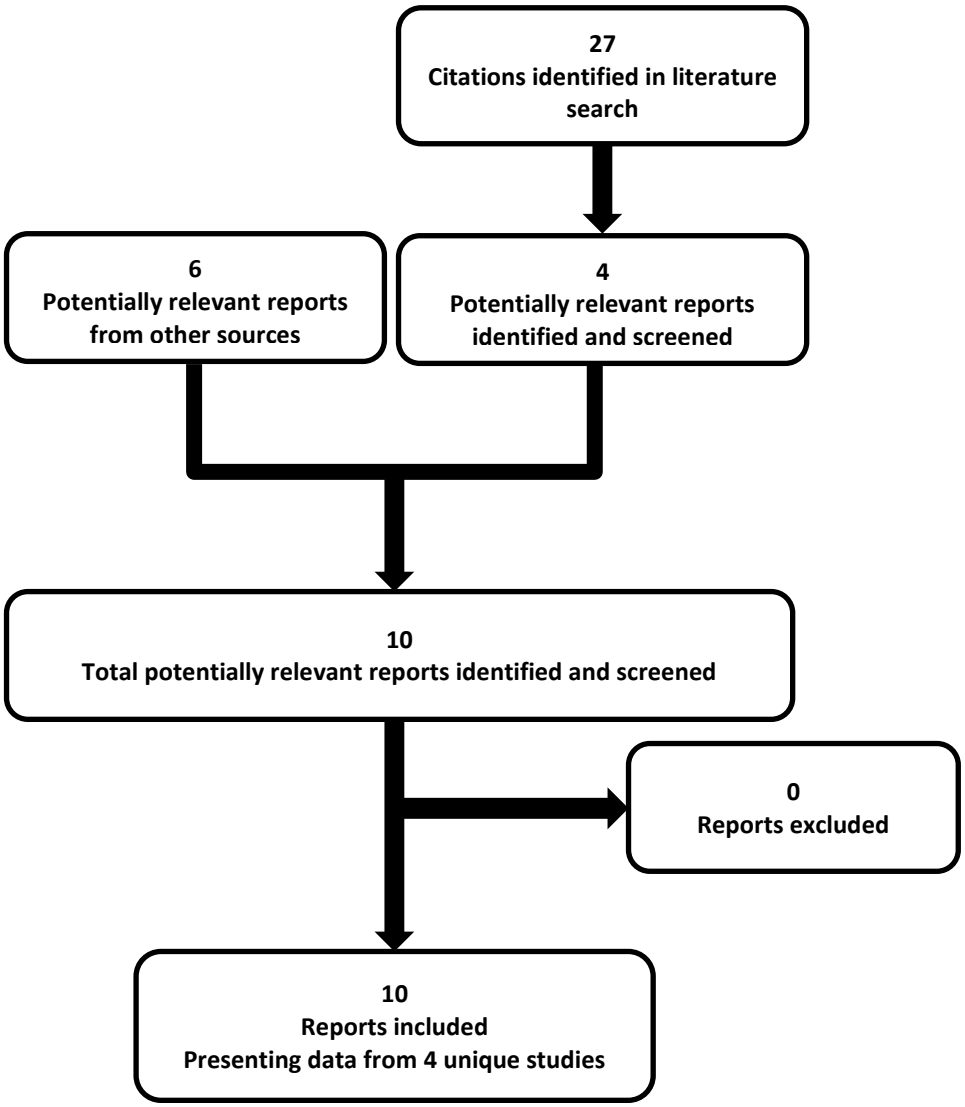


TABLE 6: DETAILS OF PLACEBO-CONTROLLED STUDIES

		MOBILITY (Part B)		TARGET

DESIGNS AND POPULATIONS	**Study Design**	Adaptive DB RCT with two phases:
		• Part A (dose ranging): 12-week, 6-arm, DB, RCT to select the two regimens for part B
		• Part B (pivotal): 52-week, DB RCT:
		  ○ Cohort 1: 6-arm RCT (as per part A)
		  ○ Cohort 2: 3-arm RCT (recruited after part A)
				3-arm, multi-centre, DB, parallel-group, placebo-controlled 24-week phase III RCT

	Locations	199 sites in 30 countries (Europe, North America, South America, Asia, Australia, New Zealand, South Africa)		240 sites in 27 countries (North America, South America, Europe, Asia, Australia, New Zealand)
	Randomized (N)	1369 (172 in cohort 1 and 1,197 in cohort 2)		546
	Inclusion Criteria	• Adults with RA for ≥ 3 months • Stable dose of MTX for ≥ 12 weeks • Active RA: ≥ 8 of 68 tender joints and ≥ 6 of 66 swollen joints, or CRP ≥ 8 mg/L • ≥ 1 documented bone erosion, anti-CCP antibody positive, or positive rheumatoid factor		• Adults with RA for ≥ 6 months • Class I-III functional status • Active RA: ≥ 8 of 68 tender joints and ≥ 6 of 66 swollen joints, or CRP ≥ 8 mg/L • Inadequate response/intolerance to ≥ 1 anti-TNF • Treatment with ≥ 1 DMARD(s) for ≥ 12 weeks
	Exclusion Criteria	• Treatment with DMARD(s) other than MTX • Previous nonresponse to a BRM • Severe systemic RA • Abnormal laboratory measurements[a]		• Prior treatment with IL-6 inhibitor, JAK inhibitor • Severe systemic RA • Abnormal laboratory measurements[a]
DRUGS	**Interventions**	**Cohort 1**	**Cohort 2**	• SARI 150 mg Q2W + DMARD • SARI 200 mg Q2W + DMARD
		• SARI 100 mg QW + MTX • SARI 150 mg QW + MTX • SARI 100 mg Q2W + MTX • SARI 150 mg Q2W + MTX • SARI 200 mg Q2W + MTX	• SARI 150 mg Q2W + MTX • SARI 200 mg Q2W + MTX	
	Comparator(s)	• Placebo QW + MTX	• Placebo Q2W + MTX	• Placebo Q2W + DMARD
DURATION	**Phase**			
	Run-in	Up to 4 weeks		Up to 4 weeks
	Double-blind	52 weeks		24 weeks
	Follow-up	Up to 6 weeks		Up to 6 weeks
OUTCOMES	**Primary End Points**	• 20 response at 24 weeks • HAQ-DI at 16 weeks • mTSS at 52 weeks		• 20 response at 24 weeks • HAQ-DI at 12 weeks
	Other End Points	• HAQ-DI at 16 weeks; HAQ-DI response 52 weeks • Major clinical response (70 for 24 weeks) • 50/70 response at 24 weeks • DAS 28-CRP and DAS 28-CRP < 2.6 at 24 weeks • EULAR response; SDAI remission (≤ 3.3) • CDAI; CDAI ≤ 2.8 at 24 weeks • Radiographic progression • SF-36, FACIT-Fatigue, WPAI		• 20/50/70 at week 12, 24 • DAS 28/EULAR Response at week 12, 24 • DAS 28-CRP < 2.6 at week 12, 24 • /EULAR remission at week 12, 24 • SDAI; SDAI remission (≤ 3.3) at week 12, 24 • CDAI; CDAI ≤ 2.8 at week 12, 24 • SF-36, FACIT-Fatigue, EQ-5D-3L, WPS-RA, RAID, morning stiffness VAS

		MOBILITY (Part B)	TARGET
NOTES	**Publications**	• Genovese et al., 2015,[25] Strand et al., 2016,[26] Boyapati et al., 2016,[27] Huizinga et al., 2014[28] • Clinical Study Report[10] • Clinicaltrials.gov[29]	• Fleischmann et al., 2016[30] • Clinical Study Report[7] • Clinicaltrials.gov[31]

AMR = American College of Rheumatology; anti-TNF = anti–tumour necrosis factor; BRM = biologic response modifier; CDAI = Clinical Disease Activity Index; CCP = cyclic citrullinated peptide; CRP = C-reactive protein; DAS = Disease Activity Score 28; DB = double blind; DMARD = disease-modifying antirheumatic drug; EQ-5D-3L = EuroQol 5-Dimensions 3-Levels questionnaire; EULAR = European League Against Rheumatism; FACIT = Functional Assessment of Chronic Illness Therapy; HAQ-DI = Health Assessment Questionnaire–Disability Index; IL = interleukin; JAK = janus kinase; mTSS = modified Total Sharp Score; MTX = methotrexate; QW = administered weekly; Q2W = administered once every two weeks; RA = rheumatoid arthritis; RAID = rheumatoid arthritis impact of disease; RCT = randomized controlled trial; SARI = sarilumab; SC = subcutaneous; SDAI = Simplified Disease Activity Index; SF-36 = Short Form (36) Health Survey; ULN = upper limit of normal; VAS = visual analogue scale; WPAI = Work Productivity and Activity Impairment; WPS-RA = rheumatoid arthritis–specific work productivity survey.

[a] Defined in both trials as any of the following: hemoglobin < 8.5 g/dL; white blood cells < 3000/mm^3; neutrophils < 2000/mm^3; platelets < 150,000 cells/mm^3; aspartate transaminase and alanine transaminase > 1.5 × the upper limit of normal (ULN); bilirubin > ULN; uncontrolled hypercholesterolemia (9.1 mmol/L) or hypertriglyceridemia (5.6 mmol/L); creatinine clearance < 30 mL/min.

TABLE 7: DETAILS OF ACTIVE-CONTROLLED STUDIES

		MONARCH	ASCERTAIN
DESIGNS AND POPULATIONS	**Study Design**	24-week, 2-arm, multi-centre, DB, double-dummy, parallel-group, active-controlled phase III, superiority RCT	3-arm, multi-centre, DB, double-dummy, parallel-group, active-controlled 24-week phase III RCT
	Locations	86 sites in 15 countries (North America, South America, Europe, Asia, South Africa)	86 sites in 19 countries (Europe, North America, South America)
	Randomized (N)	369	202
	Inclusion Criteria	• Adults with RA for ≥ 3 months • Class I to III functional status • Active RA: ≥ 8 tender joints, ≥ 6 swollen joints, CRP ≥ 8 mg/L or ESR ≥ 28 mm/h; DAS 28-ESR > 5.1 • Inadequate response, intolerance, or inappropriate candidate for MTX	• Adults with RA for ≥ 3 months • Class I to III functional status • Moderate to severe active RA: ≥ 4 tender joints, ≥ 4 swollen joints, CRP ≥ 8 mg/L • Inadequate response to ≥ 1 anti-TNF • Treatment with ≥ 1 DMARD(s) for ≥ 12 weeks
	Exclusion Criteria	• Prior treatment with BRM or JAK inhibitor • Current treatment with DMARDs or immunosuppressives (including MTX)[a] • Severe systemic RA • Abnormal laboratory measurements[b]	• Prior treatment with IL-6 inhibitor or JAK inhibitor • Severe systemic RA • Abnormal laboratory measurements[b]
DRUGS	**Intervention**	• SARI 200 mg SC Q2W	• SARI 150 mg SC Q2W + DMARD • SARI 200 mg SC Q2W + DMARD
	Comparator(s)	• Adalimumab SC 40 mg Q2W (could be increased to 40 mg QW from weeks 16 to 23 if patients had an inadequate response)	• Tocilizumab 4 mg/kg (could be increased to 8 mg/kg starting at week 4 if patients had an inadequate response) IV Q4W + DMARD
DURATION	**Phase**		
	Run-in	Up to 4 weeks	Up to 4 weeks
	Double-blind	24 weeks	24 weeks
	Follow-up	Up to 276 weeks (open-label)	Up to 6 weeks
OUTCOMES	**Primary End Point**	• DAS 28-ESR at 24 weeks	• All end points were exploratory • Safety and tolerability
	Other End Points	• DAS 28-ESR < 2.6 and < 3.2 at 24 weeks • DAS 28-CRP and DAS 28-CRP < 2.6 at 24 weeks • 20/50/70 response at 24 weeks • CDAI and CDAI score ≤ 2.8 at 24 weeks	• 20/50/70 response at 24 weeks • DAS 28-CRP < 2.6 at 24 weeks • HAQ-DI at 24 weeks[c]

		MONARCH	ASCERTAIN
		• SF-36, FACIT-Fatigue, EQ-5D-3L, WPS-RA, RAID, morning stiffness VAS	
NOTES	**Publications**	• Clinical Study Report[9] • Burmester et al., 2016[32] • Clinicaltrials.gov[33]	• Clinical Study Report[8] • Clinicaltrials.gov[34]

AMR = American College of Rheumatology; anti-TNF = anti–tumour necrosis factor; BRM = biologic response modifier; CDAI = Clinical Disease Activity Index; CRP = C-reactive protein; DAS = Disease Activity Score 28; DB = double blind; DMARD = disease-modifying antirheumatic drug; EQ-5D-3L = EuroQol 5-Dimensions 3-Levels questionnaire; ESR = erythrocyte sedimentation rate; FACIT = Functional Assessment of Chronic Illness Therapy; HAQ-DI = Health Assessment Questionnaire–Disability Index; IL = interleukin; IV = intravenous; JAK = janus kinase; MTX = methotrexate; QW = administered weekly; Q2W = administered once every two weeks; Q4W = administered once every four weeks; RA = rheumatoid arthritis; RAID = rheumatoid arthritis impact of disease; RCT = randomized controlled trial; SARI = sarilumab; SC = subcutaneous; SF-36 = Short Form (36) Health Survey; VAS = visual analogue scale; ULN = upper limit of normal; WPS-RA = rheumatoid arthritis–specific work productivity survey.

[a] Current treatment with DMARDS or immunosuppressive drugs including MTX, cyclosporine, mycophenolate, tolimus, gold, penicillamine, sulfasalazine, or hydroxychloroquine within two weeks prior to the baseline visit; azathioprine, cyclophosphamide within 12 weeks prior to baseline; leflunomide within 8 weeks prior to baseline; or 4 weeks after standard cholestyramine washout.[32]

[b] Defined in both trials as any of the following: hemoglobin < 8.5 g/dL; white blood cells < 3000/mm3; neutrophils < 2000/mm^3; platelets < 150,000 cells/mm^3; aspartate transaminase and alanine transaminase > 1.5 × ULN; bilirubin > ULN; uncontrolled hypercholesterolemia (9.1 mmol/L) or hypertriglyceridemia (5.6 mmol/L); creatinine clearance < 30 mL/min.[8,9]

[c] Measured as part of the evaluation for 20/50/70 responses at 24 weeks.

3.1.1 Description of Studies

a) Placebo-Controlled Studies

TARGET was a phase III, 24-week, multi-centre, double-blind, parallel-group, placebo-controlled randomized controlled trial. The study consisted of a screening phase (up to 4 weeks), a double-blind treatment phase (24 weeks), and a post-treatment follow-up phase (6 weeks). Beginning at week 12, patients were eligible for rescue therapy and enrolment in the EXTEND open-label long-term safety study if they failed to demonstrate an improvement of at least 20% from baseline in either swollen joint count or tender joint count for two assessments at least four weeks apart. Patients who completed the treatment phase were also allowed to enter the EXTEND study. In TARGET, eligible patients were randomized (1:1:1) to receive sarilumab 150 mg once every two weeks, sarilumab 200 mg once every two weeks, or matching placebo. Randomization was stratified by region and the number of previous treatments with TNF alpha antagonists (i.e., 1 versus > 1).

MOBILITY was a double-blind, placebo-controlled, adaptive randomized controlled trial conducted in patients with an inadequate response or loss of response to MTX. The randomized controlled trial was conducted in two phases, Part A and Part B. Randomization was stratified according to prior BRM use and region. Part A was a phase II, 12-week, six-arm, double-blind, dose-ranging study conducted to select the two dosage regimens for investigation in Part B, the confirmatory phase of the study. Patients in Part A were randomized (1:1:1:1:1:1) to placebo or to one of five sarilumab treatment groups (100 mg once weekly, 150 mg once weekly, 100 mg once every two weeks, 150 mg once every two weeks, or 200 mg once every two weeks). Part B was a phase III, 52-week, double-blind randomized controlled trial that was conducted using the following two cohorts of patients:

- Cohort 1: Patients were randomized to one of the six study treatments that were used in Part A. Those receiving placebo or the two doses identified in Part A (i.e., 150 mg once every two weeks or 200 mg once every two weeks) were to continue on the study treatments, and those who were receiving nonselected doses were to discontinue the study treatments and were eligible for enrolment in the EXTEND study.
- Cohort 2: Patients were randomized (1:1:1) to placebo or to one of the two doses that were identified in Part A (i.e., 150 mg once every two weeks or 200 mg once every two weeks).

Patients who demonstrated a lack of efficacy could be rescued beginning at week 16 if they failed to demonstrate at least a 20% improvement from baseline in either swollen joint count or tender joint count for two consecutive study visits or for any other clear lack of efficacy based on the judgment of the investigator.

In accordance with the review protocol, the CADTH Common Drug Review (CDR) systematic review is focused on the phase III component of the MOBILITY trial (i.e., Part B). The data included in the CDR review reflect the manufacturer's planned analysis populations; therefore, efficacy data are reported for cohort 2 of the study and safety data reflect both cohort 2 and patients in cohort 1 who were randomized to either 200 mg or 150 mg sarilumab once every two weeks (i.e., the two doses selected in Part A).

b) Active-Controlled Studies

MONARCH was a 24-week, multi-centre, parallel-group, double-blind, double-dummy, active-controlled randomized controlled trial. The study consisted of a screening phase (up to 4 weeks), a double-blind treatment phase (24 weeks), and an open-label extension period (up to commercial availability or 276 weeks). Eligible patients were randomized (1:1) to either sarilumab 200 mg once every two weeks or adalimumab 40 mg once every two weeks. Randomization was stratified by region. Between weeks 16 and 23, patients who had demonstrated an inadequate response to the study treatment (i.e., less than 20% improvement from baseline in tender joint count and swollen joint count for two consecutive study visits) could undergo one of the following: the dosing frequency of adalimumab (or matching placebo) could be increased to 40 mg every week, or the study treatment could be discontinued. All patients who completed the 24-week double-blind period were eligible to enter into an open-label treatment period where they would receive sarilumab 200 mg once every two weeks.

ASCERTAIN was a 24-week, multi-centre, double-blind, double-dummy, parallel-group, three-arm, active-controlled randomized controlled trial. The study consisted of a screening phase (up to 4 weeks), a double-blind treatment phase (24 weeks), and a post-treatment follow-up phase (6 weeks). Eligible patients were randomized (1:1:2) to receive sarilumab 150 mg every two weeks, sarilumab 200 mg every two weeks, or an intravenous infusion of tocilizumab once every four weeks (4 mg/kg that could be increased to 8 mg/kg based on clinical response). Each treatment was added to the patient's current DMARD background regimen. [redacted]. Patients who completed the treatment phase were allowed to enter the EXTEND extension study.

3.1.2 Populations

a) Inclusion and Exclusion Criteria

TARGET required patients to have had RA for at least six months prior to screening; MOBILITY, MONARCH, and ASCERTAIN used a threshold of at least three months.[7-10] All of the trials specified that patients had to have active RA; however, the inclusion criteria related to the severity of RA at screening were variable oss the studies with respect to tender joint count (range ≥ 4 to ≥ 8) and swollen joint count (range ≥ 4 to ≥ 6). Enrolment in MOBILITY also required patients to have at least one documented bone erosion, be positive for anti–cyclic citrullinated peptide antibodies, or be positive for rheumatoid factor.[10] MONARCH also specified that patients were required to have a Disease Activity Score 28 (DAS 28) erythrocyte sedimentation rate (ESR) above 5.1 at screening (indicating a high degree of disease activity).[9]

The trials had important differences with regard to previous and concomitant exposure to RA treatments. The MOBILITY and MONARCH studies required patients to have been treatment-

experienced with MTX at the time of screening.[9,10] Specifically, MOBILITY required patients to have been receiving treatment with MTX for at least 12 weeks and using a stable dose ranging from 10 mg/week to 25 mg/week for at least six weeks prior to screening, with the exception of those recruited at sites within the Asia-Pacific region, where a range of 6 mg/week to 25 mg/week was applied.[10] The inclusion criteria for the MONARCH study stated that patients had to have demonstrated an inadequate response to MTX or intolerance to MTX or had to be considered an inappropriate candidate for MTX treatment (in the opinion of the investigator).[9] Unlike the MOBILITY trial, patients in MONARCH were excluded if they were receiving current treatment with DMARDs or immunosuppressive drugs, including MTX.[9] The TARGET and ASCERTAIN trials were conducted in patients who were treatment-experienced with one or more TNF alpha antagonists therapies.[7,8] Patients who had demonstrated an inadequate response to at least one TNF alpha antagonist were eligible for both studies; however, patients who had demonstrated intolerance were eligible only for TARGET (all based on the opinion of the investigator). Both TARGET and ASCERTAIN required patients to have been receiving treatment with one or more DMARDs for at least 12 weeks prior to screening.[7,8] Patients were required to be receiving treatment at a stable dose within the following thresholds: 10 mg/week to 25 mg/week of MTX, 10 mg/day to 20 mg/day of leflunomide, 1 g/day to 3 g/day of sulfasalazine, and 200 mg/day to 400 mg/day of hydroxychloroquine.[7,8]

All studies excluded patients who had received treatment with parenteral or intra-articular corticosteroids within four weeks of enrolment or who were using oral corticosteroids at a dosage greater than 10 mg prednisone equivalent per day or who had had a change in dosage within the previous four weeks.[7-10] Patients with a history of tuberculosis or invasive opportunistic infections were excluded from the studies, as were those with interstitial lung disease, inflammatory bowel disease, or severe diverticulitis.

b) Baseline Characteristics

Key baseline and demographic characteristics are summarized Table 8 for the placebo-controlled trials and Table 9 for the active-controlled trials. A majority of the participants in all four studies were female (range 80% to 83%) and Caucasian (range 71% to 93%). The mean age of participants was similar oss the four studies (range 50.4 years to 53.6 years). The [redacted]. The mean tender joint count and swollen joint count were [redacted] compared with the other three trials (range 26.5 to 29.6 and 16.5 to 20.0, respectively).[8]

In both TARGET and MOBILITY, the baseline characteristics were generally balanced between the placebo and sarilumab groups. The only differences were a lower mean baseline C-reactive protein (CRP) in the placebo group (26.02 versus 30.77) and a higher proportion of patients in the placebo group who were positive for rheumatoid factor (78.9% versus 72.9%) or had anti–cyclic citrullinated peptide antibodies (83.3% versus 76.1%).[7,10] The following imbalances between the adalimumab and sarilumab groups were noted in the MONARCH study: the sarilumab group had a greater mean duration of RA compared with the placebo group (8.1 years versus 6.6 years), a greater proportion of females (85.3% versus 81.1%), and a lower mean age at baseline (50.9 years versus 53.6 years) and baseline CRP (17.36 versus 24.05).[9] The following imbalances were noted in the baseline characteristics of the ASCERTAIN trial: [redacted]; the sarilumab group had a lower proportion of females (76.5% versus

80.4%), [redacted].[8]

TABLE 8: SUMMARY OF BASELINE CHARACTERISTICS FROM PLACEBO-CONTROLLED TRIALS

Characteristics		TARGET		MOBILITY	
		PLC + DMARD N = 181	SARI + DMARD N = 184	PLC + MTX [redacted]	SARI + MTX [redacted]
Age (years)	Mean (SD)	51.9 (12.4)	52.9 (12.9)	[redacted]	[redacted]
	< 65	[redacted]	[redacted]	[redacted]	[redacted]
	≥ 65 and < 75	[redacted]	[redacted]	[redacted]	[redacted]
	≥ 75	[redacted]	[redacted]	[redacted]	[redacted]
Sex (n [%])	Male	27 (14.9%)	33 (17.9%)	[redacted]	[redacted]
	Female	154 (85.1%)	151 (82.1%)	[redacted]	[redacted]
Race (n [%])	Caucasian	124 (68.5%)	130 (70.7%)	[redacted]	[redacted]
	Black	7 (3.9%)	5 (2.7%)	[redacted]	[redacted]
	Asian	1 (0.6%)	1 (0.5%)	[redacted]	[redacted]
	Other	49 (27.1%)	48 (26.1%)	[redacted]	[redacted]
Ethnicity (n [%])	Hispanic	[redacted]	[redacted]	[redacted]	[redacted]
	Not Hispanic	[redacted]	[redacted]	[redacted]	[redacted]
Weight (kg)	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	< 60	[redacted]	[redacted]	[redacted]	[redacted]
	≥ 60 and < 100	[redacted]	[redacted]	[redacted]	[redacted]
	≥ 100	[redacted]	[redacted]	[redacted]	[redacted]
BMI (kg/m^2)	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	< 25	[redacted]	[redacted]	[redacted]	[redacted]
	≥ 25 and < 30	[redacted]	[redacted]	[redacted]	[redacted]
	≥ 30	[redacted]	[redacted]	[redacted]	[redacted]
Years since diagnosis	Mean (SD)	12.04 (9.99)	12.68 (9.63)	[redacted]	[redacted]
RA functional class (n [%])	I	[redacted]	[redacted]	[redacted]	[redacted]
	II	[redacted]	[redacted]	[redacted]	[redacted]
	III	[redacted]	[redacted]	[redacted]	[redacted]
	IV	[redacted]	[redacted]	[redacted]	[redacted]
Rheumatoid factor (n [%])	Positive	142 (78.9%)	132 (72.9%)	[redacted]	[redacted]
	Negative	38 (21.1%)	49 (27.1%)	[redacted]	[redacted]
Anti-CCP antibody (n [%])	Positive	150 (83.3%)	137 (76.1%)	[redacted]	[redacted]
	Negative	30 (16.7%)	43 (23.9%)	[redacted]	[redacted]
Number of non-biological DMARDs (n [%])	None	[redacted]	[redacted]	[redacted]	[redacted]
	1	[redacted]	[redacted]	[redacted]	[redacted]
	2	[redacted]	[redacted]	[redacted]	[redacted]
	≥ 3	[redacted]	[redacted]	[redacted]	[redacted]
Previous anti-TNFs (n [%])	1	135 (74.6%)	140 (76.5%)	[redacted]	[redacted]
	> 1	46 (25.4%)	43 (23.5%)	[redacted]	[redacted]
Prior biologic use (n [%])	Yes	[redacted]	[redacted]	[redacted]	[redacted]
	No	[redacted]	[redacted]	[redacted]	[redacted]
Tender joint count	Mean (SD)	29.42 (14.54)	29.55 (15.54)	[redacted]	[redacted]

Characteristics		TARGET		MOBILITY	
		PLC + DMARD N = 181	SARI + DMARD N = 184	PLC + MTX [redacted]	SARI + MTX [redacted]
(0 to 68)					
Swollen joint count (0 to 66)	Mean (SD)	20.21 (11.34)	19.97 (11.94)	[redacted]	[redacted]
CRP (mg/L)	Mean (SD)	26.02 (25.20)	30.77 (28.35)	[redacted]	[redacted]
	Median (range)	[redacted]	[redacted]	[redacted]	[redacted]
HAQ-DI	Mean (SD)	1.80 (0.64)	1.82 (0.62)	[redacted]	[redacted]
DAS 28-CRP	Mean (SD)	6.23 (0.86)	6.29 (0.98)	[redacted]	[redacted]

BMI = body mass index; CCP = cyclic citrullinated peptide; CRP = C-reactive protein; DAS 28-CRP = Disease Activity Score 28 using C-reactive protein; DMARD = disease-modifying antirheumatic drugs; HAQ-DI = Health Assessment Questionnaire–Disability Index; MTX = methotrexate; n = number of patients; NR = not reported; PLC = placebo; RA = rheumatoid arthritis; SARI = sarilumab; SD = standard deviation; anti-TNF = anti–tumour necrosis factor alpha antagonist.
Source: Clinical Study Reports for TARGET[7] and MOBILITY.[10]

TABLE 9: SUMMARY OF BASELINE CHARACTERISTICS FROM ACTIVE-CONTROLLED TRIALS

Characteristics		MONARCH		ASCERTAIN	
		Adalimumab N = 185	SARI N = 184	TOC + DMARD N = 102	SARI + DMARD N = 51
Age (years)	Mean (SD)	53.6 (11.9)	50.9 (12.6)	50.4 (13.0)	51.7 (13.1)
	< 65	[redacted]	[redacted]	[redacted]	[redacted]
	≥ 65 and < 75	[redacted]	[redacted]	[redacted]	[redacted]
	≥ 75	[redacted]	[redacted]	[redacted]	[redacted]
Sex (n [%])	Male	35 (18.9%)	27 (14.7%)	20 (19.6%)	12 (23.5%)
	Female	150 (81.1%)	157 (85.3%)	82 (80.4%)	39 (76.5%)
Race (n [%])	Caucasian	164 (88.6%)	171 (92.9%)	94 (92.2%)	46 (90.2%)
	Black	[redacted]	[redacted]	[redacted]	[redacted]
	Asian	[redacted]	[redacted]	[redacted]	[redacted]
	Other	[redacted]	[redacted]	[redacted]	[redacted]
Ethnicity (n [%])	Hispanic	[redacted]	[redacted]	[redacted]	[redacted]
	Not Hispanic	[redacted]	[redacted]	[redacted]	[redacted]
Weight (kg)	Mean (SD)	71.79 (17.79)	72.30 (16.54)	[redacted]	[redacted]
	< 60	[redacted]	[redacted]	[redacted]	[redacted]
	≥ 60 and < 100	[redacted]	[redacted]	[redacted]	[redacted]
	≥ 100	[redacted]	[redacted]	[redacted]	[redacted]
BMI (kg/m2)	Mean (SD)	27.26 (6.45)	27.09 (5.64)	[redacted]	[redacted]
	< 25	[redacted]	[redacted]	[redacted]	[redacted]
	≥ 25 and < 30	[redacted]	[redacted]	[redacted]	[redacted]
	≥ 30	[redacted]	[redacted]	[redacted]	[redacted]
Duration of RA (years)	Mean (SD)	6.56 (7.80)	8.11 (8.12)	[redacted]	[redacted]
RA functional class (n [%])	I	[redacted]	[redacted]	[redacted]	[redacted]
	II	[redacted]	[redacted]	[redacted]	[redacted]
	III	[redacted]	[redacted]	[redacted]	[redacted]
Rheumatoid factor (n [%])	Positive	116 (64.8%)	119 (66.9%)	[redacted]	[redacted]
	Negative	63 (35.2%)	59 (33.1%)	[redacted]	[redacted]

Characteristics		MONARCH		ASCERTAIN	
		Adalimumab N = 185	SARI N = 184	TOC + DMARD N = 102	SARI + DMARD N = 51
Anti-CCP antibody (n [%])	Positive	138 (76.7%)	134 (75.3%)	[redacted]	[redacted]
	Negative	42 (23.3%)	44 (24.7%)	[redacted]	[redacted]
Prior DMARDs or Immunosuppressives (n [%])	None	0	0	[redacted]	[redacted]
	1	88 (47.6%)	83 (45.1%)	[redacted]	[redacted]
	2	58 (31.4%)	57 (31.0%)	[redacted]	[redacted]
	≥ 3	39 (21.1%)	44 (23.9%)	[redacted]	[redacted]
Tender joint count (0 to 68)	Mean (SD)	26.68 (13.63)	27.96 (13.19)	[redacted]	[redacted]
Swollen joint count (0 to 66)	Mean (SD)	17.51 (10.25)	18.57 (10.74)	[redacted]	[redacted]
HAQ-DI (0 to 3)	Mean (SD)	1.63 (0.64)	1.64 (0.55)	[redacted]	[redacted]
CRP (mg/L)	Mean (SD)	24.05 (30.98)	17.36 (21.31)	[redacted]	[redacted]
	Median (range)	[redacted]	[redacted]	[redacted]	[redacted]
DAS 28-CRP	Mean (SD)	6.02 (0.89)	6.00 (0.88)	[redacted]	[redacted]
DAS 28-ESR	Mean (SD)	6.76 (0.83)	6.83 (0.76)	[redacted]	[redacted]
ESR (mm/hr)	Mean (SD)	47.51 (23.23)	46.48 (21.75)	[redacted]	[redacted]
Baseline CDAI	Mean (SD)	42.40 (11.97)	43.62 (12.10)	[redacted]	[redacted]

BMI = body mass index; CCP = cyclic citrullinated peptide; CDAI = Clinical Disease Activity Index; CRP = C-reactive protein; DAS 28 = Disease Activity Score 28; DMARD = disease-modifying antirheumatic drug; ESR = erythrocyte sedimentation rate; HAQ-DI = Health Assessment Questionnaire–Disability Index; n = number of patients; NR = not reported; RA = rheumatoid arthritis; SARI = sarilumab; SD = standard deviation; TOC = tocilizumab.
Source: Clinical Study Reports for ASCERTAIN[8] and MONARCH.[9]

c) Prior Rheumatoid Arthritis Treatments

Placebo-Controlled Trials

In accordance with the protocol for the TARGET trial, all of the patients were treatment-experienced with at least one BRM. Nearly all of the patients enrolled in TARGET reported an inadequate response to their last TNF alpha antagonist (92.3%) and a small minority reported intolerance to their last treatment with a TNF alpha antagonist ([redacted]).[7] [redacted]. Prior exposure to at least one non-biologic DMARD was reported in slightly fewer patients in the [redacted]. The most commonly used DMARDs in the sarilumab and placebo groups (respectively) were [redacted].[7] Table 33 provides a summary of prior exposure to BRM and non-biologic DMARDs in the TARGET trial.

Only a minority of patients in the MOBILITY study had previous exposure to a BRM (20.6% for placebo and 19.5% for sarilumab 200 mg) or non-biologic DMARD ([redacted]) other than MTX; however, prior DMARD use was captured based on use in the three months before study inclusion only. [redacted].[10]

Active-Controlled Trials

All of patients enrolled in the ASCERTAIN trial were treatment-experienced with at least one BRM;[8] however, there were some differences between the two groups with respect to the specific BRMs that had been used. [redacted].

Prior RA treatments for patients enrolled in MONARCH trial are summarized in Table 34. There were slightly more patients in the trial who were considered to be inadequate responders to prior MTX treatment (54.2%) than those who were considered to be intolerant to MTX (45.5%).[9] The mean duration of treatment with MTX was approximately [redacted] and the mean highest dosage was 16.9 mg per week. Approximately half of the patients enrolled in the trial reported previous exposure to a DMARD other than MTX (52.8%), and 21.4% reported treatment experience with a combination of MTX and another non-biologic DMARD.[9]

3.1.3 Interventions

In both of the placebo-controlled trials (MOBILITY and TARGET), sarilumab or matching placebo was administered once every two weeks using pre-filled syringes.[7,10] In both of the active-controlled trials (MONARCH and ASCERTAIN), the study drugs were administered using a double-dummy design; therefore, in addition to their randomized treatment, the patients were also administered the matching placebo for the other study treatment. In both studies, sarilumab was administered at a dosage of 200 mg once every two weeks throughout the study period. In MONARCH, adalimumab 40 mg (or matching placebo) was administered subcutaneously once every two weeks.[9] For patients who required dose escalation, 40 mg adalimumab (or matching placebo) was administered once per week. In ASCERTAIN, tocilizumab (or matching placebo) was administered as a 60-minute single intravenous infusion at an initial dosage of 4 mg/kg once every four weeks. The dosage could be increased to 8 mg/kg once every four weeks based on clinical response (specific criteria were not reported).[8]

3.1.4 Outcomes

Table 10 summarizes the primary, secondary, and exploratory efficacy end points from each of the included studies. There were three pre-specified co-primary end points in the MOBILITY trial: 20 response at 24 weeks, change from baseline in Health Assessment Questionnaire–Disability Index (HAQ-DI) at 16 weeks, and change from baseline in modified Total Sharp Score (mTSS) at 52 weeks. Major clinical response (defined as an 70 response for at least 24 consecutive weeks) was specified as the main secondary end point of MOBILITY. There were 17 additional secondary end points in MOBILITY that were included in the manufacturer's pre-specified statistical testing hierarchy. The TARGET study also included multiple primary end points: 20 response at 24 weeks and change from baseline in HAQ-DI at 16 weeks. Similar to the MOBILITY trial, the protocol for TARGET also included a pre-specified statistical testing hierarchy for secondary end points. As shown in Table 10, all efficacy end points in both MOBILITY and TARGET that were not included in the statistical testing hierarchy were considered to be exploratory.

Change from baseline in DAS 28-ESR at 24 weeks was the primary end point of the MONARCH study.[9] There were eight pre-specified secondary end points that were included in the statistical testing hierarchy, and all other evaluations were considered to be exploratory. Safety and tolerability were the primary end points of the ASCERTAIN trial; therefore, all efficacy end points were considered to be exploratory.[8]

TABLE 10: SUMMARY OF END POINTS IN THE INCLUDED STUDIES

End Point	Evaluation	Weeks	Placebo-Controlled		Active-Controlled	
			MOBILITY	TARGET	MONARCH	ASCERTAIN
response	20 response	12	NA	Exploratory	Exploratory	[redacted]
		24	**Primary**	**Primary**	Secondary	[redacted]
	50 response	12	NA	Exploratory	Exploratory	[redacted]
		24	Secondary	Secondary	Secondary	[redacted]
	70 response	12	NA	Exploratory	Exploratory	[redacted]
		24	Secondary	Secondary	Secondary	[redacted]
	Major clinical response[a]	52	Secondary (main)	NA	NA	[redacted]
HAQ-DI	Change from baseline	12	NA	**Primary**	NA	[redacted]
		16	**Primary**	NA	NA	[redacted]
		24	NA	Secondary	Secondary	[redacted]
		52	Exploratory	NA	NA	[redacted]
	Response (> 0.22)	12	NA	Exploratory	Exploratory	[redacted]
		16	Exploratory	NA	NA	[redacted]
		24	Exploratory	Exploratory	Exploratory	[redacted]
		52	Exploratory	NA	NA	[redacted]
		Through 52	Secondary	NA	NA	[redacted]
	Response (> 0.3)	12	NA	Exploratory	Exploratory	[redacted]
		16	Exploratory	NA	NA	[redacted]
		24	Exploratory	Exploratory	Exploratory	[redacted]
		52	Exploratory	NA	NA	[redacted]
		Through 52	Exploratory	NA	NA	[redacted]
DAS 28-CRP	Change from baseline	12	NA	Exploratory	NA	[redacted]
		24	Exploratory	Secondary	Exploratory	[redacted]
		52	Exploratory	NA	NA	[redacted]
	Remission (< 2.6)	12	NA	Exploratory	NA	[redacted]
		24	Secondary	Secondary	NA	[redacted]
		52	Exploratory	NA	NA	[redacted]
	Low activity (< 3.2)	24	NA	NA	Exploratory	[redacted]
DAS 28-ESR	Change from baseline	12	NA	NA	Exploratory	[redacted]
		24	NA	NA	**Primary**	[redacted]
	Remission (< 2.6)	12	NA	NA	Exploratory	[redacted]
		24	NA	NA	Secondary	[redacted]
	Low activity (< 3.2)	12	NA	NA	Exploratory	[redacted]
		24	NA	NA	Exploratory	[redacted]
mTSS	Change from baseline	52	**Primary**	NA	NA	[redacted]
	No progression (≤ 0)	52	Secondary	NA	NA	[redacted]
CDAI	Change from	12	NA	Exploratory	NA	[redacted]

End Point	Evaluation	Weeks	Placebo-Controlled		Active-Controlled	
			MOBILITY	TARGET	MONARCH	ASCERTAIN
	baseline	24	Secondary	Secondary	Exploratory	[redacted]
	Remission (≤ 2.8)	12	NA	Exploratory	Exploratory	[redacted]
		24	Exploratory	Exploratory	Exploratory	[redacted]
		52	Exploratory	NA	NA	[redacted]
SDAI	Change from baseline	12	NA	Exploratory	NA	[redacted]
		24	Exploratory	Exploratory	NA	[redacted]
		52	Exploratory	NA	NA	[redacted]
	Remission (≤ 3.3)	12	NA	Exploratory	NA	[redacted]
		24	Exploratory	Exploratory	NA	[redacted]
		52	Exploratory	NA	NA	[redacted]
EULAR	Response	12	NA	Exploratory	Exploratory	[redacted]
		24	Exploratory	Exploratory	Exploratory	[redacted]
		52	Exploratory	NA	NA	[redacted]
/EULAR	Remission	12	NA	Exploratory	NA	[redacted]
		24	Exploratory	Exploratory	NA	[redacted]
		52	Exploratory	NA	NA	[redacted]
SF-36PCS	Change from baseline	12	NA	Exploratory	Exploratory	[redacted]
		24	Secondary	Secondary	Secondary	[redacted]
		52	Secondary	NA	NA	[redacted]
SF-36MCS	Change from baseline	12	NA	Exploratory	Exploratory	[redacted]
		24	Secondary	Secondary	Secondary	[redacted]
		52	Secondary	NA	NA	[redacted]
EQ-5D-3L	Change from baseline	24	NA	Secondary	Exploratory	[redacted]
FACIT-Fatigue	Change from baseline	12	NA	NA	Exploratory	[redacted]
		24	Secondary	Secondary	Secondary	[redacted]
		52	Secondary	NA	NA	[redacted]
WPAI	Change from baseline	12	Secondary	NA	NA	[redacted]
		52	Secondary	NA	NA	[redacted]
RAID	Change from baseline	24	NA	Secondary	Exploratory	[redacted]
WPS-RA	Change from baseline	24	NA	Secondary	Exploratory	[redacted]
Sleep VAS	Change from baseline	24	Secondary	NA	NA	[redacted]
		52	Secondary	NA	NA	[redacted]
Morning stiffness VAS	Change from baseline	24	NA	Secondary	Exploratory	[redacted]

AMR = American College of Rheumatology; CDAI = Clinical Disease Activity Index; CRP = C-reactive protein; DAS = Disease Activity Score 28; EQ-5D-3L = EuroQol 5-Dimensions 3-Levels questionnaire; ESR = erythrocyte sedimentation rate; EULAR = European League Against Rheumatism; FACIT = Functional Assessment of Chronic Illness Therapy; HAQ-DI = Health Assessment Questionnaire–Disability Index; MCS = mental component summary; mTSS = modified Total Sharp Score; NA = not applicable; PCS = physical component summary; RAID = rheumatoid arthritis impact of disease; SDAI = Simplified Disease Activity Index; SF-36 = Short Form (36) Health Survey; VAS = visual analogue scale; WPAI = Work Productivity and Activity Impairment questionnaire; WPS-RA = rheumatoid arthritis–specific work productivity survey.

[a] 70 response for ≥ 24 consecutive weeks.

Source: Clinical Study Reports for TARGET,[7] MOBILITY,[10] ASCERTAIN,[8] and MONARCH.[9]

Only those efficacy outcomes identified in the review protocol are described below.

a) American College of Rheumatology Response

A responder using 20 criteria was calculated as follows:

- ≥ 20% improvement in tender or painful joint count (out of 68 joints) and swollen joint count (out of 66 joints)
- ≥ 20% improvement in at least three of the five remaining core set measures: patient global assessment, physician global assessment, patient assessment of arthritis pain, disability (HAQ-DI), and an acute-phase reactant (CRP).

Similarly, 50 and 70 were calculated using 50% and 70% improvement from baseline, respectively. The responses were evaluated at 12 weeks and 24 weeks in all four of the included studies.[7-10] Major clinical response was defined as an 70 response for at least 24 consecutive weeks and was a key secondary end point of the MOBILITY trial.[10]

b) Health Assessment Questionnaire–Disability Index

Physical function was assessed using the HAQ-DI. The HAQ-DI measures the degree of difficulty a patient had experienced during the previous week using the following eight domains of daily living activities: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and other activities.[35,36] For each item in the questionnaire, the level of difficulty is scored using a four-option scale ranging from 0 for "no difficulty" to 3 for "unable to do." The minimal clinically important difference is estimated to be a change of 0.22.[35] The manufacturer conducted responder analyses to evaluate differences in the proportion of patients who achieved improvements of at least 0.22 and an additional analysis using a more conservative threshold of 0.3.[7,10]

c) Disease Activity Score

Changes in the activity of the patient's RA were evaluated using the DAS 28. Depending on the biomarker used to measure inflammation, the DAS 28 scale is referred to as the DAS 28-CRP if C-reactive protein is used or DAS 28-ESR if erythrocyte sedimentation rate is used. Both MOBILITY and TARGET used the DAS 28-CRP scale, and MONARCH used the DAS 28-ESR scale. Higher DAS 28 scores indicate greater disease activity. The components of the DAS 28 arthritis assessments were as follows: tender or painful joint count (28 joints), swollen joint count (28 joints), patient global assessment of arthritis, and marker of inflammation (either CRP or ESR). Remission was defined as a DAS 28-CRP score or DAS 28-ESR score of less than 2.6.

d) Modified Total Sharp Score

The van der Heijde mTSS was used in the MOBILITY trial to evaluate changes in joint damage.[10] The mTSS is calculated using the sum of the erosion score (range from 0 [normal] to 5 [complete collapse]) and the joint space narrowing score (range from 0 [normal] to 5 [mutilating changes]).[37] Data on the progression of joint structural damage were obtained using x-rays taken at baseline (or screening) and then at 24 and 52 weeks. The X-ray images were analyzed by two independent readers who were instructed to quantify the erosion and joint space narrowing. The average of the two scores was used for the analysis of mTSS in MOBILITY. As shown in Table 10, change from baseline in mTSS at 52 weeks was a co-primary end point of MOBILITY. A change from baseline in the mTSS of ≤ 0 was considered to be an event of "no progression," which was a pre-specified secondary end point of the MOBILITY trial.[10]

e) Short Form (36) Health Survey

The Short Form (36) Health Survey (SF-36) is a 36-item generic health status measure. It measures eight general health domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. Higher scores indicate better health-related quality of

life. The eight subdomains are each measured on a scale of 0 to 100, with an increase in score indicating improvement in health status. The SF-36 items can be analyzed in the following two categories: the physical component summary (PCS; physical functioning, role physical, bodily pain, and general health) and the mental component summary (MCS; vitality, social functioning, role emotional, and mental health). The minimal clinically important difference is estimated at 2.5 units to 5 units.[38-40]

f) Functional Assessment of Chronic Illness Therapy–Fatigue Scale

The Functional Assessment of Chronic Illness Therapy (FACIT)–Fatigue scale is a patient-reported questionnaire consisting of 13 items that assess fatigue. FACIT-Fatigue scores range from 0 to 52, with higher scores representing less fatigue. A suggested minimal clinically important difference for the FACIT-Fatigue in patients living with RA is a change of 3 to 4 units.[41]

g) EuroQoL 5-Dimensions 3-Levels Questionnaire

EuroQoL 5-Dimensions 3-Levels questionnaire (EQ-5D-3L) is a generic utility measure of health-related quality of life used to evaluate the current health states of patients at least 12 years of age.[42] The EQ-5D-3L consists of two sections:

- The EQ-5D descriptive system consists of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (scored as one of three levels: no problems, some problems, or extreme problems). The EQ-5D index score is generated by applying a multi-attribute utility function to the descriptive system. The lowest possible overall score (corresponding to severe problems on all five attributes) is −0.109 (based on the US algorithm). Scores less than 0 represent health states that are valued by society as being worse than dead, while scores of 0 and 1.00 are assigned to the health states "dead" and "perfect health," respectively. The minimal clinically important difference for the EQ-5D ranges from 0.033 to 0.074.[43]
- The EQ visual analogue scale captures the patient's self-rated health on a scale where the end points are labelled "best imaginable health state" (score of 100) and "worst imaginable health state" (score of 0).[44]

3.1.5 Statistical Analysis

a) Primary End Points

There were three primary end points in the MOBILITY trial (proportion of patients with 20 at week 24, change from baseline in HAQ-DI at week 16, and change from baseline in mTSS at week 52).[10] There were two primary end points in the TARGET trial (proportion of patients with 20 at 24 weeks and change from baseline in HAQ-DI at 12 weeks).[7] Change from baseline in DAS 28-ESR was the primary end point of MONARCH. There was no primary efficacy end point in the ASCERTAIN study.[8]

20

In the primary analyses of MONARCH and TARGET, any data that were collected after treatment discontinuation or the initiation of rescue therapy were considered to be missing and there was no imputation of missing values.[7,10] Patients who discontinued or who initiated rescue therapy were considered to be nonresponders. 20 response rate at 24 weeks was analyzed using the two-sided Cochran–Mantel–Haenszel test stratified by prior BRM use and region (MONARCH) or by number of previous TNF alpha antagonists (1 versus > 1) and region (TARGET).[7,10] The Mantel–Haenszel estimate of the odds ratio (OR) and the corresponding 95% confidence interval (CI) were derived by testing each active dosage group versus placebo separately (i.e., 200 mg or 150 mg versus placebo).[7,10]

Health Assessment Questionnaire–Disability Index
In the primary analyses of MONARCH and TARGET, change from baseline in HAQ-DI was analyzed with a mixed model for repeated measures approach.[7,10] The model included treatment, region, prior use of a BRM (MOBILITY) or the number of previous TNF alpha antagonists (TARGET), visit, and treatment-by-visit interaction as fixed effects and baseline HAQ-DI as a covariate.[7,10] Differences between treatments were reported as least squares mean differences (LSMDs) with corresponding 95% CIs and *P* values.[7,10] Data collected after treatment discontinuation were handled as missing in the analysis.

Modified Total Sharp Score
Missing or post-rescue week 52 data for mTSS, erosion scores, or joint narrowing scores were imputed using a linear extrapolation approach.[10] The manufacturer noted that the distribution of mTSS data was non-normal; therefore, a two-sided rank-based ANCOVA model was used for the primary analysis. The model adjusted for baseline, prior BRM use, and region.[10]

Disease Activity Score Using Erythrocyte Sedimentation Rate
Change from baseline in DAS 28-ESR was analyzed with a mixed model for repeated measures approach. The model included terms for treatment, visit (week 12 or week 24), treatment-by-visit interaction, and region as fixed effects and baseline DAS 28-ESR as a continuous covariate. Data that were collected after permanent treatment discontinuation were excluded from the primary efficacy analysis. The manufacturer reported that the ASCERTAIN study was not powered for efficacy comparisons between sarilumab and tocilizumab. All of the efficacy variables that were measured were summarized descriptively, and no statistical testing was performed.[8]

b) Secondary and Exploratory End Points
In all of the included studies, categorical end points were evaluated using a two-sided Cochran–Mantel–Haenszel test and continuous end points were analyzed using a mixed model for repeated measures. Stratification was conducted according to the variables that were used in the analyses of the primary end points.[7,9,10]

c) Multiple Comparisons
In TARGET, MOBILITY, and MONARCH, a hierarchical testing procedure was used for the analysis of the primary and secondary end points to control the overall alpha error rate at either the 0.05 level (MONARCH) or 0.025 level (TARGET and MOBILITY). An alpha of 0.025 was used in MOBILITY and TARGET due to the use of a Bonferroni correction to account for multiple testing of the two active dosage regimens (i.e., 150 mg or 200 mg once every two weeks). The statistical hierarchies are summarized in Table 11.

TABLE 11: STATISTICAL HIERARCHIES USED IN THE INCLUDED STUDIES

MOBILITY	TARGET	MONARCH
Primary End Points 1. 20 (week 24) 2. HAQ-DI (week 16) 3. mTSS (week 52) **Secondary End Points** 4. DAS 28-CRP (week 24) 5. 50 (week 24) 6. 70 (week 24) 7. DAS 28-CRP < 2.6 (week 24) 8. HAQ-DI (AUC) (week 52) 9. mTSS progression (week 52) 10. CDAI (week 24) 11. FACIT-Fatigue (week 24) 12. SF-36 PCS (week 24) 13. SF-36 MCS (week 24) 14. WPAI (week 12) 15. Sleep (week 24) 16. FACIT-Fatigue (week 52) 17. SF-36 PCS (week 52) 18. SF-36 MCS (week 52) 19. Sleep (week 52) 20. WPAI (week 52)	**Primary End Points** 1. 20 (week 24) 2. HAQ-DI (week 12) **Secondary End Points** 3. DAS 28-CRP (week 24) 4. 50 (week 24) 5. 70 (week 24) 6. DAS 28-CRP < 2.6 (week 24) 7. CDAI (week 24) 8. HAQ-DI (week 24) 9. SF-36 Physical (week 24) 10. SF-36 Mental (week 24) 11. FACIT-Fatigue (week 24) 12. Morning stiffness (week 24) 13. WPS-RA (week 24) 14. RAID (week 24) 15. EQ-5D-3L (week 24)	**Primary End Points** 1. DAS 28-ESR **Secondary End Points** 2. DAS 28-ESR < 2.6 (week 24) 3. 50 (week 24) 4. 70 (week 24) 5. 20 (week 24) 6. HAQ-DI (week 24) 7. SF-36 Physical (week 24) 8. FACIT-Fatigue (week 24) 9. SF-36 Mental (week 24)

AMR = American College of Rheumatology; CDAI = Clinical Disease Activity Index; CRP = C-reactive protein; DAS 28 = Disease Activity Score 28; EQ-5D-3L = EuroQol 5-Dimensions 3-Levels questionnaire; ESR = erythrocyte sedimentation rate; FACIT = Functional Assessment of Chronic Illness Therapy; HAQ-DI = Health Assessment Questionnaire–Disability Index; MCS = mental component summary; mTSS = modified Total Sharp Score; PCS = physical component summary; RAID = rheumatoid arthritis impact of disease; SF-36 = Short Form (36) Health Survey; WPAI = Work Productivity and Activity Impairment questionnaire; WPS-RA = rheumatoid arthritis–specific work productivity survey.
Note: The dashed lined denotes the end point where the statistical testing hierarchies were stopped during the analysis due to failure to demonstrate statistical significance for the sarilumab 200-mg-once-every-two-weeks treatment group.

d) Analysis Populations

The manufacturer reported that the primary efficacy analyses in TARGET, MOBILTY, and MONARCH were conducted using intention-to-treat analysis populations, which consisted of all randomized patients according to the treatment to which they were randomized. This appears to be an accurate description for the categorical end points (e.g., 20); however, the primary analyses of the continuous end points (with the exception of mTSS) were conducted without imputation, and the patients included in the analyses are restricted to those who had evaluations at both baseline and the time of end point evaluation. Efficacy evaluations in ASCERTAIN were conducted using a modified intention-to-treat population, which included all randomized patients who received at least one dose of the study drugs. Patients in cohort 2 were included in the efficacy analyses only in the MOBILITY study.

The safety populations of all the studies consisted of patients who received at least one dose or a partial dose of the study drugs and were analyzed according to the treatment received. The safety population for MOBILITY presented in the CDR report consists of patients who were randomized in cohort 2 or who had received the selected dosage regimens in part B of cohort 1.

e) Handling of Missing Data

As shown in Table 12, there was no imputation of missing data in the primary analyses of categorical end points. Patients who discontinued the studies or initiated rescue therapy in the placebo-controlled studies were considered to be nonresponders for the categorical end points. Sensitivity analyses were conducted using a last observation carried forward (LOCF) approach or through the inclusion of data gathered from patients after they discontinued the study treatments. Continuous variables, with the exception of mTSS, were analyzed using a mixed-effect model repeat measurement approach without imputation of missing data. The data for mTSS were evaluated using a linear extrapolation approach to impute missing data in the primary analysis. This analysis was supported by five sensitivity analyses that were conducted to investigate the impact of missing post-baseline data (i.e., mean rank imputation, LOCF, and observed cases [with and without imputation], and through the use of an alternative linear extrapolation approach).[10]

TABLE 12: APPROACHES TO HANDLING MISSING DATA IN THE INCLUDED STUDIES

Comparison	Study	End Point Type	Primary Analysis	Sensitivity Analyses
Placebo-controlled studies	TARGET[7]	Categorical	Discontinuations counted as nonresponders	• LOCF
		Continuous	No imputation	• LOCF • Multiple imputation
	MOBILITY[10]	Categorical	Discontinuations counted as nonresponders	• LOCF
		Continuous	No imputation	• LOCF
		mTSS	Linear extrapolation[a]	• Mean rank imputation • LOCF • As-observed cases • Observed cases • Linear extrapolation[a]
Active-controlled studies	MONARCH[9]	Categorical	Discontinuations counted as nonresponders	• Discontinuations included[b]
		Continuous	No imputation	• Discontinuations included[b] • Multiple imputation
	[redacted][8]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]

LOCF = last observation carried forward; mTSS = modified Total Sharp Score.

[a] Post-rescue or discontinuation data were considering missing in the linear extrapolation for the primary analysis and were included in the linear extrapolation of the sensitivity analysis.[10]

[b] All patients were requested to return for week 24 assessments even if they had previously discontinued treatment.[9]

f) Sample Size

The sample size calculation for TARGET was based on change from baseline in HAQ-DI at 24 weeks (i.e., one of two co-primary end points) and the manufacturer reported that 522 patients were required (174 per treatment group).[7] The following assumptions were used in the sample size calculation: mean change from baseline of −0.05 in the placebo group and −0.35 in the sarilumab groups, a common standard deviation of 0.79, and a two-group t-test of equal means at a two-sided alpha of 0.025 with 90% power. The sample size calculation for MOBILITY (Part B) was based on change from baseline in mTSS and on the fact that 372 patients would be required for the treatment group. This calculation was based on the following assumptions: an alpha of 0.025 with 90% poweror the, mean changes from baseline in mTSS of 1.10 in the placebo group and 0.35 in both the sarilumab groups, a standard deviation of 2.6, and 15% of mTSS measurements missing.[10]

The sample size calculation for MONARCH was based on change from baseline in DAS 28-ESR at 24 weeks (i.e., the primary end point), and the manufacturer estimated that 170 patients were required.[9] The following assumptions were used in the calculation: a common standard deviation of 1.7, a difference in DAS 28-ESR of 0.6 between the sarilumab and adalimumab groups, and a t-test using a two-sided 5% significance level with 90% power [redacted].[8]

3.2 Patient Disposition

3.2.1 Placebo-Controlled Trials

Patient disposition is summarized in Table 13 for the placebo-controlled trials. In the TARGET study, a total of 1224 patients were screened and 546 patients were randomized. Screening failures were primarily attributed to not satisfying the inclusion criterion for disease severity or not having CRP ≥ 8 mg/L (53%) or for meeting the exclusion criteria for tuberculosis (21%). A greater proportion of patients in the placebo group discontinued the study treatment compared with the sarilumab group (44.2% versus 27.7%). Rescue therapy was initiated in 34.8% of patients in the placebo group compared with 14.1% in the sarilumab group. Overall discontinuation from the study (irrespective of rescue therapy) was greater in the sarilumab group (13.6%) than in the placebo group (9.4%), largely due to an increase in withdrawals due to adverse events (9.2% versus 5.0%).

In the MOBILITY study, a total of 2,978 patients were screened and 1,369 patients were randomized (172 in cohort 1 and 1,197 in cohort 2). [redacted]. Rescue therapy was required for a greater proportion of patients in the placebo group compared with the sarilumab group (39.2% versus 11.5%). Overall discontinuations were greater in the sarilumab group compared with the placebo group (20.6% versus 11.6%). This difference was primarily due to differences in the proportion of patients who withdrew as a result of adverse events (14.3% versus 5.3%). Kaplan–Meier curves showing the time to discontinuation of the study treatments are shown in Figure 6A for TARGET and Figure 6B for MOBILITY.

TABLE 13: PATIENT DISPOSITION FROM PLACEBO-CONTROLLED TRIALS

Disposition, n (%)	MOBILITY		TARGET	
	Placebo	SARI 200 mg	Placebo	SARI 200 mg
Screened	2,978		1,224	
Randomized[a]	398 (100)	399 (100)	181 (100)	184 (100)
Randomized and treated	398 (100)	398 (99.7)	181 (100)	184 (100)
Completed	196 (49.2)	270 (67.7)	101 (55.8)	133 (72.3)
Rescued	156 (39.2)	46 (11.5)	63 (34.8)	26 (14.1)
Discontinued	46 (11.6)	82 (20.6)	17 (9.4)	25 (13.6)
Adverse event	21 (5.3)	57 (14.3)	9 (5.0)	17 (9.2)
Lack of efficacy	3 (0.8)	6 (1.5)	5 (2.8)	2 (1.1)
Poor compliance to protocol	6 (1.5)	5 (1.3)	1 (0.6)	1 (0.5)
Other reasons	16 (4.0)	14 (3.5)	2 (1.1)	5 (2.7)

SARI = sarilumab.
[a] Numbers of people randomized in the table are fewer than what are reported in the above paragraph because the sarilumab 150 mg group is not reported (as per the CDR systematic review protocol).
Source: Common Technical Document section 2.7.3.[45]

3.2.3 Active-Controlled Trials

Patient disposition is summarized in Table 14 for the active-controlled trials. In the MONARCH study, a total of 540 patients were screened and 369 were randomized. The manufacturer reported that screening failures were primarily due to the exclusion criterion related to tuberculosis (12.0%) and failure to meet the inclusion criterion for disease severity (8.1%). A greater proportion of adalimumab-treated patients discontinued the double-blind study treatments compared with the sarilumab-treated patients (15.1% versus 10.3%). There were numerically more discontinuations due to adverse events and lack of efficacy in the adalimumab group than in the sarilumab group (8.1% versus 6.0% and 2.2% versus 1.1%, respectively).[9]

In the ASCERTAIN study, a total [redacted] and 202 were randomized. [redacted].

Kaplan–Meier curves for the time to discontinuation of the study treatments are shown in Figure 7A for ASCERTAIN and Figure 7B for MONARCH.

TABLE 14: PATIENT DISPOSITION FROM ACTIVE-CONTROLLED TRIALS

Disposition, n (%)	MONARCH		ASCERTAIN[a]	
	Adalimumab	SARI 200 mg	Tocilizumab	SARI 200 mg
Randomized and treated	184 (99.5)	184 (100)	102 (100%)	51 (100%)
Completed DB treatment	156 (84.3)	165 (89.7)	[redacted]	[redacted]
Enrolled in OL extension/LTS	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued DB treatment	28 (15.1)	19 (10.3)	[redacted]	[redacted]
Request for discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
Reason for discontinuation				
Adverse event	15 (8.1)	11 (6.0)	4 (3.9%)	8 (15.7%)
Lack of efficacy	4 (2.2)	2 (1.1)	[redacted]	[redacted]
Poor compliance to protocol	3 (1.6)	1 (0.5)	[redacted]	[redacted]
Other reasons	6 (3.2)	5 (2.7)	[redacted]	[redacted]

DB = double blind; LTS = long-term extension study; n = number of patients; OL = open-label; SARI = sarilumab.
[a] Numbers of people randomized in the table are fewer than what are reported in the above paragraph because the sarilumab 150 mg group is not reported (as per the CDR systematic review protocol).
Source: Clinical Study Reports for ASCERTAIN[8] and MONARCH.[9]

3.3 Exposure to Study Treatments

3.3.1 Study Treatments

Table 15 summarizes the exposure to the study treatments oss the included studies. [redacted].

Cumulative exposure and mean exposure were similar between the sarilumab and adalimumab groups in the MONARCH trial. In the MONARCH study, the dosage of adalimumab could be increased from

40 mg once every two weeks to 40 mg once per week. [redacted]. As noted in section 3.1.3, patients in the tocilizumab group started at a dose of 4 mg/kg and could be increased to 8 mg/kg based on the opinion of the investigator and clinical response. A majority of patients (60.8%) had their dose of tocilizumab increased during the treatment period. [redacted] (Table 16). [redacted]. Although a double-dummy design was used in ASCERTAIN, it was not reported what proportion of sarilumab-treated patients were requested to receive an escalated dosage of the matching placebo.

TABLE 15: EXPOSURE TO THE STUDY TREATMENTS

Comparison	Study	Treatment	Cumulative (P-Y)	Days of Exposure	
				Mean (SD)	Median
Active-controlled RCTs	ASCERTAIN	Tocilizumab	[redacted]	[redacted]	[redacted]
		Sarilumab 200 mg	[redacted]	[redacted]	[redacted]
	MONARCH	Adalimumab	[redacted]	[redacted]	[redacted]
		Sarilumab 200 mg	[redacted]	[redacted]	[redacted]
Placebo-controlled RCTs	MOBILITY	Placebo	[redacted]	[redacted]	[redacted]
		Sarilumab 200 mg	[redacted]	[redacted]	[redacted]
	TARGET	Placebo	65.0	[redacted]	[redacted]
		Sarilumab 200 mg	72.5	[redacted]	[redacted]

P-Y = patient-year; RCT = randomized controlled trial; SD = standard deviation.
Source: Clinical Study Reports.

TABLE 16: [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]

n = number of patients with event; N = total number of patients; NA = not applicable.
Source: Clinical Study Report for ASCERTAIN[8] (reported as stated in the CSR, although CADTH noticed that the numbers do not appear to add up to the total sample size).

3.3.2 Concomitant Medications

a) Placebo-Controlled Trials

Concomitant RA treatments for patients enrolled in the TARGET trial are summarized in Table 17. In accordance with the eligibility criteria of the study, all of the patients in TARGET were receiving treatment with at least one concomitant DMARD. [redacted]

[redacted]

Concomitant RA treatments for patients enrolled in the MOBILITY trial are summarized in Table 18. All of the patients were required to be receiving a stable dose of MTX for at least 12 weeks. As shown in Table 18, [redacted]. The mean weekly dose of MTX at baseline was similar in the placebo and sarilumab group (15.61 mg versus 15.26 mg per week). A majority of study participants were receiving concomitant treatment with folic acid and corticosteroids in both the sarilumab ([redacted] and 64.7%) and placebo groups ([redacted] and 63.3%), respectively.[10]

b) Active-Controlled Trials

Concomitant RA treatments for patients enrolled in the MONARCH trial are summarized in Table 18. At baseline, 54.7% of the study population was receiving concomitant treatment with corticosteroids and [redacted]. Concomitant RA treatments for patients enrolled in the ASCERTAIN trial are summarized in Table 17. [redacted]

[redacted][8]

[redacted][8]

TABLE 17: CONCOMITANT MEDICATION IN TARGET AND ASCERTAIN

Concomitant Medications		TARGET		ASCERTAIN	
		PLC + DMARD	SARI + DMARD	TOC + DMARD	SARI + DMARD
Any DMARD	n (%)	181 (100%)	184 (100%)	[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]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Concomitant Medications		TARGET		ASCERTAIN	
		PLC + DMARD	SARI + DMARD	TOC + DMARD	SARI + DMARD
[redacted]					

DMARD = disease-modifying antirheumatic drug; HCQ = hydroxychloroquine; LEF = leflunomide; MTX = methotrexate; NSAID = nonsteroidal anti-inflammatory drug; PLC = placebo; SARI = sarilumab; SD = standard deviation; SSZ = sulfasalazine; TOC = tocilizumab.
Source: Clinical Study Reports for TARGET[7] and ASCERTAIN.[8]

TABLE 18: CONCOMITANT MEDICATION IN MOBILITY AND MONARCH

Concomitant Medications		MOBILITY		MONARCH	
		Placebo + MTX	SARI + MTX	Adalimumab	SARI
MTX at BL	n (%)	[redacted]	[redacted]	NA	
Mean dosing at BL (SD)	MTX (mg/week)	15.61 (4.29)	15.26 (4.25)		
Other	Folic acid	[redacted]	[redacted]	NA	NA
	Corticosteroids	252 (63.3%)	258 (64.7%)	104 (56.2%)	98 (53.3%)
	NSAIDs	NA		[redacted]	[redacted]

BL = baseline; MTX = methotrexate; NA = not applicable; NSAID = nonsteroidal anti-inflammatory drug; SARI = sarilumab; SD = standard deviation.
Source: Clinical Study Reports for MOBILITY[10] and MONARCH.[9]

3.4 Critical Appraisal

3.4.1 Internal Validity

Randomization in all four studies was conducted using appropriate methods with adequate measures to conceal treatment allocation (i.e., [redacted]).[7-10] Randomization was stratified according to region in all four studies, and the following additional stratification variables were used in select studies: prior BRM use (MOBILITY), number of previous TNF alpha antagonists (TARGET), and [redacted]. Prior BRM exposure, including TNF alpha antagonist exposure, is a relevant prognostic factor for the efficacy of RA treatments. [redacted], which was designed to evaluate the comparative safety of the two interleukin-6 inhibitors (sarilumab and tocilizumab), both of which are associated with a risk of neutropenia.[12,13] European Medicines Agency guidance on the design and conduct of pivotal RA trials recommends that randomization be stratified based on whether or not a patient had experienced inadequate efficacy or intolerance with prior DMARD therapy. None of the four included studies conducted stratification based on these criteria; however, the treatment groups were reasonably well balanced with regard to the reasons for treatment failure.

Key baseline and demographic characteristics were generally balanced between the placebo and sarilumab groups in TARGET and MOBILITY. There were several imbalances noted between the groups in the MONARCH and ASCERTAIN active-controlled trials (see section 3.1.2). The clinical expert consulted

by CADTH indicated that these differences did not appear to be clinically relevant and would not be expected to compromise the interpretation of the study results.

Concomitant medications received during the trial were balanced in the MOBILITY, TARGET, and MONARCH studies. [redacted].[8] Given the relatively low dosage of the corticosteroids and the short-term duration of the studies, the clinical expert consulted by CADTH did not believe that the additional usage of corticosteroids in the tocilizumab group could have significantly influenced the results reported in this study.

All of the study treatments in the four randomized controlled trials were administered in a double-blind manner. In both of the active-controlled trials (i.e., MONARCH and ASCERTAIN), the study drugs were administered using a double-dummy design; therefore, in addition to their randomized treatment, the patients were also administered the matching placebo for the other study treatment. However, although the proportion of tocilizumab dose-escalated patients was reported, the proportion of sarilumab-treated patients who received an escalated dosage of the matching placebo was not reported.

In the ASCERTAIN study, tocilizumab (intravenous) and sarilumab (subcutaneous) were administered using different routes of administration; therefore, the matching placebo was used to conceal the allocated treatments. Although tocilizumab is available as a subcutaneous formulation, the initiation of the ASCERTAIN trial (March 25, 2013)[8] predated regulatory approval of this formulation in Canada (May 6, 2014) and in the US (October 21, 2013). Similarly, adalimumab and sarilumab were administered using a double-dummy design in the MONARCH study due to the differential appearance of the two active drugs and the ability to escalate the dose of adalimumab (i.e., from 40 mg once every two weeks to once per week).[9]

Injection-site erythema, pruritus, and rash were more commonly reported in the sarilumab group than in the placebo groups; however, this was unlikely to significantly compromise blinding of the study as only a small minority of patients were affected (e.g., 3.8% to 6.6% experienced erythema). Neutropenia was more commonly reported with sarilumab than placebo in MOBILITY and TARGET (range 12.5% to 14.4% versus 0.2% to 1.1%) and adalimumab in MONARCH (13.6% versus 0.5%). Given that sarilumab is associated with a risk of neutropenia, it is possible that patients and investigators may have surmised that these patients were receiving the treatment with sarilumab, potentially resulting in unblinding.

The disposition of patients who were screened and enrolled in the included trials was appropriately reported in the clinical study reports.[7-10] The design of the placebo-controlled trials allowed patients in both treatment groups who demonstrated less than 20% improvement in tender joint count or swollen joint count to receive open-label treatment with sarilumab from week 12 (TARGET) or week 16 (MOBILITY). The use of early escape criteria for patients who fail to achieve a response after 12 weeks is consistent with FDA guidance on the design of placebo-controlled trials in the treatment of RA.[46] Rescue therapy was more commonly initiated in the placebo groups (39.3% to 34.8%) compared with the sarilumab groups (12.9% to 14.1%).[7,10] Including those who initiated rescue therapy, the overall rate of discontinuation from the study treatments was high in both the placebo (range 44.2% to 50.8%) and sarilumab groups (range 27.7% to 32.3%). These rates of discontinuation are large and are disproportionate oss the active and placebo groups; therefore, there is a risk that the baseline comparability between treatment groups achieved by randomization may not have been preserved after

early escape criteria were applied and that the patients remaining in the trial are reflective of a healthier population (i.e., those at greater risk of clinical deterioration withdrew from the study treatment). Overall, the early escape design limits the ability to interpret the safety and efficacy of sarilumab compared with placebo beyond the 12-week and 16-week time points, respectively.

The primary end points of the pivotal placebo-controlled studies included those related to clinical responses (i.e., 20), physical function (i.e., HAQ-DI), clinical remission (i.e., or European League Against Rheumatism), and radiographic evidence of structural damage progression (i.e., mTSS). These four categories of end points address the important efficacy domains recommended in the FDA's 2013 draft guidance for the development of RA drugs.[46] The FDA has indicated that 12 weeks can be sufficient for demonstrating changes between an active treatment and placebo for end points related to clinical response and physical function;[46] hence, the time points used in the MOBILITY and TARGET studies were appropriate for evaluating short-term improvements in HAQ-DI (e.g., 12 to 16 weeks) and the onset of responses (e.g., 24 weeks).

The van der Heijde mTSS was used to evaluate changes in the erosion and space narrowing of joints from baseline to 52 weeks in the MOBILITY study; however, there are important challenges and limitations with evaluating changes in radiographic disease progression in the setting of a placebo-controlled trial.[46,47] For example, the long-term follow-up required to observe clinically relevant changes in disease progression means that data are unlikely to be available for a large number of patients, particularly for those randomized to placebo (e.g., less than half of placebo group completed the MOBILITY study). Both the FDA and the European Medicines Agency have suggested that an active comparator could be used to reduce some of the issues in the collection and interpretation of placebo-controlled studies;[46,47] however, radiographic disease progression was not included as an outcome in either the MONARCH or the ASCERTAIN trials and these studies were too short to observe meaningful differences for these outcomes.[8,9] Both the FDA and the European Medicines Agency suggest that the use of a categorical end point, such as the proportion of patients with radiographic progression, could be useful for evaluating the clinical relevance of any improvement in radiographic progression.[46,47] The proportion of patients with no radiographic progression was included as a secondary end point in MOBILITY, and the results were supportive of the primary change from baseline analysis (i.e., favoured treatment with sarilumab over placebo).[10] However, a one-year study is likely too short to accurately observe and to conclude that treatment with sarilumab results in clinically meaningful improvements in radiographic progression of disease.

oss all four included studies, the analyses of primary, secondary, and exploratory categorical end points (e.g., responses, DAS 28 remission) were conducted using the intention-to-treat study populations that consisted of all randomized patients. Patients who discontinued the study treatments were considered to be nonresponders in the primary analyses of categorical end points, which is consistent with guidance from regulatory authorities.[47] Sensitivity analyses were conducted for the primary categorical end point in MOBILITY and TARGET (i.e., 20) using LOCF to impute missing values for the evaluations, and the results were supportive of the primary analyses. No such sensitivity analyses were reported for the secondary categorical end points. The manufacturer indicated that an intention-to-treat approach was used for the continuous end points; however, the primary analyses of these end points were conducted without imputation, and the patients included in the analyses are restricted to those who had evaluations at both baseline and the time of end point evaluation. Hence, the primary evaluation of the continuous end points was not conducted using a true intention-to-treat analysis. The manufacturer conducted sensitivity analyses for HAQ-DI in MOBILITY and TARGET using LOCF to impute missing data,

and the results were similar to the primary analyses; however, such analyses were not reported for any of the secondary continuous end points.

Multiplicity adjustment (i.e., Bonferroni correction for multiple treatment groups) and hierarchical testing were used to control the overall type I error rate at 0.05 for the primary and secondary end points in TARGET, MOBILITY, and MONARCH.[7,9,10] Failure to demonstrate statistically significant differences stopped the statistical testing hierarchy at change from baseline in the Work Productivity and Activity Impairment questionnaire at week 12 in MOBILITY,[10] change from baseline in the SF-36 MCS at week 24 in TARGET,[7] and change from baseline in the FACIT-Fatigue at week 24 in MONARCH.[9] However, the manufacturer continued to calculate and report *P* values for the remaining secondary end points. The subgroup analyses were pre-specified in the study protocols and investigated treatment effects based on relevant patient characteristics. Statistical tests for subgroup analyses in TARGET, MOBILITY, and MONARCH were conducted without adjustment for multiple comparisons.

Despite the inclusion of relevant efficacy end points (20, 50, or 70 responses, HAQ-DI, and DAS 28-CRP), the ASCERTAIN study lacked any pre-specified statistical analyses. All of the efficacy end points captured in the ASCERTAIN study were considered to be exploratory by the manufacturer, and no statistical analyses were conducted.[8] Descriptive statistics were reported for the efficacy end points (e.g., proportion of responders); however, there were no treatment differences calculated or statistical tests performed.

3.4.2 External Validity

The clinical expert noted that study populations were a reasonable reflection of the target populations in Canada; however, the mean severity of disease at baseline was greater than would be expected for a typical patient in Canadian practice. All of the studies appear to represent a carefully selected patient population, as there was a high proportion of screening failures oss all four of the included studies, ranging from 54.0% to 55.4% in the placebo-controlled trials to 48.1% and 31.7% in the active-controlled trials. In all of the studies, screening failures were primarily attributed to not satisfying inclusion criteria related to disease severity or for meeting the exclusion criteria related to tuberculosis. The clinical expert consulted by CADTH indicated that the criteria for disease severity that are used for initiating therapy with sarilumab in Canadian practice could be less restrictive than those used in the clinical trials, as some patients with milder disease could be initiated on treatment in order to achieve or maintain clinical responses or remission. The expert noted that patients in Canadian practice are carefully screened for latent tuberculosis before treatment with a BRM is initiated; therefore, the exclusions related to tuberculosis in the clinical trials may be reflective of Canadian practice.

Recent guidance from the European Medicines Agency on the design and conduct of RA trials has indicated that remission (e.g., DAS 28 < 2.6) or low disease activity (e.g., DAS 28 < 3.2) are the most appropriate primary end points for trials involving patients with early and more refractory disease, respectively.[47] The clinical expert consulted by CADTH for this review indicated that clinical remission is the treatment target that is typically used in Canadian clinical practice. As shown in Table 10, clinical remission based on DAS 28 scores was included as a pre-specified secondary end point in the MOBILITY, TARGET, and MONARCH studies. The results were supportive of the primary end points (i.e., sarilumab was statistically superior to both placebo and adalimumab).

The comparators used in the active-controlled trials were relevant in the Canadian context, with one TNF alpha antagonist (adalimumab) and one interleukin-6 inhibitor (tocilizumab). In both studies, the treatments were administered at a dose and frequency that are consistent with recommendations in the

Canadian product monographs.[13,14] In MONARCH, adalimumab was initiated at a dose of 40 mg once every two weeks and the dose could be increased to 40 mg once per week; however, the dose could be escalated only beginning at week 16. The Canadian product monograph for adalimumab states that clinical response for RA is usually achieved within 12 weeks of treatment with adalimumab and that continued therapy should be carefully reconsidered in a patient not responding within this time period.[14] The manufacturer stated that 16 weeks was selected as the time point for initiating dose escalation with adalimumab because previous data suggested that some RA patients continued to improve through 12 weeks to 16 weeks when receiving a dosage of 40 mg adalimumab every two weeks.[9,48] The clinical expert consulted by CADTH indicated that the dosage regimen used for adalimumab in MONARCH was appropriate and reflective of clinical practice. However, the expert noted that adalimumab is typically provided in combination with MTX, as it has been demonstrated that monotherapy with adalimumab is less effective than combination therapy with adalimumab and MTX.[3] In the ASCERTAIN study, tocilizumab was initiated at a dosage of 4 mg/kg once every four weeks, which could be increased to 8 mg/kg once every four weeks.[8] [redacted]. This is reflective of the Canadian product monograph, which also does not recommend a particular period of time before dose escalation; however, the clinical expert consulted by CADTH suggested that the majority of patients would likely receive at least 12 weeks of treatment before up-titrating the dosage.

[redacted][8]

[redacted][8]

RA is a chronic disease with the expectation that patients will be on treatment for many years. Although longer term harms data were reported in the EXTEND study (Appendix 5), the controlled data for sarilumab are limited to 6 months for active comparisons and 12 months for the placebo comparisons; therefore, the long-term efficacy and safety profile of sarilumab is uncertain.

The inclusion criteria in the MONARCH and MOBILITY trials were less restrictive regarding prior DMARD therapy than the criteria that are currently applied for reimbursement of many BRMs in Canada, particularly those that are used for TNF alpha antagonists and the other interleukin-6 inhibitor (tocilizumab). The Ontario Exceptional Access Program, for example, requires a trial of at least two DMARDs, including MTX. In addition, the minimum dosage specified for the non-biologic DMARDs was lower in the inclusion criteria of the studies (e.g., 10 mg/week of MTX, 10 mg/day of leflunomide, 1 g/day of sulfasalazine, and 200 mg/day of hydroxychloroquine) than those specified in the Exceptional Access Program criteria (e.g., 20 mg/week of MTX, 20 mg/day of leflunomide, 2 g/day of sulfasalazine, and up to 400 mg/day of hydroxychloroquine). However, the EAP criteria specify that the minimum exposure threshold is not required in the event of a contraindication or intolerance; therefore, not all patients would have received the higher doses before initiating treatment with a BRM.

A large proportion of patients were receiving treatment with concomitant steroids in the four included studies (range [redacted]). The clinical expert consulted by CADTH indicated that usage of corticosteroids in patients with RA can vary considerably oss Canadian clinical practice. The expert noted

that corticosteroids are often used as a bridging mechanism for patients who are transitioning between treatments (i.e., as a short-term strategy to improve the patient's condition before response or remission being achieved with the new therapy). Hence, many physicians would initiate tapering of corticosteroids in patients who respond to treatment with a BRM. However, the included studies did not permit changes in the dosage of corticosteroids unless the patient developed an adverse event. Nevertheless, the included trials only enrolled patients who were using a relatively low dose of corticosteroids (i.e., ≤ 10 mg prednisone equivalents per day); therefore, these aspects of the trial protocol and the study populations were not considered to significantly limit the generalizability of the results to the target population in Canada. In response to an inquiry from Health Canada, the manufacturer reported that results for 20, HAQ-DI, and mTSS in MOBILITY were superior with sarilumab than with placebo regardless of concomitant use of corticosteroids.[49]

3.5 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Section 2.2, Table 5). See Appendix 4 for additional detailed efficacy data.

3.5.1 American College of Rheumatology Response

a) Placebo-Controlled Trials

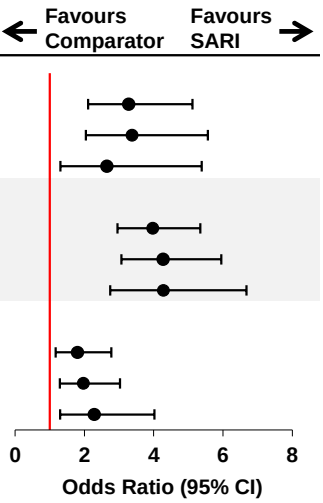
Results for 20, 50, and 70 responses are summarized in Figure 2. In both MOBILITY and TARGET, sarilumab was associated with a statistically significantly greater proportion of patients with 20, 50, and 70 responses compared with placebo at 24 weeks (all $P < 0.0001$). Similar results were observed at 12 weeks in TARGET and at 52 weeks in MOBILITY. Sensitivity analyses for 20 responses conducted using LOCF demonstrated results that were similar to the primary analyses for both MOBLITY (OR 4.495; 95% CI, 3.334 to 6.061) and TARGET (OR 3.720; 95% CI, 2.378 to 5.819). Subgroup analyses were similar to the primary analysis for patients who were positive for rheumatoid factor (both studies), for those with and without prior exposure to a BRM (MOBILITY), and for different categories of baseline body weight (both studies) (Figure 8). In both studies, the response rate was lower for patients who were negative for rheumatoid factor compared with those who were positive, though the sample size was considerably smaller. In MOBILITY, major clinical response was defined as achieving and maintaining an 70 response for at least 24 consecutive weeks. A statistically significantly greater proportion of sarilumab-treated patients achieved the major clinical response end point compared with placebo-treated patients (14.8% versus 3.0%; OR 5.57; 95% CI, 2.95 to 10.52).

b) Active-Controlled Trials

In the MONARCH study, sarilumab was associated with a statistically significantly greater proportion of patients who an achieved an 20 response (OR 1.80; 95% CI, 1.17 to 2.77), 50 response (OR 1.98; 95% CI, 1.29 to 3.03), or 70 response (OR 2.29; 95% CI, 1.30 to 4.02) compared with adalimumab.[9] [redacted].[8]

FIGURE 2: SUMMARY OF 20, 50, AND 70 RESPONSES AT 24 WEEKS

Study	Response	ACR Response, n (%) Comparator	SARI	OR (95% CI)	P value
Sarilumab + DMARD versus Placebo + DMARD					
TARGET	ACR 20	61 (33.7)	112 (60.9)	3.284 (2.108, 5.115)	<0.0001
	ACR 50	33 (18.2)	75 (40.8)	3.374 (2.045, 5.566)	<0.0001
	ACR 70	13 (7.2)	30 (16.3)	2.653 (1.308, 5.383)	0.0056
Sarilumab + MTX versus Placebo + MTX					
MOBILITY	ACR 20	133 (33.4)	265 (66.4)	3.975 (2.957, 5.344)	<0.0001
	ACR 50	66 (16.6)	182 (45.6)	4.269 (3.064, 5.948)	<0.0001
	ACR 70	29 (7.3)	99 (24.8)	4.280 (2.743, 6.678)	<0.0001
Sarilumab versus Adalimumab					
MONARCH	ACR 20	108 (58.4)	132 (71.7)	1.800 (1.168, 2.773)	0.0074
	ACR 50	55 (29.7)	84 (45.7)	1.976 (1.289, 3.028)	0.0017
	ACR 70	22 (11.9)	43 (23.4)	2.286 (1.300, 4.020)	0.0036



AMR = American College of Rheumatology; CI = confidence interval; DMARD = disease-modifying antirheumatic drug; MTX = methotrexate; n = number of patients with a response; N = number of patients included in the analysis; NR = not reported; OR = odds ratio; SARI = sarilumab.
Source: Clinical Study Reports for TARGET,[7] MOBILITY,[10] ASCERTAIN,[8] and MONARCH.[9]

3.5.2 Modified Total Sharp Score

Change from baseline to 52 weeks in mTSS was a co-primary end point and progression based on mTSS was a secondary end point of the MOBILITY study. Results for change from baseline in mTSS in MOBILITY are summarized in Table 19. After 52 weeks of treatment, the mean change in mTSS was statistically significantly smaller in people who received sarilumab compared with placebo ($P < 0.0001$). The mean mTSS increased by 2.78 in the placebo group compared with 0.25 in the sarilumab group. Sarilumab was also associated with a statistically significantly smaller change from baseline in mTSS at 24 weeks (0.13 versus 1.22; $P < 0.0001$). The manufacturer conducted a number of sensitivity analyses for the mTSS evaluation to account for patients who had no post-baseline X-ray data, including the use of LOCF, observed cases, linear extrapolation, and mean rank imputation. All of these analyses supported the primary analysis, with sarilumab being associated with statistically significantly smaller increases in mTSS compared with placebo (Table 37). The absence of progression (defined as a change in the mTSS from baseline to week 52 of ≤ 0) based on mTSS assessments was a secondary end point of MOBILITY. After 52 weeks, a statistically significantly greater proportion of sarilumab-treated patients had no disease progression compared with placebo (55.6% versus 38.7%; OR 2.00; 95% CI, 1.51 to 2.66).

TABLE 19: MODIFIED TOTAL SHARP SCORE

Analysis	Time	Parameter	Placebo + MTX	SARI + MTX	*P* value
Change from baseline	Week 52	n	352	359	< 0.0001
		BL mean (SD)	48.01 (65.23)	46.34 (57.43)	
		Mean change (SD)	2.78 (7.73)	0.25 (4.61)	
	Week 24	n	[redacted]	[redacted]	[redacted]
		BL mean (SD)	[redacted]	[redacted]	
		Mean change (SD)	[redacted]	[redacted]	
No mTSS progression	Week 52	n	398	399	< 0.0001
		No progression[a]	154 (38.7%)	222 (55.6%)	
		OR (95% CI)	2.001 (1.506 to 2.660)		

BL = baseline; CI = confidence interval; mTSS = modified Total Sharp Score; MTX = methotrexate; n = number of patients; SARI = sarilumab; SD = standard deviation.
[a] Change from baseline to week 52 in the mTSS of ≤ 0 was considered to be an event of "no progression."[10]
Source: Clinical Study Report for MOBILITY.[10]

3.5.3 Changes in Disease Activity Scales

a) Disease Activity Score 28

Results for change from baseline in DAS 28-CRP and DAS 28-ESR are summarized in Table 20. Results for the DAS 28-CRP responder analysis are summarized in Figure 3.

Placebo-Controlled Trials

In both MOBILITY and TARGET, treatment with sarilumab was associated with statistically significant improvements in DAS 28-CRP between baseline and 24 weeks compared with placebo [redacted] and −1.444 [95% CI, −1.752 to −1.135], respectively). Similar results were observed at 12 weeks in TARGET [redacted] and 52 weeks in MOBILITY (LSMD −[redacted]). As shown in Table 20, sarilumab-treated patients were more likely to achieve DAS 28-CRP remission (i.e., a score < 2.6). The difference between sarilumab and placebo was statistically significant at weeks 12 and 24 in TARGET and weeks 24 and 52 in MOBILITY (*P* < 0.0001 for all). In TARGET, the proportion of patients with DAS 28-CRP remission increased from week 12 to week 24 in both the sarilumab (17.9% to 28.8%) and placebo groups (3.9% to 7.2%). In MOBILITY, the proportion of patients with DAS 28-CRP remission was the same at weeks 24 and 52 (i.e., 34.1%).

Active-Controlled Trials

The MONARCH study included assessments of both the DAS 28-ESR scale (primary end point) and the DAS 28-CRP scale (exploratory end point). After 24 weeks of treatment, sarilumab was associated with a statistically significantly greater improvement in DAS 28-ESR (LSMD −1.077; 95% CI, −1.361 to −0.793) and DAS 28-CRP (LSMD −0.884; 95% CI, −1.138 to −0.629) compared with adalimumab (Table 20). Subgroup analyses based on MTX history (inadequate response or intolerance), [redacted] were similar to the primary analysis (Figure 9). A statistically significantly greater proportion of sarilumab-treated patients achieved DAS 28-CRP remission compared with adalimumab ([redacted]). In the ASCERTAIN study, [redacted]. The proportion of patients with DAS 28-CRP remission was similar between the sarilumab (31.4%) and tocilizumab groups (29.4%).

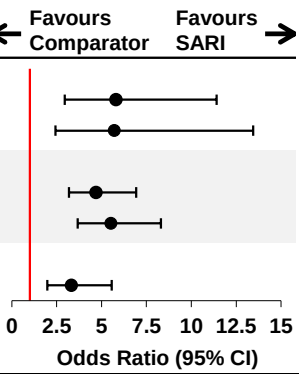
TABLE 20: SUMMARY OF RESULTS FOR CHANGE FROM BASELINE IN DAS 28-CRP AND DAS 28-ESR

Study	Scale	Time	Parameter	Comparator	SARI 200 mg
Sarilumab + DMARD versus Placebo + DMARD					
MOBILITY	DAS 28-CRP	24 weeks	n	[redacted]	[redacted]
			BL mean (SD)	[redacted]	[redacted]
			Change LSM (SE)	[redacted]	[redacted]
			LSMD (95% CI)	[redacted]	
			P value	[redacted]	
		52 weeks	n	[redacted]	[redacted]
			BL mean (SD)	[redacted]	[redacted]
			Change LSM (SE)	[redacted]	[redacted]
			LSMD (95% CI)	[redacted]	
			P value	[redacted]	
Sarilumab + MTX versus Placebo + MTX					
TARGET	DAS 28-CRP	24 weeks	n	99	136
			BL mean (SD)	6.11 (0.82)	6.32 (0.97)
			Change LSM (SE)	−1.38 (0.119)	−2.82 (0.108)
			LSMD (95% CI)	−1.444 (−1.752 to −1.135)	
			P value	< 0.0001	
		[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]	
			[redacted]	[redacted]	
Sarilumab versus Adalimumab					
MONARCH	DAS 28-ESR	24 weeks	n	163	165
			BL mean (SD)	6.73 (0.83)	6.81 (0.76)
			Change LSM (SE)	−2.20 (0.106)	−3.28 (0.105)
			LSMD (95% CI)	−1.077 (−1.36 to −0.793)	
			P value	< 0.0001	
	DAS 28-CRP	24 weeks	n	156	163
			BL mean (SD)	5.98 (0.88)	6.00 (0.87)
			Change LSM (SE)	−1.97 (0.094)	−2.86 (0.093)
			LSMD (95% CI)	−0.884 (1.138,o −0.629)	
			P value	< 0.0001	

BL = baseline; CI = confidence interval; CRP = C-reactive protein; DAS 28 = Disease Activity Score 28; DMARD = disease-modifying antirheumatic drug; ESR = erythrocyte sedimentation rate; LSM = least squares mean; LSMD = least squares mean difference; MTX = methotrexate; n = number of patients; NR = not reported; SARI = sarilumab; SD = standard deviation; SE = standard error.
Source: Clinical Study Reports for TARGET,[7] MOBILITY,[10] and MONARCH.[9]

FIGURE 3: SUMMARY OF RESULTS FOR DAS 28-CRP REMISSION

Study	Time	DAS28 Remission, n (%) Comparator	SARI	OR (95% CI)	P value
Sarilumab + DMARD versus Placebo + DMARD					
TARGET	24 weeks	13 (7.2)	53 (28.8)	5.801 (2.948, 11.413)	<0.0001[a]
	12 weeks	7 (3.9)	33 (17.9)	5.713 (2.428, 13.441)	<0.0001[a]
Sarilumab + MTX versus Placebo + MTX					
MOBILITY	24 weeks	40 (10.1)	136 (34.1)	4.690 (3.176, 6.926)	<0.0001[a]
	52 weeks	34 (8.5)	136 (34.1)	5.525 (3.673, 8.310)	<0.0001[a]
Sarilumab versus Adalimumab					
MONARCH	24 weeks	25 (13.5)	63 (34.2)	3.314 (1.973, 5.566)	<0.0001[a]



CI = confidence interval; DAS 28-CRP = Disease Activity Score 28 using C-reactive protein; DMARD = disease-modifying antirheumatic drug; MTX = methotrexate; n = number of patients; OR = odds ratio; SARI = sarilumab.
[a] Exploratory end point evaluated outside of the statistical testing hierarchy.
Source: Clinical Study Reports for TARGET[7] MOBILITY,[10] and MONARCH.[9]

b) Clinical Disease Activity Index

Change from baseline in CDAI at 24 weeks was a secondary end point in both TARGET and MOBILITY and an exploratory end point in MONARCH.[7,9,10] CDAI evaluations at 12 weeks and 52 weeks were exploratory end points in TARGET and MOBILITY, respectively.[7,10] Responder analyses based on achieving a CDAI score of ≤ 2.8 were exploratory end points in TARGET, MOBILITY, and MONARCH. Results for change from baseline in CDAI are summarized in Table 21, and the CDAI responder analysis is summarized Table 22.

Placebo-Controlled Trials

Sarilumab was associated with a statistically significant improvement in CDAI compared with placebo at 24 weeks in both TARGET ([redacted]) and MOBILITY [redacted].[7,10]

Active-Controlled Trials

Sarilumab was associated with a statistically significant improvement in CDAI compared with adalimumab at 24 weeks in MONARCH (LSMD −3.741; 95% CI, −6.016 to −1.466).[9] As shown in Table 22, there was no statistically significance difference between sarilumab and adalimumab for the proportion of patients with a CDAI response at week 12 (OR 1.935; 95% CI, 0.695 to 5.382; *P* = 0.2007); however, there was a statistically significant difference at week 24 (OR 2.869; 95% CI, 0.981 to 8.389; *P* = 0.0468).[9]

TABLE 21: SUMMARY OF CLINICAL DISEASE ACTIVITY INDEX

Study	Time Point	Parameter	Comparator	Sarilumab	LSMD (95% CI) *P* value
Sarilumab + DMARD versus Placebo + DMARD					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sarilumab + MTX versus Placebo + MTX					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sarilumab versus Adalimumab					
MONARCH	24 weeks	[redacted]	[redacted]	[redacted]	−3.741 (−6.016 to −1.466) 0.0013[a]

BL = baseline; CI = confidence interval; DMARD = disease-modifying antirheumatic drug; LSM = least squares mean; LSMD = least squares mean difference; MTX = methotrexate; n = number of patients; SD = standard deviation; SE = standard error.
[a] Exploratory end point evaluated outside of the statistical testing hierarchy.
Source: Clinical Study Reports for TARGET,[7] MOBILITY,[10] and MONARCH.[9]

TABLE 22: SUMMARY OF CLINICAL DISEASE ACTIVITY INDEX–RESPONDER ANALYSIS

Study	Time	CDAI Response, n (%)		SARI versus Comparator	
		Comparator	SARI 200 mg	OR (95% CI)	*P* value
Sarilumab + DMARD versus Placebo + DMARD					
TARGET	12 weeks	1 (0.6%)	9 (4.9%)	9.180 (1.177 to 71.619)	0.0106[a]
	24 weeks	9 (5.0%)	15 (8.2%)	1.724 (0.726 to 4.092)	0.2134[a]
Sarilumab + MTX versus Placebo + MTX					
MOBILITY	24 weeks	20 (5.0%)	55 (13.8%)	3.035 (1.783 to 5.165)	< 0.0001[a]
	52 weeks	19 (4.8%)	72 (18.0%)	4.446 (2.618 to 7.552)	< 0.0001[a]
Sarilumab versus Adalimumab					
MONARCH	12 weeks	[redacted]	[redacted]	[redacted]	[redacted]
	24 weeks	5 (2.7%)	13 (7.1%)	2.869 (0.981 to 8.389)	0.0468[a]

CDAI = Clinical Disease Activity Index; CI = confidence interval; DMARD = disease-modifying antirheumatic drug; n = number of patients; MTX = methotrexate; OR = odds ratio; SARI = sarilumab.
[a] Exploratory end point evaluated outside of the statistical testing hierarchy.
Source: Clinical Study Reports for TARGET,[7] MOBILITY,[10] and MONARCH.[9]

3.5.4 Physical Function

a) Health Assessment Questionnaire–Disability Index

Change in HAQ-DI was a co-primary end point of both TARGET (12 weeks) and MOBILITY (16 weeks), a secondary end point in MONARCH (24 weeks), and an exploratory end point in ASCERTAIN (24 weeks).[7-10] Responder analyses based on achieving an HAQ-DI unit difference greater than 0.3 or 0.22 were included as exploratory end points, with the exception of an HAQ-DI unit difference greater than 0.22 at 52 weeks, which was a secondary end point in MOBILITY. Figure 4 provides a summary of results for change from baseline in HAQ-DI in both the placebo- and active-controlled trials. The responder analyses are summarized in Figure 5.

Placebo-Controlled Trials

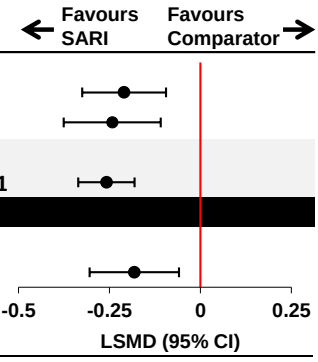
In both TARGET and MOBILITY, treatment with sarilumab was associated with a statistically significant improvement in HAQ-DI compared with placebo. The LSMDs between the sarilumab and placebo groups were −0.210 (95% CI, −0.325 to −0.095) in TARGET and −0.258 (95% CI, −0.336 to −0.181) in MOBILITY.[7,10] [redacted]. Compared with placebo, a greater proportion of sarilumab-treated patients achieved an HAQ-DI unit difference greater than 0.3 or 0.22 at all time points (Figure 5). Results for subgroup analyses based on baseline weight, prior use of a BRM, rheumatoid factor, and number of prior DMARDs were similar to those reported for 20 (Figure 10).

Active-Controlled Trials

Treatment with sarilumab was associated with a statistically significant improvement in HAQ-DI compared with adalimumab in MONARCH (LSMD −0.182; 95% CI, −0.305 to −0.059).[9] [redacted].[8] A statistically significantly greater proportion of sarilumab-treated patients achieved an HAQ-DI unit difference greater than 0.3 or 0.22 at week 24 in MONARCH (OR 1.747 [95% CI, 1.147 to 2.663] and OR 1.785 [95% CI, 1.180 and 2.698]).[9]

FIGURE 4: DIFFERENCE IN CHANGE FROM BASELINE IN HEALTH ASSESSMENT QUESTIONNAIRE–DISABILITY INDEX

Study	Time	Change HAQ-DI (LSM [SE]) Comparator	SARI	LSMD (95% CI)	P value
Sarilumab + DMARD versus Placebo + DMARD					
TARGET	12 weeks	-0.26 (0.043)	-0.47 (0.043)	-0.210 (-0.325, -0.095)	0.0004
	24 weeks	-0.34 (0.051)	-0.58 (0.048)	-0.242 (-0.376, -0.109)	0.0004
Sarilumab + MTX versus Placebo + MTX					
MOBILITY	16 weeks	-0.29 (0.028)	-0.55 (0.029)	-0.258 (-0.336, -0.181)	<0.0001
[redacted]					
Sarilumab versus Adalimumab					
MONARCH	24 weeks	-0.43 (0.045)	-0.61 (0.045)	-0.182 (-0.305, -0.059)	0.0037

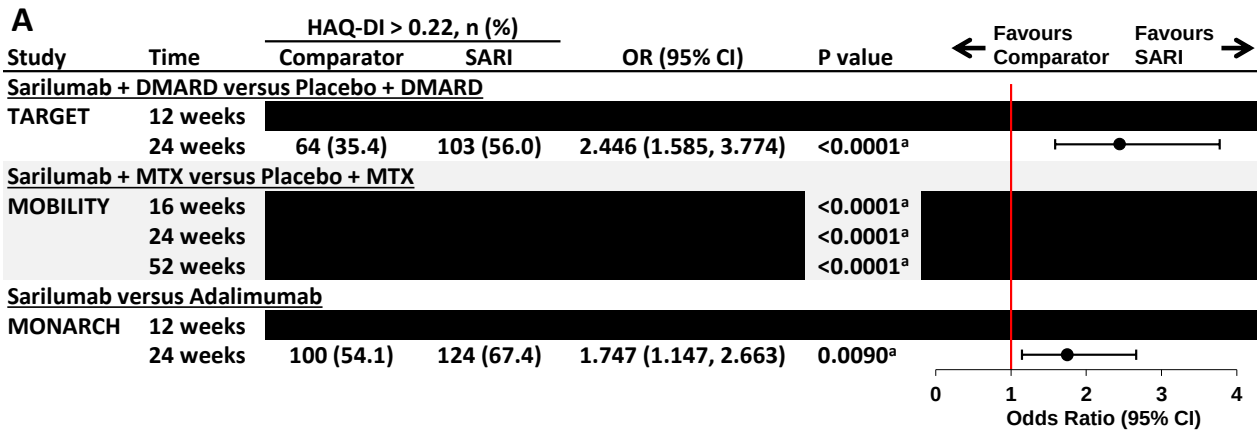


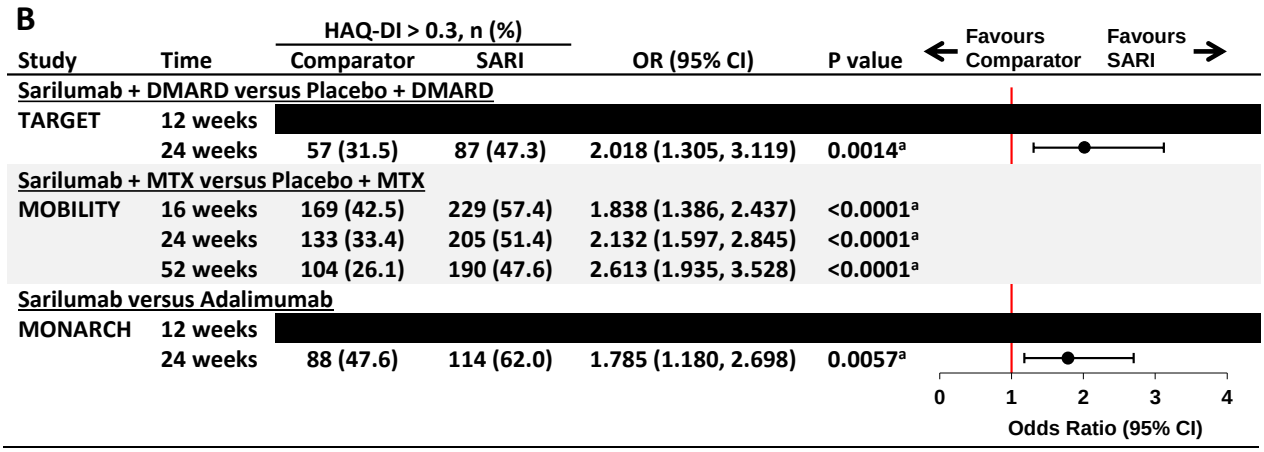
CI = confidence interval; DMARD = disease-modifying antirheumatic drug; HAQ-DI = Health Assessment Questionnaire–Disability Index; LSMD = least squares mean difference; MTX = methotrexate; n = number of patients; OR = odds ratio; SARI = sarilumab; SE = standard error.

[a] Exploratory end point evaluated outside of the statistical testing hierarchy.

Source: Clinical Study Reports for TARGET,[7] MOBILITY,[10] and MONARCH.[9]

FIGURE 5: RESPONDER ANALYSES FOR CHANGE IN HAQ-DI OF AT LEAST 0.22 (A) OR 0.3 (B)





CI = confidence interval; DMARD = disease-modifying antirheumatic drug; HAQ-DI = Health Assessment Questionnaire–Disability Index; MTX = methotrexate; n = number of patients; OR = odds ratio; SARI = sarilumab.
[a] Exploratory end point evaluated outside of the statistical testing hierarchy.
Source: Clinical Study Reports for TARGET,[7] MOBILITY,[10] and MONARCH.[9]

3.5.5 Patient-Reported Outcomes

a) Short Form (36) Health Survey

The results for change from baseline in SF-36 are summarized in Table 23. Changes in baseline for the SF-36 questionnaire were evaluated separately for the SF-36 PCS and the SF-36 MCS.

Placebo-Controlled Trials

Changes in the SF-36 PCS and the SF-36 MCS were secondary end points in MOBILITY (weeks 24 and 52) and TARGET (week 24). Compared with placebo, treatment with sarilumab was associated with a statistically significant improvement in the SF-36 PCS at 24 weeks in both TARGET (LSMD 4.075; 95% CI, 2.305 to 5.846) and MOBILITY (LSMD 3.201; 95% CI, 1.978 to 4.423).[7,10] There was a statistically significant difference favouring sarilumab over placebo for change from baseline in SF-36 MCS at week 24 in MOBILITY (LSMD 4.271; 95% CI, 2.761 to 5.781);[10] however, there was no statistically significant difference in TARGET (LSMD 2.013; 95% CI, −0.282 to 4.309).[7] Failure to demonstrate a statistically significant difference between sarilumab and placebo in the SF-36 MCS at 24 weeks in TARGET stopped the statistical testing hierarchy at this end point. Compared with placebo, sarilumab resulted in greater improvement in SF-36 PCS (LSMD 3.530; 95% CI, 2.164 to 4.897) and SF-36 MCS (LSMD 2.896; 95% CI, 1.199 to 4.593) in MOBILITY at week 52. However, these differences are not considered to be

statistically significant due to the failure of the statistical testing hierarchy at a higher-level comparison.[10]

Active-Controlled Trials

In the MONARCH study, treatment with sarilumab was associated with a statistically significant difference in SF-36 PCS compared with adalimumab at 24 weeks (LSMD 2.650; 95% CI, 1.147 to 4.153).[9] The statistical testing hierarchy used in MONARCH had failed at a higher-level end point; however, there was no apparent difference between sarilumab and adalimumab in SF-36 MCS at 24 weeks (LSMD 1.036; 95% CI, −1.061 to 3.132).

TABLE 23: SUMMARY OF RESULTS FOR THE SHORT FORM (36) HEALTH SURVEY

Study	End Point	Time Point	Parameter	Comparator	Sarilumab	LSMD (95% CI) *P* value
Sarilumab + DMARD versus Placebo + DMARD						
TARGET	SF-36 PCS	24 weeks	n	[redacted]	[redacted]	4.075 (2.305 to 5.846) < 0.0001
			BL mean (SD)	[redacted]	[redacted]	
			Change LSM (SE)	[redacted]	[redacted]	
	SF-36 MCS	24 weeks	n	[redacted]	[redacted]	2.013 (−0.282 to 4.309) 0.0854[b]
			BL mean (SD)	[redacted]	[redacted]	
			Change LSM (SE)	[redacted]	[redacted]	
Sarilumab + MTX versus Placebo + MTX						
MOBILITY	SF-36 PCS	24 weeks	n	[redacted]	[redacted]	3.201 (1.978 to 4.423) 0.0001
			BL mean (SD)	32.15 (7.01)	31.24 (6.90)	
			Change LSM (SE)	5.15 (0.496)	8.35 (0.446)	
		52 weeks	[redacted]	[redacted]	[redacted]	[redacted]
	SF-36 MCS	24 weeks	n	246	309	4.271 (2.761 to 5.781) 0.0001
			BL mean (SD)	37.82 (10.55)	38.92 (11.75)	
			Change LSM (SE)	3.90 (0.614)	8.17 (0.552)	
		52 weeks	[redacted]	[redacted]	[redacted]	[redacted]
Sarilumab versus Adalimumab						
MONARCH	SF-36 PCS	24 weeks	n	157	159	2.650 (1.147 to 4.153) 0.0006
			BL mean (SD)	31.53 (6.48)	30.77 (6.09)	
			Change LSM (SE)	6.09 (0.555)	8.74 (0.555)	
	SF-36 MCS	24 weeks	n	157	159	1.036 (−1.061 to 3.132) 0.3319[a]
			BL mean (SD)	36.93 (11.59)	36.43 (10.43)	
			Change LSM (SE)	6.83 (0.774)	7.86 (0.773)	

BL = baseline; CI = confidence interval; DMARD = disease-modifying antirheumatic drug; LSM = least squares mean; LSMD = least squares mean difference; MCS = mental component summary; n = number of patients; MTX = methotrexate; PCS = physical component summary; SD = standard deviation; SE = standard error; SF-36 = Short Form (36) Health Survey; VAS = visual analogue scale.

[a] Statistical testing hierarchy used in MOBILITY had stopped before these analyses.

[b] Failure to demonstrate a statistically significant difference stopped the statistical testing hierarchy at this end point.

Source: Clinical Study Reports for TARGET,[7] MOBILITY,[10] and MONARCH.[9]

b) EuroQol 5-Dimensions Questionnaire

The results for change from baseline in the EQ-5D Visual Analogue Scale and utility scores are summarized in Table 24. Change from baseline in EQ-5D-3L at 24 weeks was a secondary end point in the TARGET study and an exploratory end point in the MONARCH study.

Placebo-Controlled Trials

[redacted].

Active-Controlled Trials

[redacted][9].

TABLE 24: [redacted]

Study	End Point	Parameter	Comparator	Sarilumab	LSMD (95% CI) *P* value
Sarilumab + DMARD versus Placebo + DMARD					
[redacted]					
Sarilumab versus Adalimumab					
[redacted]					

BL = baseline; CI = confidence interval; DMARD = disease-modifying antirheumatic drug; EQ-5D = EuroQol 5-Dimensions questionnaire; LSM = least squares mean; LSMD = least squares mean difference; n = number of patients; SD = standard deviation; SE = standard error; VAS = visual analogue scale.

[a] Statistical testing hierarchy had stopped before these analyses.

[b] Exploratory end point evaluated outside of the statistical testing hierarchy.

Source: Clinical Study Reports for TARGET[7] and MONARCH.[9]

c) Functional Assessment of Chronic Illness Therapy

The results for change from baseline in FACIT-Fatigue are summarized in Table 25. Change from baseline in FACIT-Fatigue was a secondary end point of both placebo-controlled trials and one of the active-controlled trials (MONARCH).

Placebo-Controlled Trials

Treatment with sarilumab was associated with greater improvements in FACIT-Fatigue at 24 weeks in TARGET (LSMD 3.246; 95% CI, 1.037 to 5.456) and at 24 weeks and 52 weeks in MOBILITY (LSMD 3.351

[95% CI, 2.092 to 4.611] and LSMD 3.148 [95% CI, 1.746 to 4.551], respectively).[7,10] However, the statistical testing hierarchy had stopped before these analyses in both trials; therefore, the differences are not considered to be statistically significantly.[10]

Active-Controlled Trials

There was no statistically significant difference between sarilumab and adalimumab for change from baseline in FACIT-Fatigue at 24 weeks in MONARCH (LSMD 1.768; 95% CI, −0.137 to 3.674).[9] Failure to demonstrate a statistically significant difference between sarilumab and adalimumab in the FACIT-Fatigue at 24 weeks in MONARCH stopped the statistical testing hierarchy at this end point.[9]

TABLE 25: SUMMARY OF RESULTS FOR FACIT-FATIGUE

Study	End Point	Parameter	Comparator	Sarilumab	LSMD (95% CI) *P* value
Sarilumab + DMARD versus Placebo + DMARD					
TARGET	24 weeks	n	98	136	3.246 (1.037 to 5.456) 0.0040[a]
		BL mean (SD)	24.00 (10.42)	23.71 (10.17)	
		Change LSM (SE)	6.82 (0.863)	10.06 (0.778)	
Sarilumab + MTX versus Placebo + MTX					
MOBILITY	24 weeks	n	252	320	3.351 (2.092 to 4.611) < 0.0001[a]
		BL mean (SD)	27.24 (9.99)	26.16 (10.46)	
		Change LSM (SE)	5.80 (0.482)	9.15 (0.449)	
	52 weeks	n	195	271	3.148 (1.746 to 4.551) < 0.0001[a]
		BL mean (SD)	27.51 (9.95)	26.81 (10.59)	
		Change LSM (SE)	6.06 (0.544)	9.20 (0.487)	
Sarilumab versus Adalimumab					
MONARCH	24 weeks	n	158	165	1.768 (−0.137 to 3.674) 0.0689[b]
		BL mean (SD)	24.43 (10.26)	23.59 (8.92)	
		Change LSM (SE)	8.41 (0.709)	10.18 (0.701)	

BL = baseline; CI = confidence interval; DMARD = disease-modifying antirheumatic drug; FACIT = Functional Assessment of Chronic Illness Therapy; LSM = least squares mean; LSMD = least squares mean difference; MTX = methotrexate; n = number of patients; SD = standard deviation; SE = standard error.

[a] Statistical testing hierarchy had stopped before these analyses.

[b] Failure to demonstrate a statistically significant difference stopped the statistical testing hierarchy at this end point.

Source: Clinical Study Reports for TARGET,[7] MOBILITY,[10] and MONARCH.[9]

3.6 Harms

Only those harms identified in the review protocol are reported below (see 2.2.1, Protocol). See Appendix 4 for additional harms data.

Table 26 provides a summary of total adverse events, serious adverse events, and withdrawals due to adverse events from the placebo-controlled and active-controlled trials included in the CDR review.

TABLE 26: SUMMARY OF ADVERSE EVENTS

AEs n (%)	MOBILITY		TARGET		MONARCH		ASCERTAIN	
	PLC + MTX (N = 427)	SARI + MTX (N = 424)	PLC + DMARD (N = 181)	SARI + DMARD (N = 184)	ADA (N = 184)	SARI (N = 184)	TOC + DMARD (N = 102)	SARI + DMARD (N = 51)
TEAE	263 (61.6)	331 (78.1)	90 (49.7)	120 (65.2)	117 (63.6)	118 (64.1)	68 (66.7)	36 (70.6)
SAE	23 (5.4)	48 (11.3)	6 (3.3)	10 (5.4)	12 (6.5)	9 (4.9)	7 (6.9)	3 (5.9)
WDAE	20 (4.7)	59 (13.9)	8 (4.4)	17 (9.2)	13 (7.1)	11 (6.0)	4 (3.9)	8 (15.7)

ADA = adalimumab; AE = adverse event; DMARD = disease-modifying antirheumatic drug; MTX = methotrexate; n = number of patients with event; N = number of patients in the safety analysis; PLC = placebo; SAE = serious adverse event; SARI = sarilumab; TEAE = treatment-emergent adverse event; TOC = tocilizumab; WDAE = withdrawal due to adverse event.
Source: Clinical Study Reports for TARGET,[7] MOBILITY,[10] ASCERTAIN,[8] and MONARCH.[9]

3.6.1 Adverse events

a) Placebo-Controlled Trials

Adverse events that occurred in the placebo-controlled trials are summarized in Table 40. The proportion of patients who experienced at least one adverse event was greater in the sarilumab groups compared with the placebo groups of both MOBILITY (78.1% versus 61.6%) and TARGET (65.2% versus 49.7%). Neutropenia was more commonly reported with sarilumab in both MOBILITY (14.4% versus 0.2%) and TARGET (12.5% versus 1.1%). A greater proportion of sarilumab-treated patients experienced at least one adverse event that was classified as an infection or infestation (39.6 versus 31.1% in MOBILITY and 30.4% versus 26.5% in TARGET).[7,10]

[redacted]. Compared with placebo, gastrointestinal disorders were more commonly reported in the sarilumab group of both MOBILITY (15.1% versus 10.8%) and [redacted]. There was no consistent trend between the different individual gastrointestinal adverse events oss the two studies. [redacted]. Injection-site reactions were more frequently reported for sarilumab-treated patients than for placebo-treated patients. This included an increase in the proportion of patients with erythema, pruritus, or rash.[7,10]

b) Active-Controlled Trials

Table 27 provides a summary of adverse events that were reported in the two active-controlled trials (MONARCH and ASCERTAIN). The proportion of patients with at least one adverse event was similar between the sarilumab and adalimumab groups in MONARCH (64.1% versus 63.6%). Sarilumab was associated with an increase in events of neutropenia compared with adalimumab (13.6% versus 0.5%). Infections and infestations were reported for a similar proportion of patients in both the sarilumab and adalimumab groups (28.8% versus 27.7%). Injection-site erythema was more frequently reported for sarilumab-treated patients than for adalimumab-treated patients (7.6% versus 3.3%). Headaches were

more frequently reported in the adalimumab group compared with the sarilumab group (6.5% versus 3.8%). Worsening of RA was cited as an adverse event more frequently in the adalimumab group compared with the sarilumab group (3.8% versus 0.5%).

The proportion of patients with at least one adverse event was slightly higher with sarilumab compared with tocilizumab in ASCERTAIN (70.6% versus 66.7%). Sarilumab was also associated with an increase in events of neutropenia compared with tocilizumab (15.7% versus 3.9%). [redacted]. Contributing to this difference was an increase in upper respiratory infections in the tocilizumab group (6.9% versus 2.0%). [redacted] nausea was more commonly reported with tocilizumab compared with sarilumab (6.9% versus 2.0%). Worsening of RA was cited as an adverse event more frequently in the tocilizumab group compared with the sarilumab group (5.9% versus 0%).

TABLE 27: SUMMARY OF ADVERSE EVENTS IN ACTIVE-CONTROLLED TRIALS

Adverse Events, n (%)	MONARCH[a]		ASCERTAIN[a]	
	Adalimumab (N = 184)	SARI (N = 184)	TOC + DMARD (N = 102)	SARI + DMARD (N = 51)
Any class	117 (63.6%)	118 (64.1%)	68 (66.7%)	36 (70.6%)
Infections and infestations	51 (27.7%)	53 (28.8%)	[redacted]	[redacted]
Bronchitis	7 (3.8%)	12 (6.5%)	[redacted]	[redacted]
Nasopharyngitis	14 (7.6%)	11 (6.0%)	4 (3.9%)	3 (5.9%)
Urinary tract infection	[redacted]	[redacted]	6 (5.9%)	2 (3.9%)
Pharyngitis	[redacted]	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	7 (3.8%)	3 (1.6%)	7 (6.9%)	1 (2.0%)
Sinusitis	[redacted]	[redacted]	[redacted]	[redacted]
Blood/lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	1 (0.5%)	25 (13.6%)	4 (3.9%)	8 (15.7%)
Anemia	[redacted]	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]	[redacted]
Hypercholesterolemia	[redacted]	[redacted]	6 (5.9%)	1 (2.0%)
Psychiatric disorders	[redacted]	[redacted]	[redacted]	[redacted]
Depression	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Headache	12 (6.5%)	7 (3.8%)	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	4 (3.9%)	3 (5.9%)
Eye disorders	[redacted]	[redacted]	[redacted]	[redacted]
Conjunctival hemorrhage	[redacted]	[redacted]	[redacted]	[redacted]
Ear and labyrinth disorders	[redacted]	[redacted]	[redacted]	[redacted]
Vertigo	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhea	[redacted]	[redacted]	[redacted]	[redacted]

Adverse Events, n (%)	MONARCH[a]		ASCERTAIN[a]	
	Adalimumab (N = 184)	SARI (N = 184)	TOC + DMARD (N = 102)	SARI + DMARD (N = 51)
Nausea	[redacted]	[redacted]	7 (6.9%)	1 (2.0%)
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]
Skin/SC tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and CTD	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]	[redacted]	[redacted]
Rheumatoid arthritis	7 (3.8%)	1 (0.5%)	6 (5.9%)	0
Spinal osteoarthritis	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and admin. site	[redacted]	[redacted]	[redacted]	[redacted]
Injection-site erythema	6 (3.3%)	14 (7.6%)	1 (1.0%)	4 (7.8%)
Injection-site pruritus	[redacted]	[redacted]	[redacted]	[redacted]
Injection-site swelling	[redacted]	[redacted]	[redacted]	[redacted]
Injection-site pain	[redacted]	[redacted]	[redacted]	[redacted]
Peripheral swelling	[redacted]	[redacted]	[redacted]	[redacted]
Non-cardiac chest pain	[redacted]	[redacted]	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]	[redacted]
ALT increased	7 (3.8%)	7 (3.8%)	[redacted]	[redacted]
Blood creatinine increased	[redacted]	[redacted]	[redacted]	[redacted]
AST increased	[redacted]	[redacted]	[redacted]	[redacted]
Injury, poisoning, procedural complications	[redacted]	[redacted]	[redacted]	[redacted]
Accidental overdose	11 (6.0%)	6 (3.3%)	9 (8.8%)	3 (5.9%)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTD = connective tissue disorders; DMARD = disease-modifying antirheumatic drug; SARI = sarilumab; SC = subcutaneous; TOC = tocilizumab.

[a] Adverse events for ASCERTAIN are reported for events that occurred in at least 5% of patients in at least one of the treatment groups. Adverse events for MONARCH are reported for events that occurred in at least 2% of patients in at least one of the treatment groups or those events with a difference of at least 1% between the groups.

Source: Clinical Study Reports for ASCERTAIN[8] and MONARCH.[9]

3.6.2 Serious Adverse Events

a) Placebo-Controlled Trials

Serious adverse events that occurred in the placebo-controlled trials are summarized in Table 41. A greater proportion of sarilumab-treated patients experienced at least one serious adverse event compared with placebo-treated patients in both the 52-week MOBILITY trial (11.3% versus 5.4%) and the 24-week TARGET trial (5.4% versus 3.3%).[7,10] [redacted].[10] [redacted].[7] Serious adverse events categorized as infections and infestations were more commonly reported in the sarilumab group of MOBILITY (4.0% versus 2.3%); however, the proportions were the same in the sarilumab and placebo groups of TARGET (1.1% in both).[7,10]

b) Active-Controlled Trials

Table 28 provides a summary of serious adverse events that were reported in the two active-controlled trials. The proportion of patients with at least one serious adverse event was similar between sarilumab (4.9%) and adalimumab (6.5%) in MONARCH and between sarilumab (5.9%) and tocilizumab (6.9%) In ASCERTAIN.[8,9] There were no differences between the treatments for the proportion of patients who experienced a serious infection or infestation in both MONARCH (1.1% in each group) and ASCERTAIN (2.0% in each group).[8,9] [redacted].[9] [redacted].[8]

TABLE 28: SUMMARY OF SERIOUS ADVERSE EVENTS FROM ACTIVE-CONTROLLED TRIALS

Serious Adverse Events	MONARCH		ASCERTAIN	
	Adalimumab (N = 184)	SARI (N = 184)	TOC + DMARD (N = 102)	SARI + DMARD (N = 51)
Any class	12 (6.5)	9 (4.9)	7 (6.9%)	3 (5.9%)
Infections and infestations	2 (1.1)	2 (1.1)	2 (2.0%)	1 (2.0%)
Urinary tract infection	[redacted]	[redacted]	[redacted]	[redacted]
Erysipelas	[redacted]	[redacted]	[redacted]	[redacted]
Septic shock	[redacted]	[redacted]	[redacted]	[redacted]
Bursitis infective	0	1 (0.5)	[redacted]	[redacted]
Mastitis	0	1 (0.5)	[redacted]	[redacted]
Arthritis bacterial	1 (0.5)	0	[redacted]	[redacted]
Respiratory tract infection	1 (0.5)	0	[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]

Serious Adverse Events	MONARCH		ASCERTAIN	
	Adalimumab (N = 184)	SARI (N = 184)	TOC + DMARD (N = 102)	SARI + DMARD (N = 51)
[redacted]				

CTD = connective tissue disorders; DMARD = disease-modifying antirheumatic drug; NR = not reported; RTM = respiratory, thoracic, and mediastinal; SARI = sarilumab; TOC = tocilizumab.
Source: Clinical Study Reports for ASCERTAIN[8] and MONARCH.[9]

3.6.3 Withdrawals Due to Adverse Events

Withdrawals due to adverse events that were reported in the placebo-controlled trials are summarized in Table 42 and those from the active-controlled trials are provided in Table 29.

a) Placebo-Controlled Trials

Withdrawals due to adverse events were more commonly reported in the sarilumab groups than in the placebo groups (13.9% versus 4.7% in MOBILITY and 9.2% versus 4.4% in TARGET).[7,10] [redacted]

[7,10]

b) Active-Controlled Trials

The proportion of patients who withdrew as a result of adverse events was similar between the sarilumab and adalimumab groups in MONARCH (6.0% versus 7.1%, respectively).[10] [redacted]

[10]

[redacted][7]

TABLE 29: SUMMARY OF WITHDRAWALS DUE TO ADVERSE EVENTS FROM ACTIVE-CONTROLLED TRIALS

WDAEs, n (%)	MONARCH		ASCERTAIN	
	Adalimumab (N = 184)	SARI (N = 184)	TOC + DMARD (N = 102)	SARI + DMARD (N = 51)
Any class	13 (7.1)	11 (6.0)	4 (3.9)	8 (15.7)
[redacted]				

WDAEs, n (%)	MONARCH		ASCERTAIN	
	Adalimumab (N = 184)	SARI (N = 184)	TOC + DMARD (N = 102)	SARI + DMARD (N = 51)
[redacted]				

CTD = connective tissue disorders; DMARD = disease-modifying antirheumatic drug; NR = not reported; RTM = respiratory, thoracic, and mediastinal; SARI = sarilumab; TOC = tocilizumab; WDAEs = withdrawals due to adverse events.
Source: Clinical Study Report for MONARCH[9] and ASCERTAIN.[8]

3.6.4 Mortality

Deaths were rare in the four included studies. In the double-blind phase of the MOBILITY study, there were one death in the sarilumab 200 mg group and two deaths in placebo group.[10] In the TARGET study, there was one death reported in a placebo-treated patient.[7] In MONARCH, there was one death reported in the sarilumab treatment group and none in the adalimumab group.[9] There was one death in a tocilizumab-treated patient in the ASCERTAIN study.[8]

3.6.5 Adverse Events of Special Interest

In consultation with a clinical expert, the CDR review included serious infections, neutropenia, malignancies, major cardiovascular events, anaphylaxis, bowel perforations, liver toxicity, and dyslipidemia as adverse events of special interest for this review. These adverse events were aligned with those identified by the manufacturer as being of special interest in their safety evaluation plan for sarilumab. These adverse events of special interest were identified by the manufacturer using MedDRA searches based on the preferred terms recorded by the investigators (i.e., these represent aggregate measures of different adverse events as opposed to pre-specified trial end points). A summary of the proportion of patients who reported one or more adverse events of special interest is provided in Table 30 for the placebo-controlled studies and in Table 31 for the active-controlled studies. Similar tables summarizing rates of adverse events of special interest per 100 patient-years are provided in Appendix 4 (Table 43 and Table 44).

TABLE 30: SUMMARY OF ADVERSE EVENTS OF SPECIAL INTEREST IN PLACEBO-CONTROLLED STUDIES

AESI, n (%)	MOBILITY		TARGET	
	PLC + MTX (N = 427)	SARI + MTX (N = 424)	PLC + DMARD (N = 181)	SARI + DMARD (N = 184)
Serious infections	10 (2.3)	17 (4.0)	2 (1.1)	2 (1.1)
Leukopenia[a]	NR	NR	[redacted]	[redacted]
Neutropenia[a]	[redacted]	[redacted]	NR	NR
[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]

AESI = adverse event of special interest; DMARD = disease-modifying antirheumatic drug; GI = gastrointestinal; MTX = methotrexate; n = number of patients with event; N = number of patients in included in the safety analysis; PLC = placebo; SARI = 200 mg sarilumab once every two weeks.
[a] Reported as neutropenia for MOBILITY and leukopenia for TARGET.
Source: Clinical Study Report for MOBILITY[10] and TARGET.[7]

TABLE 31: SUMMARY OF ADVERSE EVENTS OF SPECIAL INTEREST IN ACTIVE-CONTROLLED STUDIES

AESI, n (%)	MONARCH		ASCERTAIN	
	ADA (N = 184)	SARI (N = 184)	TOC + DMARD (N = 102)	SARI + DMARD (N = 51)
Serious Infections	2 (1.1)	2 (1.1)	2 (2.0)	1 (2.0)
[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]

ADA = adalimumab; AESI = adverse event of special interest; DMARD = disease-modifying antirheumatic drug; GI = gastrointestinal; n = number of patients with event; N = number of patients in included in the safety analysis; SARI = 200 mg sarilumab once every two weeks; TOC = tocilizumab.
Source: Clinical Study Report for MONARCH[9] and ASCERTAIN.[8]

a) Serious Infections

The proportion of patients with serious infections was the same in the sarilumab 200 mg group and the placebo group in the 24-week TARGET study (1.1% in both); however, the proportion was greater in the sarilumab group of the 52-week MOBILITY study (4.0% versus 2.3%). [redacted]. The manufacturer reported that none of the patients who experienced serious infections were reported to have grade 3 to grade 4 neutropenia at the time of the event in MOBILITY or to have an absolute neutrophil count below the lower limit of normal in TARGET. The proportion of patients with at least one serious infection was the same in both of the adalimumab

and sarilumab groups in MONARCH (1.1%) and in the tocilizumab and sarilumab groups in ASCERTAIN (2.0%).

b) Neutropenia

In the placebo-controlled trials, the proportion of patients with neutropenia or leukopenia was higher in the sarilumab groups compared with the placebo groups in [redacted][7,10]. [redacted][7,10] There were [redacted]. Events of neutropenia or leukopenia resulted in discontinuation of 10 (2.4%) sarilumab-treated patients in the 52-week MOBILITY study and [redacted][9] [redacted][8] [redacted] The manufacturer reported that patients who had neutropenia in the included studies did not have an increased rate of serious infections.[50]

c) Malignancies

The proportions of patients with a malignancy during the study period were 0.7% (n = 3) and 0.5% (n = 1) in the sarilumab groups and 0.2% (n = 1) and 0.6% (n = 1) in the placebo groups of the MOBILITY and TARGET studies, respectively.[7,10] There were no malignancies reported in the ASCERTAIN trial, and a single patient developed a malignancy in MONARCH (adalimumab-treated).[8,9]

d) Bowel Perforations

The manufacturer's safety evaluation grouped adverse events related to diverticulitis, gastrointestinal ulceration, and gastrointestinal perforations. There were no events in either the sarilumab 200 mg group or the placebo group in any of the 24-week studies (TARGET, MONARCH, ASCERTAIN).[7-9] [redacted][10]. [redacted][10].

e) Liver Toxicity

[redacted][7,10] [redacted][7,10]. [redacted]

f) Dyslipidemia

Lipid elevation (i.e., adverse events recorded as hypertriglyceridemia, hypercholesterolemia, triglycerides increased, dyslipidemia, cholesterol increased, high density lipoprotein increased, or low density lipoprotein increased) was [redacted][7,10]. In the two active-controlled trials, sarilumab was associated with a lower proportion of patients with elevated lipids compared with adalimumab in MONARCH (4.3% versus 1.6%)[9] and [redacted]

[redacted].[8] No events were considered serious or resulted in discontinuation of the study treatments.[7-10] Lipid elevation reported according to preferred terms is summarized in Table 45 for the placebo-controlled trials and Table 46 for the active-controlled trials.

g) Major Cardiovascular Events

[redacted].[7-10]

h) Anaphylaxis

There were no events of anaphylaxis reported in any of the included studies.[7-10]

4. DISCUSSION

4.1 Summary of Available Evidence

The CDR systematic review included four double-blind randomized controlled trials that investigated the safety and efficacy of sarilumab for the treatment of patients with moderately to severely active RA. These included one 24-week placebo-controlled trial (TARGET, N = 546), one 52-week placebo-controlled trial (MOBILITY, N = 1,197), and two 24-week active-controlled trials that compared sarilumab against adalimumab (MONARCH, N = 369) or tocilizumab (ASCERTAIN, N = 202). The MOBILITY and MONARCH studies required patients to have been treatment-experienced with MTX,[9,10] whereas the TARGET and ASCERTAIN trials were conducted in patients who were treatment-experienced with one or more TNF alpha antagonists.[7,8] The studies investigated the use of sarilumab as monotherapy (MONARCH), in combination with MTX (MOBILITY), and in combination with various DMARDs (ASCERTAIN and TARGET). Multiple primary efficacy end points were used within and oss the studies, including 20 response, HAQ-DI, DAS 28-ESR, and mTSS. These categories of end points address the important efficacy domains recommended in the FDA's 2013 draft guidance for the development of RA drugs (clinical response, physical function, clinical remission, and radiographic evidence of structural damage progression).[46] Safety and tolerability were the primary end points of the ASCERTAIN trial.

Three of the included studies (MOBILITY, TARGET, and ASCERTAIN) randomized patients to two different dosages of sarilumab (i.e., 150 mg or 200 mg once every two weeks).[7,8,10] The recommended dosage of sarilumab is 200 mg once every two weeks, with a 150 mg dosage recommended for patients with neutropenia, thrombocytopenia, or elevated liver enzymes.[12] The CDR review focused primarily on the Health Canada–approved dosage regimen and, because the 150 mg dosage regimens were not restricted to patients with the adverse events noted above, the emphasis is placed on the efficacy and safety data for the 200-mg-once-every-two-weeks regimen.

Consistent with guidance from the FDA and the European Medicines Agency on the design and conduct of placebo-controlled trials in patients with active RA,[46,47] both the TARGET and the MOBILITY studies allowed patients who failed to demonstrate at least a 20% improvement in tender joint count or swollen joint count to receive rescue therapy with open-label sarilumab from week 12 and week 16, respectively.[7,10] In both studies, rescue therapy was more commonly initiated in the placebo groups (39.3% to 34.8%) than in the sarilumab groups (12.9% to 14.1%).[7,10] These large and disproportionate rates of discontinuation limit the ability to interpret the safety and efficacy of sarilumab compared with placebo beyond the 12-week and 16-week time points, respectively.

The controlled studies were relatively short term, ranging from 6 to 12 months in duration; therefore, CADTH also summarized the available data from the manufacturer's long-term extension trial (EXTEND), which provides additional, uncontrolled, efficacy and safety data for up to 264 weeks. However, it must be noted that because EXTEND was an open-label trial, the potential for overestimation of benefit and underestimation of harm exists due to the likelihood of those experiencing a response with sarilumab continuing on in the EXTEND study.

4.2 Interpretation of Results

4.2.1 Efficacy

The included studies demonstrated that treatment with sarilumab was consistently statistically superior to placebo and adalimumab for achieving clinical response (20, 50, or 70), clinical remission (DAS 28 < 2.6), and improved physical functioning (HAQ-DI). Of the four subgroups of patients that were identified as being of particular interest for the CDR review of sarilumab, there were no analyses conducted for concomitant use of DMARDs or disease severity. There was a subgroup analysis conducted for 20 response in the MOBILITY trial based on whether or not a patient had prior exposure to a BRM, and the response rates were similar in patients who were treatment-experienced and patients who were treatment-naive. As each of the study protocols had clear requirements regarding concomitant use of MTX or other DMARDs, subgroup analyses based on these parameters were not possible. However, the proportion of people who received sarilumab and met the 20 response criteria was similar when used with and without concomitant DMARDs (i.e., 71.7% without DMARDs, 66.4% with MTX, and 60.9% to 68.6% with MTX or other DMARDs or both).[7,9,10]

Structural damage to joints caused by RA is typically irreversible, and it has been reported that preventing or slowing the progression of structural damage to joints is associated with slowing the progression to RA-related disability—an outcome of tremendous importance to patients. The van der Heijde mTSS is an instrument that is used to evaluate changes in the erosion and space narrowing of joints. Change from baseline in mTSS at 52 weeks was a co-primary end point of the MOBILITY study. Although sarilumab was associated with a statistically significantly smaller change in mTSS compared with placebo after 52 weeks of treatment, the difference did not exceed the published estimates of the minimal clinically important difference of 3.0 units to 4.6 units for this scale.[51] Overall, a 52-week study is likely too short to observe and conclude that treatment with sarilumab results in clinically meaningful improvements in radiographic progression of disease.

The clinical expert consulted by CADTH indicated that the improvements in clinical response, clinical remission, and physical function that were observed with sarilumab compared with both placebo and adalimumab were clinically relevant. The superiority of sarilumab over adalimumab was established only in the clinical trial where both products were used as a monotherapy. A previous clinical study has demonstrated that adalimumab is more effective when used in combination with MTX than as monotherapy (PREMIER).[3] Monotherapy with tocilizumab was also shown to be superior to monotherapy with adalimumab for achieving clinical remission and clinical response in a head-to-head clinical trial; however, this trial compared a higher dose of tocilizumab (8 mg/kg) against a lower dose of adalimumab (40 mg once every two weeks), which may have biased the results in favour of tocilizumab.[52]

Active RA can have a profound negative impact on the quality of life of those living with the condition. The included randomized controlled trials evaluated several health-related quality of life end points, including the SF-36 and EQ-5D-3L questionnaires. Consistent with the improvements observed in physical function with the HAQ-DI assessments, treatment with sarilumab was associated with greater improvements in the physical component score of the SF-36 compared with placebo (range 3.2 units to 4.1 units) and adalimumab (2.7 units). These differences exceed the lower end of the 2.5 unit to 5 unit range of the commonly cited minimal clinically important difference for the SF-36 component scores.[38-40] Results were inconsistent oss the included studies for the mental component score of the SF-36, limiting the ability to draw conclusions about that end point. Sarilumab-treated patients demonstrated improvements in EQ-5D-3L utility scores compared with placebo and with adalimumab ([redacted]). These differences exceed or fall within the range of published minimal clinically important differences for the EQ-5D utility scores (i.e., 0.033 to 0.074);[43] however, the analyses were conducted outside the statistical testing hierarchies, which limits the ability to interpret the significance results.

For patients who experience an inadequate response or loss of response to a biologic treatment for RA, there are two commonly used approaches: switch to an alternative treatment or escalate the dosage of the current treatment. The Canadian product monographs for several biologic treatments provide dose-escalation scenarios for RA patients. These include adalimumab and subcutaneous tocilizumab where escalation occurs as a result of an increase in the frequency of administration (i.e., once every two weeks to weekly)[13,14] and infliximab or intravenous tocilizumab where escalation occurs as a result of increasing the amount of drug administered without changing the infusion frequency.[13,19,20] Dose escalation of sarilumab was not evaluated in any of the included clinical trials or in the EXTEND extension study,[53] and the current Canadian product monograph does not provide guidance on potential dose-escalation scenarios.[12]

Adequately designed direct comparisons between sarilumab and other BRMs are limited to the comparison with adalimumab in the MONARCH trial;[9] therefore, the manufacturer conducted a network meta-analysis to evaluate the comparative efficacy and safety of sarilumab against other BRMs that have been approved for use in the treatment of RA[redacted].

[redacted]

[redacted]).[54]

In their input to CADTH, patient groups emphasized that not all individuals living with RA will respond to each available treatment in the same manner. In addition, patient groups indicated that treatments can cease to be effective after a period of time, requiring patients to switch to a different therapy. Overall, to account for differential responses and gradual loss of effectiveness, patients strongly believe that multiple treatment options should be available.

4.2.2 Harms

Similar to other BRMs for the treatment of RA, the product monograph for sarilumab has a black box warning regarding the risk of serious infections and it states that patients should be tested for tuberculosis before initiating treatment.[12] All of the studies enrolled patients who were carefully selected on the basis of their risk for tuberculosis. The exclusion criterion related to tuberculosis was cited as a reason for 12.0% to 25.1% of screening failures oss the included studies.[7-10] The clinical expert consulted by CADTH indicated that patients in Canadian practice are screened closely for latent tuberculosis.

The included studies demonstrated that sarilumab is associated with an increased risk of neutropenia, thrombocytopenia, elevated liver enzymes, and increased lipid levels.[7-10] It is recommended in the product monograph that neutrophils, platelets, liver enzymes (aspartate transaminase and alanine transaminase), and lipid parameters be assessed four to eight weeks after initiating treatment with sarilumab and approximately every three months thereafter (six months for lipids).[12] The product monograph also recommends dosage adjustment scenarios for the management of neutropenia, thrombocytopenia, or elevated liver enzymes.[12] These typically consist of interrupting the dosage until the abnormal laboratory values have normalized and then re-initiating treatment at the reduced 150-mg every other week dosage regimen. The dosage adjustment scenarios for sarilumab are generally consistent with those recommended for tocilizumab.[12,13] However, there is no reduced dosage formulation specifically for use in the management of adverse events with tocilizumab, and patients are re-initiated at the lower end of the standard recommended dosage range (i.e., 4 mg/kg every four weeks or 162 mg every two weeks for the intravenous and subcutaneous formulations, respectively).[13]

The primary objective of the ASCERTAIN study was to compare the safety and tolerability of sarilumab with tocilizumab; however, there were no power calculations, and the sample size of the study was relatively low compared with the other phase III studies (i.e., 102 and 51 patients in the tocilizumab and 200 mg sarilumab groups, respectively).[8] [redacted]. The study also demonstrated that a greater proportion of sarilumab-treated patients withdrew as a result of adverse

events compared with tocilizumab-treated patients (15.7% [n = 8] versus 3.9% [n = 4], respectively). The 15.7% rate of withdrawal due to adverse events from the ASCERTAIN study exceeded the rates reported in the other 24-week studies (6.0% to 9.2%) and the 52-week study (13.9%). Given the limited sample size and the lack of consistency with the other randomized controlled trials, it is uncertain if the elevated rate of withdrawal from the ASCERTAIN study is an accurate reflection of the tolerability of sarilumab.

The included studies were short-term trials, and many of the adverse events of special interest were rare oss the studies. The interim results of the EXTEND study demonstrated a similar adverse event profile as was reported in short-term studies. Gastrointestinal perforations are included in the warnings and precautions section of the product monograph. [redacted], [45] [redacted] to rate reported in the intravenous tocilizumab clinical trials (range 0.22 to 0.14 per 100 patient-years).[13] In both the sarilumab and tocilizumab clinical trials, patients with a history of inflammatory bowel disease, severe diverticulitis, or a previous gastrointestinal perforation were excluded; therefore, it is unclear if these rates of gastrointestinal perforation would be reflective of those that could occur in clinical practice. The Canadian product monograph for sarilumab does not contain any warnings regarding an elevated risk of cardiovascular disease;[12] however, the product monograph for tocilizumab does contain such a warning.[13] All Canadian product monographs for biologic RA treatments contain warning statements about a potential increased risk of malignancies.

The clinical expert consulted by CADTH noted that, of the various adverse events associated with BRMs, injection-site reactions are ones that patients are often concerned about. The two active-controlled studies included in the CDR review administered treatments using a double-dummy design; hence, the patients were required to receive multiple subcutaneous injections (MONARCH) or both subcutaneous injections and intravenous infusions (ASCERTAIN).[8,9] This makes it challenging to interpret the results with respect to the comparative tolerability of administration.

[redacted]

4.3 Potential Place in Therapy[ii]

The Canadian Rheumatology Association guidelines for the management of RA support a treat-to-target strategy, where the target is attainment of remission or, when that is not possible, low disease activity.[4] Despite vast improvements in the understanding of the pathogenesis of RA and available therapeutic options for the disease, there are many important unmet needs in the management of this disease. Broadly, these unmet needs include lack of adequate response to current therapies, lack of data on best practices for switching biologic therapies, lack of predictive clinical characteristics and biomarkers for

[ii] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

response to therapies, safety profiles of current drugs, and persistence and adherence with current therapies.[5]

Traditionally, the primary outcomes in clinical trials for therapies in RA are response rates (20, 50, or 70), which represent a measure of relative incremental improvement in defined signs and symptoms of RA. These outcomes do not speak to the practice of rheumatology in 2016, where clinicians no longer look for incremental improvement, but remission. Importantly, sarilumab has demonstrated not only clinically significant response rates in populations of biologic-naive and biologic-experienced patients but also clinically significant rates of disease remission, which are a better reflection of real-world clinical practice. As monotherapy, sarilumab has shown statistically significant improvement in response rates when compared with adalimumab monotherapy. While some may argue that this trial is biased toward sarilumab given that adalimumab has been shown to more efficacious when used in combination with MTX rather than as monotherapy,[3] it is important to note that many patients are not adherent to MTX.[6] The fact that sarilumab has demonstrated superiority compared with one of the most commonly used first-line biologic therapies in RA supports the conclusion that sarilumab will be an important addition to the armamentarium for appropriate management of RA in a real-world setting where many patients are nonadherent to MTX. In addition, sarilumab has shown clinically significant response rates in patients who have failed prior biologic therapy. This is a difficult population of patients to treat because response rates to therapy tend to diminish after the first biologic therapy has been used. For this reason, sarilumab could fill an important role not only in biologic-naive patients, but also in patients who have failed prior biologic therapy.

There is a lack of predictors for evaluating which patients are more likely to respond to any particular RA medications; therefore, it is difficult to specify criteria to determine which patients should receive sarilumab, aside from patients who have active RA (i.e., those whose disease is not in remission or not in a low disease activity state) and who have failed treatment with MTX or biologic therapies or both. Based on the results of the TARGET trial,[7] the RA clinical community is likely to consider sarilumab to be one of the preferred drugs of choice when switching medications after failure with a biologic; however, more data comparing the switch to other therapies is required to definitively support this approach.

5. CONCLUSIONS

The CDR systematic review included four double-blind randomized controlled trials that investigated the safety and efficacy of sarilumab for the treatment of patients with moderately to severely active RA. Three double-blind randomized controlled studies demonstrated that treatment with sarilumab resulted in statistically significant and clinically meaningful clinical response (20, 50, or 70), clinical remission (DAS 28 < 2.6), and improvement in physical functioning (HAQ-DI) compared with placebo (MOBILITY and TARGET) and compared with adalimumab (MONARCH). The placebo-controlled trials investigated the efficacy and safety of sarilumab when used in combination with MTX or other DMARDs; the adalimumab-controlled study was conducted using monotherapy regimens. Radiographic progression was evaluated using mTSS, and sarilumab was associated with a statistically significantly smaller increase in mTSS compared with placebo after 52 weeks of treatment; however, the MOBILITY trial was likely too short to accurately observe and conclude that treatment with sarilumab results in clinically meaningful improvements in radiographic progression of disease. Sarilumab was associated with statistically significant and clinically relevant improvements in the physical component score of the SF-36 compared with placebo and adalimumab.

Treatment with sarilumab is associated with an increased risk of neutropenia, thrombocytopenia, elevated liver enzymes, and increased lipid levels; therefore, routine monitoring of neutrophils, platelets, and liver enzymes is recommended. Serious adverse events were more common with sarilumab compared with placebo (11.3% versus 5.4% in MOBILITY and 5.4% versus 3.3% in TARGET). The proportion of patients with at least one serious adverse event was similar between sarilumab and adalimumab (4.9% versus 6.5%) and sarilumab and tocilizumab (5.9% versus 6.9%). Withdrawals due to adverse events were more commonly reported with sarilumab compared with placebo (9.2% to 13.9% versus 4.4% to 4.7%) and tocilizumab (15.7% versus 3.9%), but were similar between sarilumab and adalimumab (6.0% versus 7.1%). The included studies were short-term trials, and many of the adverse events of special interest were rare oss the studies.

[redacted]

APPENDIX 1: PATIENT INPUT SUMMARY

1. Brief Description of Patient Groups Supplying Input

Three patient groups provided input for the CADTH Common Drug Review (CDR) submission for sarilumab: Arthritis Consumer Experts, the Canadian Arthritis Patient Alliance, and the Arthritis Society provided a joint submission. Arthritis Consumer Experts is a national organization that provides science-based information, education, and support programs to people living with arthritis. The Canadian Arthritis Patient Alliance is a national education and advocacy organization that creates links among Canadians with arthritis to assist them in becoming more effective advocates and to improve their quality of life. The Arthritis Society is Canada's principal health charity providing education, programs, and support to Canadians living with arthritis. The Arthritis Society has been the largest non-government funder of arthritis research in Canada.

The three patient groups declared receiving funding from the private and public sector organizations listed in Table 13. In addition, one of the authors of the patient input submission from the Canadian Arthritis Patient Alliance and the Arthritis Society had received honorariums from Sanofi in 2015 in order to provide a presentation of the journey of a person living with inflammatory arthritis. The three organizations declared no conflicts of interest with respect to their submission.

TABLE 32: FUNDING FOR ARTHRITIS CONSUMER EXPERTS AND CANADIAN ARTHRITIS PATIENT ALLIANCE

ACE	CAPA	Arthritis Society
• AbbVie Corporation • Amgen Canada • Arthritis Research Canada • CIHR • Celgene • Eli Lilly Canada • Hoffman-La Roche Canada Ltd. • Innovative Medicines Canada • Janssen Inc. • Merck Canada • Novartis • Pfizer Canada • Sanofi Canada • St. Paul's Hospital (Vancouver) • UCB Canada • University of British Columbia	• AbbVie Canada • Amgen Canada • Arthritis Alliance of Canada • The Arthritis Society • CIHR (IMHA) • CRA • Eli Lilly and • Hoffmann-La Roche Canada • Innovative Medicines Canada • Janssen Canada • Novartis Canada • ORA • Pfizer Canada • Pfizer/Hospira Canada • Schering Canada • Scleroderma Society • STA Communications • UCB Pharma	• AbbVie Canada • Amgen Canada • Bayer • Bristol • Celgene • Eli Lilly • Hospira • Janssen • Merck • Novartis Canada • Pfizer Canada • Purdue • Roche • UCB

ACE = Arthritis Consumer Experts; CAPA = Canadian Arthritis Patient Alliance; CIHR = Canadian Institutes for Health Research; CRA = Canadian Rheumatology Association; IMHA = Institute of Musculoskeletal Health & Arthritis; ORA = Ontario Rheumatology Association.

2. Condition-Related Information

This information was collected through patients' personal experiences, day-to-day interactions with patients who are living with rheumatoid arthritis (RA), researchers' experience in Canada, a broad

survey of people living with arthritis, a survey of people with arthritis in Canada who participated in the clinical trial for Sarilumab, and the use of social media to gather patient testimonials.

RA is a serious, disabling autoimmune disease that affects every aspect of day-to-day living for patients, caregivers, and families. Patients commonly experience joint pain and morning stiffness. RA affects the ability of patients to carry out the daily activities of living, including self-care, sleeping, pursuing post-secondary education, becoming and staying employed, walking, completing housework, grocery shopping and cooking, maintaining and pursuing relationships, having and caring for children, and participating in social activities and hobbies. In severe cases, patients may require surgeries (such as joint replacement or fusion) or require the use of aids such as bath lifts, canes, or wheelchairs. Some patients are forced by their disease to give up full-time employment or school and have lost their private health insurance and disability benefits. The disease is characterized by inflammation in the joints that destroys the lining of the joint and ultimately the surrounding bone. Once damage occurs, it is irreversible. It is well documented that RA is a systemic disease and can be accompanied by fatigue and numerous comorbidities, such as cardiovascular disease, osteoporosis, and lung disease. There is currently no cure for RA; once a person develops the condition, they live with it for the remainder of their life.

The following quotations provide some insight into the day-to-day challenges that living with RA poses to those who are affected by this condition:

- "Battling pain causes fatigue. Fatigue means you can't do what you used to. … I struggled to find a new career where I can be productive and also manage pain and fatigue."
- "Controlling the deterioration of my feet, knees, and hands is important. I still curl, but with a push stick. I still fish, but do not hold the rod long. I try to do everything I use to do, only slower and more carefully."
- "I have pain, interrupted sleep, low energy, and fatigue. I have compromised immunity, so I get sick easily and stay sick longer."
- "Right now the RA is under control and I am functioning well. When I'm having a flare up, the usual is fatigue, swelling and pain in hands, ankles, knees, wrists, all over body sore and swollen."
- "Daily activities are totally dependent on how I feel when I wake up. If I have a good night of uninterrupted sleep (10 to 12 hours), I am able to do more the following day (housework, grocery shopping, etc. are difficult). My quality of life has decreased substantially in the past 10 years. I used to lead a very active work/personal life. Now, I expend most of my effort taking care of myself and trying to get well."

3. Current Therapy-Related Information

Current treatments for RA include biologic and non-biologic disease-modifying antirheumatic drugs (DMARDs), nonsteroidal anti-inflammatory drugs, corticosteroids, and analgesics. Patients often require multiple drugs in combination to manage their RA. When patients respond to treatment it can be highly effective, yet for others, current therapies are only partially effective or are completely ineffective. Even when a treatment is effective, patients often fear that at some point it will stop working for them and they may not be able to find a suitable replacement. This is especially a concern for young patients who will require treatment for the rest of their lives.

The management of RA is challenging. Physicians and patients often have to try multiple different drugs to find something that works well. The side effects of existing treatments vary and may include nausea and vomiting, extreme fatigue, decreased immune function (as current medications are immunosuppressants), and injection-site or infusion-related reactions. For biologic treatments, patients

often develop antibodies to the treatments after prolonged exposure. Some medications can be administered only via an intravenous infusion, which can cause long-term issues with vein scarring, and it can become increasingly difficult to insert the intravenous needle.

Patients provided the following quotations to illustrate their experience with various treatments for their RA:

- "Finding the best RA treatment is hit and miss. It took quite some time to find a drug that fit my particular needs."
- "A lot has happened since I was diagnosed. We have gone through many trial-and-error paths in order to create a balanced point with my RA."
- "With methotrexate it's very harsh in the stomach; I really dislike taking it."
- "Oral methotrexate made me sick for 3 to 4 days per week with nausea, diarrhea, and extreme fatigue. Using the injectable version of methotrexate, I feel nauseous and tired for one day, which is better. When your drugs cause you to feel unwell, it is a lot easier not to take them."

4. Expectations About the Drug Being Reviewed

A patient who had received sarilumab through participation in a clinical trial indicated having less inflammation, less pain, and better quality of life from the treatment. Specifically, the patient stated the following:

- "The positive is that I can do more things now with sarilumab then when I was not taking it. Inflammation and pain is down, whether it is sarilumab or the combination of the drugs I really do not care. Something is working for me. My liver counts are a bit higher, so I am to cut down on methotrexate, other than that no side effects. The injections every two weeks are not a problem for me so I can feel better. I feel better than I did five years ago."
- "Sarilumab has given me higher expectations for a better life. In fact, I can now go down on the floor and play with my grandkids even though it is still difficult to get up. I would not have thought this possible five years ago. I do not expect the deforming of my joints to stop, but as long as I can keep doing things my body and mind are content with the future."

None of the patients interviewed by Arthritis Consumer Experts have had experience with sarilumab for the treatment of RA. But all of the patients interviewed by Arthritis Consumer Experts expressed the sentiment that if their current therapy works, they do not want to be switched to a new medication. The only reason they should be switched to a new medication is if their current therapy loses its efficacy. Furthermore, they believe that everyone should get equal reimbursement access to medication treatments for RA. One patient specifically commented on how having reimbursement access to the full range of the medications with targeted mechanisms of action helped her gain back her life.

5. Additional Information

Patients from the Canadian Arthritis Patient Alliance and the Arthritis Society indicated that patients with RA respond differently to each medication; thus, every biologic (originator or biosimilar) and non-biologic DMARD should be added to publicly funded drug plans. The Canadian Arthritis Patient Alliance and the Arthritis Society believe that access to sarilumab means a new chance for patients to have a treatment that may be effective in managing their disease if another biologic or non-biologic DMARD fails. They also believe that sarilumab might be another good treatment option for people with RA who commonly experience side effects from other RA treatments.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	Nov 14, 2016
Alerts:	Bi-weekly search updates until Mar 15, 2017
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj	Requires words are adjacent to each other (in any order)
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kw	Keyword
.kf	Author supplied keyword
.pt	Publication type
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
#	**Searches**
1	(Sarilumab* or Kevzara* or SAR 153191 or SAR153191 or REGN 88 or REGN88).ti,ab,kf,ot,hw,rn,nm.
2	(1189541-98-7 or NU90V55F8I).rn,nm.
3	1 or 2
4	3 use pmez
5	*Sarilumab/
6	(Sarilumab* or Kevzara* or SAR 153191 or SAR153191 or REGN 88 or REGN88).ti,ab,kw.
7	5 or 6
8	7 not conference abstract.pt.
9	8 use oemezd
10	4 or 9
11	remove duplicates from 10

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	Search current to November 9, 2016
Keywords:	Sarilumab, Kevzara, SAR153191, REGN88, rheumatoid arthritis
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for evidence-based searching" (https://www.cadth.ca/resources/finding-evidence/grey-matters-practical-search-tool-evidence-based-medicine) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Clinical Trials
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search.

APPENDIX 3: DOSAGE ADJUSTMENT FOR SARILUMAB AND TOCILIZUMAB

Adverse Event	Laboratory Value	Recommendation From Product Monograph	
		Sarilumab[12]	Tocilizumab[13]
Liver enzyme abnormalities	ALT > 1 to ≤ 3 × ULN	• Consider dose modification of concomitant DMARDs as clinically appropriate.	• Dose modify concomitant DMARDs if appropriate. • For IV tocilizumab: Reduce to 4 mg/kg or interrupt until ALT/AST have normalized. • For SC tocilizumab: Reduce injection frequency to Q2W or interrupt until ALT/AST have normalized. Restart with injection Q2W, and increase frequency to QW, as clinically appropriate.
	ALT > 3 to ≤ 5 × ULN	• Hold treatment with sarilumab until < 3 × ULN. • Sarilumab can then be resumed at 150 mg Q2W and increased to 200 Q2W as clinically	• Interrupt tocilizumab dosing until < 3 × ULN and follow recommendations above for > 1 to 3 × ULN. For persistent increases > 3 × ULN (confirmed by repeat testing), discontinue
	ALT > 5 × ULN	• Discontinue sarilumab.	• Discontinue tocilizumab.
Low platelet count	50 to 100 × 10^3/µL	• Hold treatment with sarilumab until > 100 × 10^3/µL. • Sarilumab can then be resumed at 150 mg Q2W and increased to 200 mg Q2W as clinically appropriate.	• Interrupt tocilizumab dosing. • For IV tocilizumab: When platelet count is > 100 × 10^3/µL resume at 4 mg/kg and increase to 8 mg/kg, as clinically appropriate. • For SC tocilizumab: When platelet count is > 100 × 10^3/µL
	< 50 × 10^3/µL	• If confirmed by repeat testing, discontinue sarilumab.	• Discontinue tocilizumab.
Low ANC	ANC > 1 × 10^9/L	• Maintain current dose of sarilumab.	• Maintain dose.
	ANC 0.5 to 1 × 10^9/L	• Hold treatment with sarilumab until > 1 × 10^9/L. • Sarilumab can then be resumed at 150 mg Q2W and increased to 200 mg Q2W as clinically appropriate.	• Interrupt tocilizumab dosing. • For IV tocilizumab: When ANC > 1 × 10^9/L resume at 4 mg/kg and increase to 8 mg/kg, as clinically appropriate. • For SC tocilizumab: When ANC > 1 × 10^9/L resume at Q2W and increase frequency to QW, as clinically appropriate.
	ANC < 0.5 × 10^9/L	• Discontinue sarilumab.	• Discontinue tocilizumab.

ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; DMARD = disease-modifying antirheumatic drugs; IV = intravenous; Q2W = once every two weeks; QW = once weekly; SC = subcutaneous; ULN = upper limit of normal.
Source: Adapted from the product monographs for sarilumab[12] and tocilizumab.[13]

APPENDIX 4: DETAILED OUTCOME DATA

TABLE 33: PRIOR RHEUMATOID ARTHRITIS TREATMENTS IN TARGET AND MOBILITY

Prior RA Treatments, n (%)	TARGET		MOBILITY[a]	
	Placebo	SARI 200 mg	Placebo	SARI 200 mg
Any prior DMARDs	181 (100%)	184 (100%)	[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]	[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]
[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]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

DMARD = disease-modifying antirheumatic drug; RA = rheumatoid arthritis; SARI = sarilumab.

[a] All patients in MOBILITY were receiving concomitant treatment with MTX; use of other DMARDs was evaluated in the three months before study initiation only.[10]

Source: Clinical Study Reports for TARGET[7] and MOBILITY.[10]

TABLE 34: PRIOR RHEUMATOID ARTHRITIS TREATMENTS IN MONARCH

Prior RA Treatments	MONARCH	
	Adalimumab	SARI 200 mg
[redacted]	[redacted]	[redacted]
Reason for stopping MTX		
MTX inadequate responder	103 (55.7%)	97 (52.7%)
MTX intolerant	81 (43.8%)	87 (47.3%)
MTX inappropriate	1 (0.5%)	0
Highest MTX dose (mg/week); mean (SD)	16.9 (4.7)	16.9 (4.7)
[redacted]	[redacted]	[redacted]
Sulfasalazine	44 (23.8%)	59 (32.1%)
Leflunomide	45 (24.3%)	42 (22.8%)
Hydroxychloroquine	43 (23.2%)	41 (22.3%)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Prior use of DMARD + MTX (n [%])	44 (23.8%)	35 (19.0%)

DMARD = disease-modifying antirheumatic drug; MTX = methotrexate; NSAIDs = nonsteroidal anti-inflammatory drugs; RA = rheumatoid arthritis; SARI = sarilumab; SD = standard deviation.
Source: Clinical Study Report for MONARCH.[9]

TABLE 35: [redacted]

[redacted]	ASCERTAIN	
	Tocilizumab	SARI 200 mg
[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]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]	ASCERTAIN	
	Tocilizumab	SARI 200 mg
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

BRM = biologic response modifier; DMARD = disease-modifying antirheumatic drug; SARI = sarilumab.
Source: Clinical Study Report for ASCERTAIN.[8]

Figure 6: [redacted]

Confidential figures redacted at manufacturer's request.

DMARD = disease-modifying antirheumatic drug; sari = sarilumab; q2W = every two weeks.
Source: Clinical Study Reports for TARGET[7] and MOBILITY.[10]

Figure 7: [redacted]

Confidential figures redacted at manufacturer's request.

DMARD = disease-modifying antirheumatic drug; sari = sarilumab; q2W = every two weeks.
Source: Clinical Study Reports for MONARCH[9] and ASCERTAIN.[8]

FIGURE 8: [redacted]

Confidential figure redacted at manufacturer's request.

BRM = biological response modifiers; CI = confidence interval; OR = odds ratio; SARI = sarilumab.
Source: Clinical Study Reports for TARGET[7] and MOBILITY.[10]

FIGURE 9: [redacted]

Confidential figure redacted at manufacturer's request.

BL = baseline; CI = confidence interval; DMARD = disease-modifying antirheumatic drugs; LSMD = least squares mean difference; MTX = methotrexate; SARI = sarilumab; SD = standard deviation.
Source: Clinical Study Report for MONARCH.[9]

FIGURE 10: [redacted]

Confidential figure redacted at manufacturer's request.

CI = confidence interval; DMARD = disease-modifying antirheumatic drugs; LSM = least squares mean; LSMD = least squares mean difference; SARI = sarilumab; SE = standard error.
Source: Clinical Study Report for MONARCH.[9]

TABLE 36: [redacted]

Subgroup		Scale	Placebo	Sarilumab
[redacted]				

Subgroup		Scale	Placebo	Sarilumab
		[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]	[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]

SD = standard deviation; DMARD = disease-modifying antirheumatic drugs.

TABLE 37: [redacted]

Time	Parameter	Placebo + MTX	Sarilumab + MTX	*P* Value
[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]	[redacted]
	[redacted]	[redacted]	[redacted]	
	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	

Time	Parameter	Placebo + MTX	Sarilumab + MTX	*P* Value
	[redacted]	[redacted]	[redacted]	

Abbreviations: BL = baseline; ITT = intention-to-treat; LOCF = last observation carried forward; mTSS = modified Total Sharp Score; MTX = methotrexate; n = number of patients in the analysis; SD = standard deviation.
Source: Clinical Study Reports for MOBILITY.[10]

TABLE 38: CHANGES IN HEALTH ASSESSMENT QUESTIONNAIRE–DISABILITY INDEX

Study	Time Point	Parameter	Comparator	Sarilumab	LSMD (95% CI) (*P* value)
Sarilumab + DMARD versus Placebo + DMARD					
TARGET	12 weeks	n	170	171	−0.210 (−0.325 to −0.095) 0.0004
		BL mean (SD)	1.78 (0.64)	1.82 (0.62)	
		Change LSM (SE)	−0.26 (0.043)	−0.47 (0.043)	
	24 weeks	n	101	136	−0.242 (−0.376 to −0.109) 0.0004
		BL mean (SD)	[redacted]	[redacted]	
		Change LSM (SE)	−0.34 (0.051)	−0.58 (0.048)	
Sarilumab + MTX versus Placebo + MTX					
MOBILITY	16 weeks	n	378	365	−0.258 (−0.336 to −0.181) < 0.0001
		BL mean (SD)	1.61 (0.65)	1.69 (0.63)	
		Change LSM (SE)	−0.29 (0.028)	−0.55 (0.029)	
	52 weeks	n	[redacted]	[redacted]	[redacted] < 0.0001[a]
		BL mean (SD)	[redacted]	[redacted]	
		Change LSM (SE)	[redacted]	[redacted]	
Sarilumab versus Adalimumab					
MONARCH	24 weeks	n	158	165	−0.182 (−0.305 to −0.059) 0.0037
		BL mean (SD)	1.62 (0.64)	1.64 (0.54)	
		Change LSM (SE)	−0.43 (0.045)	−0.61 (0.045)	
Sarilumab + DMARD versus Tocilizumab + DMARD					
ASCERTAIN	24 weeks	n	[redacted]	[redacted]	NR
		BL mean (SD)	[redacted]	[redacted]	
		Change LSM (SE)	[redacted]	[redacted]	

BL = baseline; CI = confidence interval; DMARD = disease-modifying antirheumatic drug; LSM = least squares mean; LSMD = least squares mean difference; MTX = methotrexate; SD = standard deviation; SE = standard error.

TABLE 39: SUMMARY OF EFFICACY RESULTS FOR 150 MG SARILUMAB FROM PLACEBO-CONTROLLED TRIALS

End Point	Time (weeks)	Parameter	TARGET		MOBILITY	
			Placebo	SARI 150 mg	Placebo	SARI 150 mg
20	24	n (%)	61 (33.7)	101 (55.8)	133 (33.4%)	232 (58.0)
		OR (95% CI)	2.711 (1.730 to 4.247)		2.773 (2.077 to 3.703)	
		P value	< 0.0001		< 0.0001	
50	24	n (%)	33 (18.2)	67 (37.0)	66 (16.6)	148 (37.0)
		OR (95% CI)	2.958 (1.764 to 4.959)		2.966 (2.125 to 4.140)	
		P value	< 0.0001		< 0.0001	
70	24	n (%)	13 (7.2)	36 (19.9)	29 (7.3)	79 (19.8)
		OR (95% CI)	3.105 (1.777 to 5.426)		3.174 (2.016 to 4.996)	
		P value	< 0.0001		< 0.0001	
HAQ-DI	12 16[a]	BL mean (SD)	1.78 (0.64)	1.73 (0.62)	1.61 (0.65)	1.63 (0.63)
		LSMD (95% CI)	−0.202 (−0.318 to −0.086)		−0.235 (−0.312 to −0.157)	
		P value	0.0007		< 0.0001	
DAS 28-CRP < 2.6	24	n (%)	13 (7.2)	45 (24.9)	40 (10.1)	111 (27.8)
		OR (95% CI)	4.622 (2.339 to 9.132)		3.551 (2.382 to 5.292)	
		P value	< 0.0001		< 0.0001	
CDAI	24	BL mean (SD)	[redacted]		[redacted]	
		LSMD (95% CI)	[redacted]		[redacted]	
		P value	[redacted]		[redacted]	
SF-36 PCS	24	BL mean (SD)	29.73 (7.76)	30.28 (6.73)	32.15 (7.01)	31.92 (6.60)
		LSMD (95% CI)	3.250 (1.450 to 5.049)		2.860 (1.630 to 4.091)	
		P value	0.0004		< 0.0001	
SF-36 MCS	24	BL mean (SD)	38.52 (12.62)	38.60 (11.36)	37.82 (10.55)	39.46 (11.49)
		LSMD (95% CI)	1.515 (−0.818 to 3.848)		1.808 (0.285 to 3.331)	
		P value	0.2026		0.0200	
EQ-5D VAS	24	BL mean (SD)	[redacted]		NA	
		LSMD (95% CI)	[redacted]			
		P value	[redacted]			
EQ-5D-Utility	24	BL mean (SD)	[redacted]		NA	
		LSMD (95% CI)	[redacted]			
		P value	[redacted]			
FACIT-Fatigue	24	BL mean (SD)	24.00 (10.42)	24.76 (10.61)	27.24 (9.99)	27.07 (9.77)
		LSMD (95% CI)	3.045 (0.806 to 5.283)		2.817 (1.552 to 4.083)	
		P value	0.0078		< 0.0001	

AMR = American College of Rheumatology; BL = baseline; CDAI = Clinical Disease Activity Index; CI = confidence interval; EQ-5D = EuroQol 5-Dimensions questionnaire; DAS 28-CRP = Disease Activity Score 28 using C-reactive protein; FACIT = Functional Assessment of Chronic Illness Therapy; HAQ-DI = Health Assessment Questionnaire–Disability Index; LSMD = least squares mean difference; MCS = mental component summary; PCS = physical component summary; OR = odds ratio; SARI = sarilumab; SD = standard deviation; SE = standard error; SF-36 = Short Form (36) Health Survey; VAS = visual analogue scale.

[a] Changes in HAQ-DI were evaluated at 12 weeks in TARGET and 16 weeks in MOBILITY.

TABLE 40: SUMMARY OF ADVERSE EVENTS FROM PLACEBO-CONTROLLED TRIALS

Adverse Events	MOBILITY		TARGET	
	Placebo (N = 427)	SARI 200 mg (N = 424)	Placebo (N = 181)	SARI 200 mg (N = 184)
Any class	263 (61.6)	331 (78.1)	90 (49.7)	120 (65.2)
Infections and infestations	133 (31.1)	168 (39.6)	48 (26.5)	56 (30.4)
Upper respiratory tract infection	24 (5.6)	37 (8.7)	6 (3.3)	6 (3.3)
Bronchitis	17 (4.0)	24 (5.7)	NR	NR
Urinary tract infection	16 (3.7)	23 (5.4)	12 (6.6)	13 (7.1)
Nasopharyngitis	[redacted]	[redacted]	9 (5.0)	7 (3.8)
Influenza	[redacted]	[redacted]	[redacted]	[redacted]
Sinusitis	[redacted]	[redacted]	[redacted]	[redacted]
Pharyngitis	[redacted]	[redacted]	3 (1.7)	6 (3.3)
Oral herpes	[redacted]	[redacted]	[redacted]	[redacted]
Gastroenteritis	NR	NR	[redacted]	[redacted]
Cellulitis	NR	NR	[redacted]	[redacted]
Pneumonia	NR	NR	[redacted]	[redacted]
Conjunctivitis	NR	NR	[redacted]	[redacted]
Fungal skin infection	NR	NR	[redacted]	[redacted]
Rhinitis	NR	NR	[redacted]	[redacted]
Blood/lymphatic disorders	11 (2.6)	80 (18.9)	9 (5.0)	29 (15.8)
Neutropenia	1 (0.2)	61 (14.4)	2 (1.1)	23 (12.5)
Leukopenia	0	18 (4.2)	0	3 (1.6)
Thrombocytopenia	[redacted]	[redacted]	0	5 (2.7)
Anemia	7 (1.6)	3 (0.7)	5 (2.8)	1 (0.5)
Metabolism/nutrition disorders	[redacted]	[redacted]	[redacted]	[redacted]
Hypertriglyceridemia	[redacted]	[redacted]	[redacted]	[redacted]
Hypercholesterolemia	NR	NR	[redacted]	[redacted]
Hyperlipidemia	NR	NR	[redacted]	[redacted]
Dyslipidemia	NR	NR	[redacted]	[redacted]
Hypokalemia	NR	NR	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]	NR	NR
Depression	[redacted]	[redacted]	NR	NR
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness	NR	NR	[redacted]	[redacted]
Eye disorders	NR	NR	[redacted]	[redacted]
Cataract	NR	NR	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
Hot flush	NR	NR	[redacted]	[redacted]
RTM disorders	NR	NR	[redacted]	[redacted]
Rhinitis allergic	NR	NR	[redacted]	[redacted]
Sinus congestion	NR	NR	[redacted]	[redacted]
Gastrointestinal disorders	46 (10.8)	64 (15.1)	[redacted]	[redacted]

Adverse Events	MOBILITY		TARGET	
	Placebo (N = 427)	SARI 200 mg (N = 424)	Placebo (N = 181)	SARI 200 mg (N = 184)
Diarrhea	9 (2.1)	17 (4.0)	[redacted]	[redacted]
Nausea	9 (2.1)	13 (3.1)	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain upper	[redacted]	[redacted]	NR	NR
Abdominal distension	NR	NR	[redacted]	[redacted]
Aphthous stomatitis	NR	NR	[redacted]	[redacted]
Abdominal discomfort	NR	NR	[redacted]	[redacted]
Food poisoning	NR	NR	[redacted]	[redacted]
Gastritis	NR	NR	[redacted]	[redacted]
Hemorrhoids	NR	NR	[redacted]	[redacted]
Hepatobiliary disorders	NR	NR	[redacted]	[redacted]
Hepatic steatosis	NR	NR	[redacted]	[redacted]
Skin/SC tissue disorders	NR	NR	[redacted]	[redacted]
Pruritus generalized	NR	NR	[redacted]	[redacted]
Pruritus	NR	NR	[redacted]	[redacted]
Musculoskeletal and CTD	[redacted]	[redacted]	[redacted]	[redacted]
Rheumatoid arthritis	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	NR	NR	[redacted]	[redacted]
Musculoskeletal pain	NR	NR	[redacted]	[redacted]
Bursitis	NR	NR	[redacted]	[redacted]
Joint swelling	NR	NR	[redacted]	[redacted]
Muscle spasms	NR	NR	[redacted]	[redacted]
Pain in extremity	NR	NR	[redacted]	[redacted]
Renal and urinary disorders	NR	NR	[redacted]	[redacted]
Reproductive/breast disorders	NR	NR	[redacted]	[redacted]
Metrorrhagia	NR	NR	[redacted]	[redacted]
General disorders and admin. site	[redacted]	[redacted]	[redacted]	[redacted]
Injection-site erythema	[redacted]	[redacted]	[redacted]	[redacted]
Injection-site pruritus	[redacted]	[redacted]	[redacted]	[redacted]
Injection-site rash	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]
Oedema peripheral	NR	NR	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	8 (4.4)	30 (16.3)
ALT increased	14 (3.3)	32 (7.5)	2 (1.1)	10 (5.4)
Transaminases increased	3 (0.7)	15 (3.5)	0	3 (1.6)
AST increased	3 (0.7)	5 (1.2)	0	6 (3.3)
Blood pressure increased	NR	NR	[redacted]	[redacted]
Hepatic enzyme increased	NR	NR	[redacted]	[redacted]
Neutrophil count decreased	NR	NR	[redacted]	[redacted]
Blood triglycerides increased	NR	NR	[redacted]	[redacted]
Injury, poisoning, procedural complications	[redacted]	[redacted]	[redacted]	[redacted]

Adverse Events	MOBILITY		TARGET	
	Placebo (N = 427)	SARI 200 mg (N = 424)	Placebo (N = 181)	SARI 200 mg (N = 184)
Accidental overdose	[redacted]	[redacted]	[redacted]	[redacted]
Fall	[redacted]	[redacted]	[redacted]	[redacted]

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTD = connective tissue disorders; RTM = respiratory, thoracic, and mediastinal; SARI = sarilumab; SC = subcutaneous.
Source: Clinical Study Reports for TARGET[7] and MOBILITY.[10]

TABLE 41: SUMMARY OF SERIOUS ADVERSE EVENTS FROM PLACEBO-CONTROLLED TRIALS

Serious Adverse Events, n (%)	MOBILITY		TARGET	
	Placebo (N = 427)	SARI 200 mg (N = 424)	Placebo (N = 181)	SARI 200 mg (N = 184)
Any class	23 (5.4)	48 (11.3)	6 (3.3)	10 (5.4)
Infections and infestations	10 (2.3)	17 (4.0)	2 (1.1)	2 (1.1)
[redacted]				

Serious Adverse Events, n (%)	MOBILITY		TARGET	
	Placebo (N = 427)	SARI 200 mg (N = 424)	Placebo (N = 181)	SARI 200 mg (N = 184)

Serious Adverse Events, n (%)	MOBILITY		TARGET	
	Placebo (N = 427)	SARI 200 mg (N = 424)	Placebo (N = 181)	SARI 200 mg (N = 184)

ALT = alanine aminotransferase; CTD = connective tissue disorders; RTM = respiratory, thoracic, and mediastinal; SARI = sarilumab; SC = subcutaneous.
Source: Clinical Study Reports for MOBILITY[10] and TARGET.[7]

TABLE 42: SUMMARY OF WITHDRAWALS DUE TO ADVERSE EVENTS FROM PLACEBO-CONTROLLED TRIALS

WDAEs, n (%)	MOBILITY		TARGET	
	Placebo (N = 427)	SARI 200 mg (N = 424)	Placebo (N = 181)	SARI 200 mg (N = 184)
Any class	20 (4.7)	59 (13.9)	8 (4.4)	17 (9.2)
Infections and infestations	6 (1.4)	13 (3.1)	1 (0.6)	5 (2.7)
[redacted]				

WDAEs, n (%)	MOBILITY		TARGET	
	Placebo (N = 427)	SARI 200 mg (N = 424)	Placebo (N = 181)	SARI 200 mg (N = 184)
[redacted]				

WDAEs, n (%)	MOBILITY		TARGET	
	Placebo (N = 427)	SARI 200 mg (N = 424)	Placebo (N = 181)	SARI 200 mg (N = 184)
[redacted]				

ALT = alanine aminotransferase; CTD = connective tissue disorders; NR = not reported; RTM = respiratory, thoracic, and mediastinal; SARI = sarilumab; SC = subcutaneous; WDAEs = withdrawals due to adverse events.
Source: Clinical Study Reports for MOBILITY[10] and TARGET.[7]

TABLE 43: SUMMARY OF AESI PER 100 PATIENT-YEARS IN PLACEBO-CONTROLLED STUDIES

AESI	MOBILITY		TARGET	
	PLC + MTX	SARI + MTX	PLC + DMARD	SARI + DMARD
[redacted]				

AESI = adverse event of special interest; DMARD = disease-modifying antirheumatic drugs; GI = gastrointestinal; nE (nE/100 PY) = number of events and number of events per 100 patient-years; MTX = methotrexate; n = number of patients with event; PLC = placebo; PY = patient-year; SARI = 200 mg sarilumab once every two weeks.
[a] Reported as neutropenia for MOBILITY and leukopenia for TARGET.
Source: Clinical Study Reports for MOBILITY[10] and TARGET.[7]

TABLE 44: SUMMARY OF AESI PER 100 PATIENT-YEARS IN ACTIVE-CONTROLLED STUDIES

AESI	MONARCH		ASCERTAIN	
	ADA	SARI	TOC + DMARD	SARI + DMARD
[redacted]				

AESI	MONARCH		ASCERTAIN	
	ADA	SARI	TOC + DMARD	SARI + DMARD
[redacted]				
[redacted]				

ADA = adalimumab; AESI = adverse event of special interest; DMARD = disease-modifying antirheumatic drugs; GI = gastrointestinal; n = number of patients with event; nE (nE/100 PY) = number of events and number of events per 100 patient-years; MTX = methotrexate; PY = patient-year; SARI = 200 mg sarilumab once every two weeks; TOC = tocilizumab.

TABLE 45: SUMMARY OF LIPID ELEVATION IN PLACEBO-CONTROLLED TRIALS

Lipid Elevation, n (%)	MOBILITY		TARGET	
	PLC + MTX	SARI + MTX	PLC + DMARD	SARI + DMARD
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				

DMARD = disease-modifying antirheumatic drugs; MTX = methotrexate; NR = not reported; PLC = placebo; SARI = 200 mg sarilumab once every two weeks.
Source: Clinical Study Reports for MOBILITY[10] and TARGET.[7]

TABLE 46: SUMMARY OF LIPID ELEVATION IN ACTIVE-CONTROLLED TRIALS

Lipid Elevation, n (%)	MONARCH		ASCERTAIN	
	ADA (N = 184)	SARI (N = 184)	TOC + DMARD	SARI + DMARD
Patients with ≥ 1 elevation in lipids (%)	8 (4.3)	3 (1.6)		
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				

ADA = adalimumab; DMARD = disease-modifying antirheumatic drugs; NR = not reported; SARI = 200 mg sarilumab once every two weeks; TOC = tocilizumab.
Source: Clinical Study Reports for MONARCH[9] and ASCERTAIN.[8]

APPENDIX 5: SUMMARY OF THE EXTEND EXTENSION STUDY

Aim

To summarize the safety and efficacy outcomes of sarilumab from the EXTEND open-label extension study.[53,55-57]

Study Design

EXTEND (N = 2,023) is an ongoing multi-centre, multinational, long-term, open-label extension study in patients with rheumatoid arthritis (RA).[53] The patients participating in EXTEND had previously been enrolled in one of the following short-term studies: MOBILITY,[10] TARGET,[7] ASCERTAIN,[8] ACT11575,[58] or SARIL-RA-ONE.[59] At the time the patients were initially enrolled in one of the short-term studies, they were either inadequate responders to methotrexate (MTX) therapy (MOBILITY), inadequate responders to or intolerant of tumour necrosis factor (TNF) alpha antagonists (TARGET[7] and ASCERTAIN),[8] inadequate responders to TNF alpha antagonists who had failed up to two TNF alpha antagonists (ACT11575), or inadequate responders to or intolerant of non-biologic disease-modifying antirheumatic drugs (DMARDs) (SARIL-RA-ONE). The previous treatments before enrolment in the EXTEND study were either sarilumab monotherapy or sarilumab in combination with a non-biologic DMARD. Patients were allowed to continue their background medication as per the trial protocol of the initial short-term study into which they had enrolled. The dosage of sarilumab in EXTEND was 200 mg every other week (or a reduced dosage of 150 mg every other week in the event of neutropenia), lasting up to 264 weeks. Patients may continue to be treated beyond 264 weeks until sarilumab is commercially available in their country or until 2020, at the latest, when the study will be closed.

The results reported in this summary are based on an interim analysis (from June 2010 to January 2016).[53] The primary objective of the study was to evaluate the long-term safety of sarilumab in patients with RA. The safety outcomes included treatment-emergent adverse events, immunogenicity, neutropenia, liver function test increases, and lipid elevations. The secondary objective of the study was to evaluate the long-term efficacy of sarilumab in patients with RA. The efficacy outcomes included the following: American College of Rheumatology () 20, 50, or 70 response and change from baseline in components, Disease Activity Score 28 (DAS 28) remission, DAS 28 using C-reactive protein, European League Against Rheumatism response, van der Heijde modified Total Sharp Score (mTSS), and physical function as assessed by Health Assessment Questionnaire–Disability Index.[53] The dosage of sarilumab varied; therefore, the outcomes reported include patients receiving either 150 mg or 200 mg every two weeks.

Patient Disposition

Exposure to the Study Treatment

[redacted].[53]

Safety

[redacted] (Table 47). [redacted]

[redacted]

[redacted] (Table 47).

[redacted] (Table 47).

TABLE 47: [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]	[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]

AE = adverse events; DMARD = disease-modifying antirheumatic drugs; GI = gastrointestinal; NMSC = non-melanoma skin cancer; NR = not reported; SAE = serious adverse event; SARI = sarilumab; WDAE = withdrawal due to adverse event.

[a] Does not include two patients who died post-study.

Source: Clinical Study Report for EXTEND.[53]

Efficacy

[redacted] (Table 48). [redacted]

TABLE 48: [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]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

DMARD = disease-modifying antirheumatic drug; n = patients with event; N = total number patients included in the analysis.
Source: Clinical Study Report for EXTEND[53]

Modified Total Sharp Score

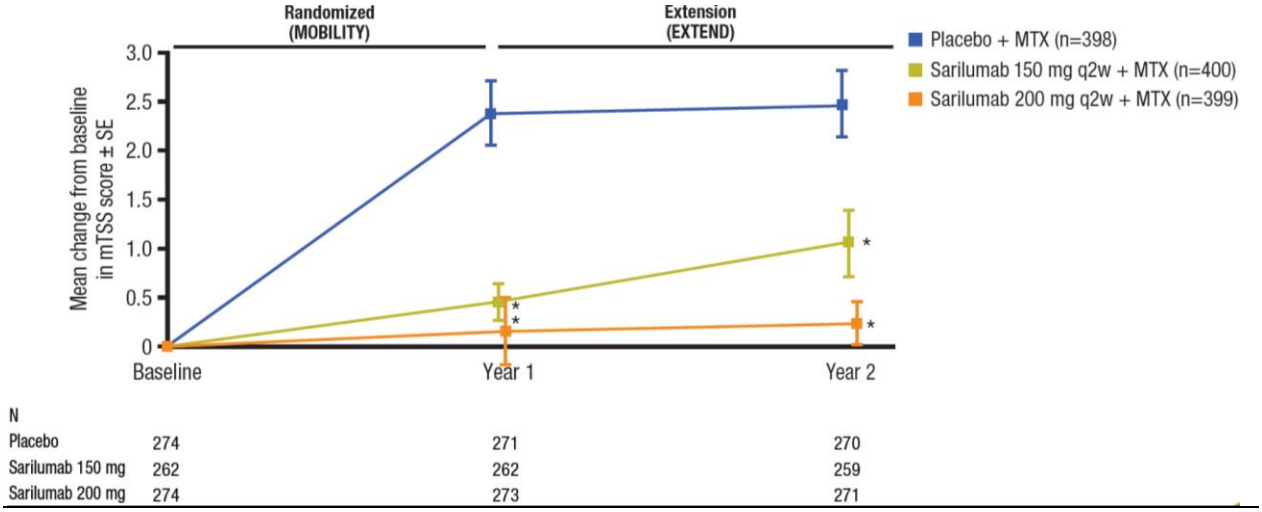
The mTSS evaluation was based on the X-ray data collected over a three-year period (one year in MOBILITY and two years in EXTEND).[60] Reported in a conference abstract,[57] the evaluation of mTSS at two years demonstrated that the group initially randomized to placebo achieved similar results to two groups that were initially randomized to sarilumab (i.e., 150 mg or 200 mg every two weeks) after being moved to active treatment with sarilumab 200 mg every two weeks (Table 49 and Figure 11).[57] At the two-year analysis (N = 889), the proportion without progression (defined as an mTSS change of ≤ 0) changed minimally from the first year (week 0, 51.9%) to the second year (51.2%). Among those with data for the three-year analysis (N = 796), the proportion without progression also demonstrated minimal change from the second year (46.6%) to the third year (44.2%).[60] The results demonstrated that treatment with sarilumab + MTX provided sustained clinical benefit in terms of mTSS up to three years in patients who have had an incomplete response to MTX or TNF alpha antagonist. In the year 3 analysis the mTSS score in the combined sarilumab + MTX treatment population (N = 755) had increased by 2.14 units from baseline to year 3.

TABLE 49: MODIFIED TOTAL SHARP SCORE RESULTS REPORTED AFTER TWO YEARS

	PLC + MTX to SARI 200 mg + MTX	SARI 150 + MTX to SARI 200 mg + MTX	SARI 200 mg + MTX
Patients in MOBILITY (RCT)	398	400	399
Patients in EXTEND (OLE)	307	300	294
mTSS score, mean ± SEM			
Baseline (at RCT, MOBILITY)	45.8 ± 3.8	49.2 ± 3.6	43.2 ± 3.4
Year 1 (RCT population)	48.4 ± 3.9	49.6 ± 3.6	43.1 ± 3.4
Year 2 (Completers)	48.3 ± 3.9	50.4 ± 3.7	43.3 ± 3.4
mTSS change from baseline, mean ± SEM			
Δ Baseline, year 1 (RCT)	2.4 ± 0.3	0.4 ± 0.2	0.2 ± 0.2
Δ Baseline, year 2 (completers)	2.4 ± 0.3	1.0 ± 0.3	0.2 ± 0.2
Δ Year 1, year 2 (completers)	0.3 ± 0.2	0.6 ± 0.2	0.2 ± 0.1

mTSS = modified Total Sharp Score; MTX = methotrexate; OLE = open-label extension; PLC = placebo; RCT = randomized controlled trial; SARI = sarilumab; SEM = standard error of the mean.
Source: van der Heijde et al., 2016.[57]

FIGURE 11: MEAN CHANGE FROM BASELINE IN MTSS



ANCOVA = analysis of covariance; mTSS = modified Total Sharp Score; MTX = methotrexate; q2w = once every two weeks; SE = standard error.
*$P < 0.01$ versus placebo using rank ANCOVA model stratified by prior biologic use and region.
Source: Reproduced from van der Heijde et al., 2016.[57]

Conclusion

EXTEND is an ongoing open-label extension study up to five years (264 weeks). The patients participating in this study were previously enrolled in a shorter-term phase II or phase III study for sarilumab (MOBILITY, TARGET, ASCERTAIN, ACT11575, and SARIL-RA-ONE). The results of EXTEND suggest that the safety profile in the extension study was similar to what was reported in short-term studies. The most frequently reported treatment-emergent adverse events were neutropenia, infections, and alanine transaminase increases, and the most frequently reported serious adverse events were infections. The most frequently reported withdrawals due to adverse events were neutropenia, alanine transaminase increases, and herpes zoster. 20, 50, and 70 responses, DAS 28 remission, and mTSS progression were maintained throughout the treatment period. The results of the EXTEND study are limited by the open-label design potentially impacting the assessment of subjective outcomes; the increased likelihood that people who experienced successful treatment with sarilumab during the shorter-term controlled trial would continue on to EXTEND, thereby potentially overestimating benefit and underestimating harms associated with sarilumab; and the absence of a control group.

APPENDIX 6: SUMMARY OF MANUFACTURER'S INDIRECT COMPARISON

Aim

[redacted][60][redacted][61,62][redacted]

[redacted]

Methods Used for the Systematic Review and Network Meta-Analysis

Eligibility Criteria

[redacted][61,62][redacted]

[44].

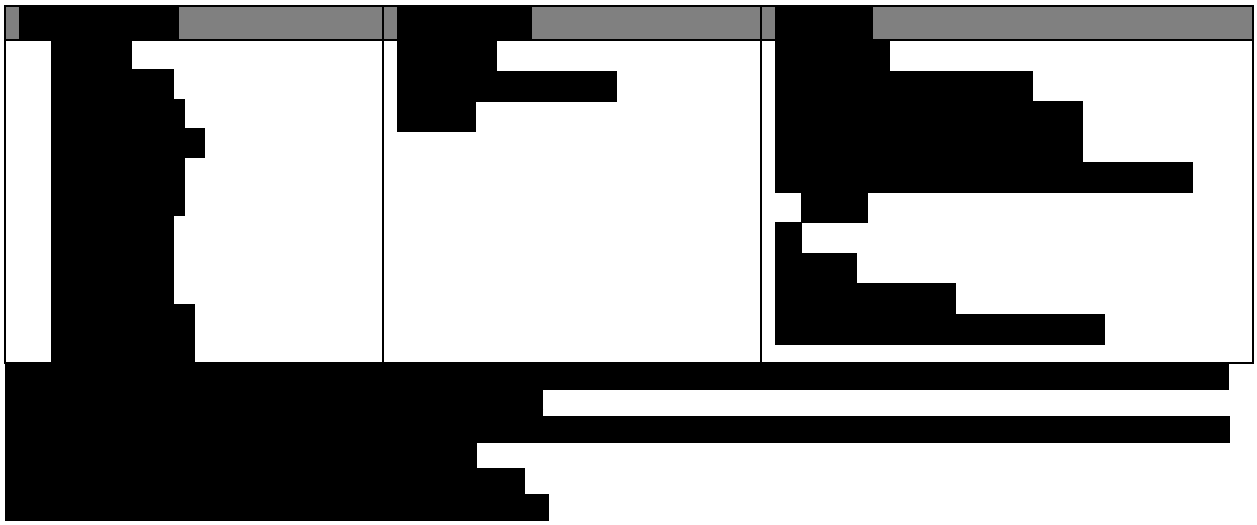
[61].

[44].

Table 50.

[redacted]

TABLE 50: [redacted]



Network Meta-Analysis

Table 51 [redacted]

[redacted] Table

51,

Table 51

TABLE 51: OVERVIEW OF NETWORK META-ANALYSIS METHODS FOR EACH END POINT

[a] Details regarding the prior distributions were provided in the manufacturer's comment on the draft CDR clinical review report.[50]

Network Meta-Analysis Findings

[redacted]

Evidence Networks

[redacted] Table 52.

TABLE 52: [redacted]

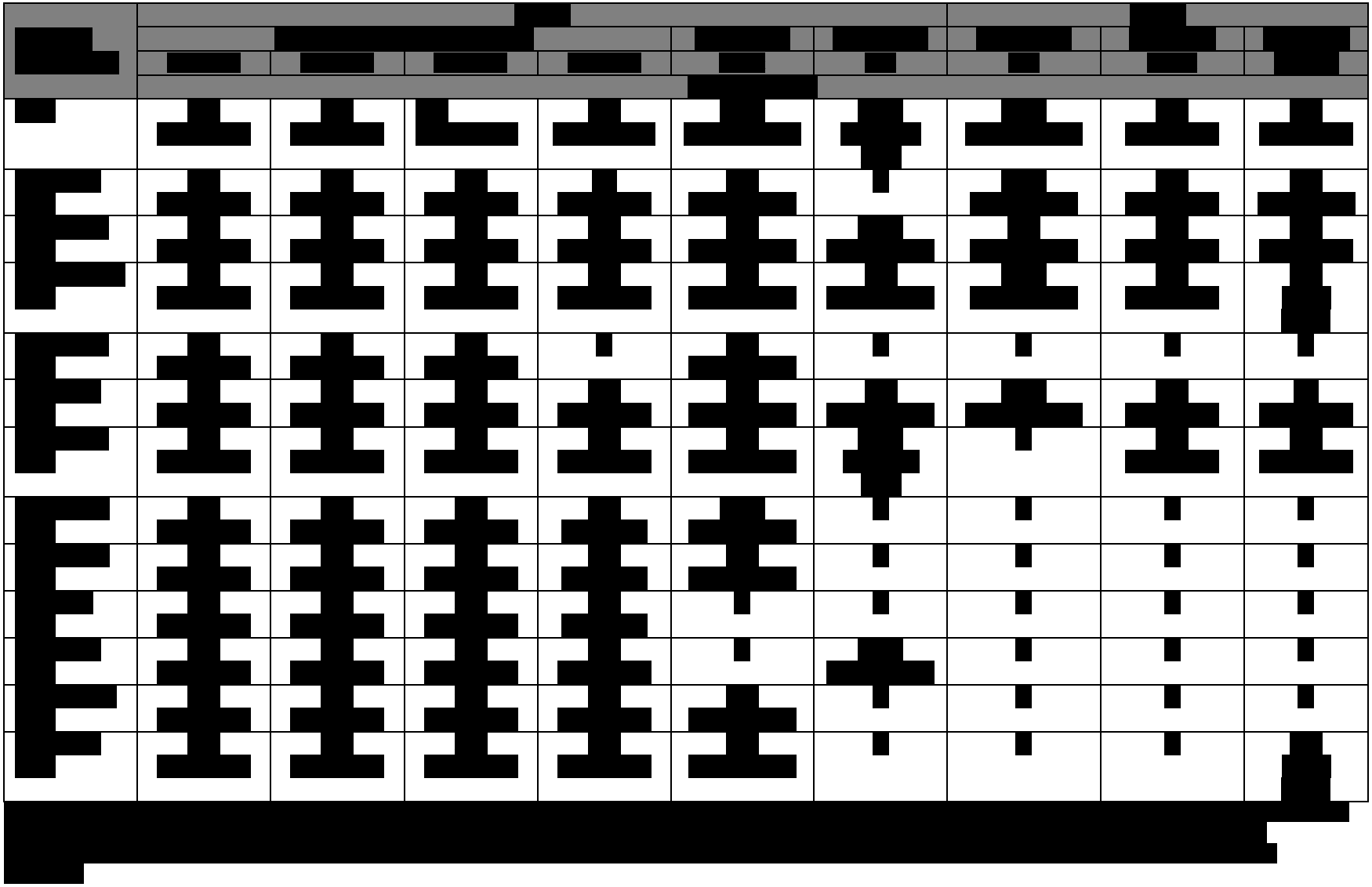
[redacted]	[redacted]	[redacted]
[redacted]	Confidential figure redacted at manufacturer’s request.	Confidential figure redacted at manufacturer’s request.
[redacted]	Confidential figure redacted at manufacturer’s request.	Confidential figure redacted at manufacturer’s request.
[redacted]	Confidential figure redacted at manufacturer’s request.	Confidential figure redacted at manufacturer’s request.
[redacted]	Confidential figure redacted at manufacturer’s request.	Confidential figure redacted at manufacturer’s request.
[redacted]	Confidential figure redacted at manufacturer’s request.	Confidential figure redacted at manufacturer’s request.
[redacted]	Confidential figure redacted at manufacturer’s request.	Confidential figure redacted at manufacturer’s request.
[redacted]	Confidential figure redacted at manufacturer’s request.	Confidential figure redacted at manufacturer’s request.
[redacted]	Confidential figure redacted at manufacturer’s request.	Confidential figure redacted at manufacturer’s request.

[redacted]

Table 53

[redacted]

TABLE 53: [redacted]



[redacted] Table 54 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted] Table 55.

[redacted]

[redacted]

[redacted]

[redacted]

TABLE 54: [redacted]

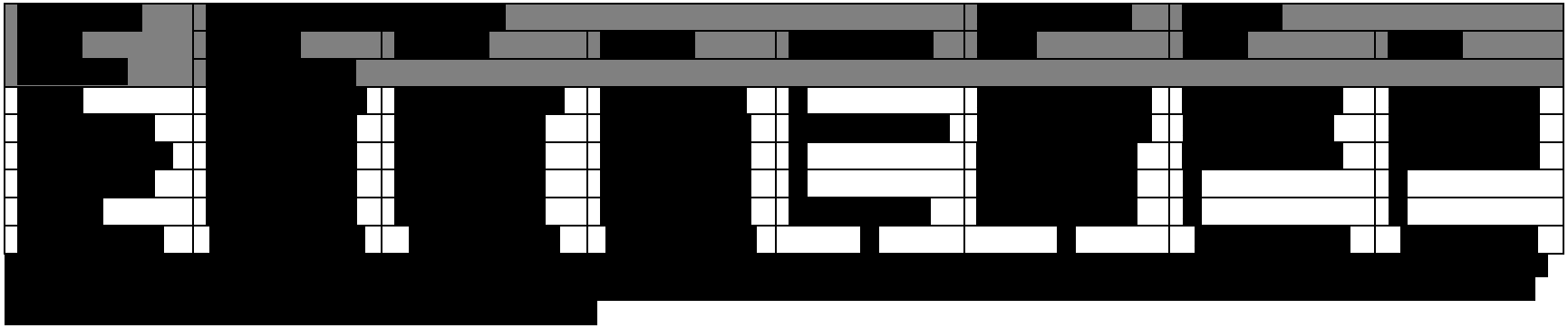


TABLE 55: [redacted]

Sarilumab 200 mg comb vs (At week 24)	RD NMA (FE)				CFB diff NMA (FE)	OR NMA (FE)	
	20 (RD)	50 (RD)	70 (RD)	DAS 28 < 2.6 (RD)	HAQ-DI	SI (OR)	SAE (OR)
	Median (95% CrI)						
[redacted]							

Critical Appraisal of the Manufacturer's Network Meta-Analysis

The methodological validity of the network meta-analysis was assessed according to recommendations provided by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons.[64]

Systematic Review Methods

Reporting of the Network Meta-Analyses

Critical Appraisal

Study Characteristics

[redacted]

[redacted]

Study Populations

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Analysis Methods

[redacted] Table 52, [redacted]

[redacted]

Table 56

[redacted]

[redacted] [50]

Critical Appraisal [redacted]

Study Characteristics

[redacted]

[redacted]

[redacted]

Study Populations

[redacted]

Analysis Methods

[redacted]

Summary and Conclusions

[redacted]

[redacted]

[redacted]

TABLE 56: APPRAISAL OF POTENTIAL EFFECT MODIFIERS IN THE NETWORK META-ANALYSIS

Characteristics	Appraisal of Heterogeneity
[redacted]	[redacted]

Characteristics	Appraisal of Heterogeneity
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

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