Baggrund for Medicinrådets anbefaling vedrørende sarilumab som mulig standardbehandling til reumatoid artritis

Handelsnavn	Kevzara
Generisk navn	Sarilumab
Firma	Sanofi-Aventis Denmark A/S
ATC-kode	L04AC14
Virkningsmekanisme	Sarilumab er et humant monoklonalt antistof (IgG1-subtype), der binder sig specifikt til både opløselige og membranbundne Interleukin-6 receptorer (IL-6Rα) og hæmmer IL-6-medieret signalering.
Administration/dosis	Subkutant, 200 mg hver anden uge.
EMA-indikation	Sarilumab er i kombination med methotrexat (MTX) indiceret til behandling af moderat til svær, aktiv reumatoid artritis (RA) hos voksne patienter, som enten har haft utilstrækkelig respons på, eller som ikke tolererer en eller flere sygdomsmodificerende antireumatiske lægemidler (DMARDs). Sarilumab kan gives som monoterapi i tilfælde af intolerans over for MTX, eller når behandling med MTX er uhensigtsmæssig.
Godkendelsesdato Offentliggørelsesdato Dokumentnummer Versionsnummer	24.07.18 24.07.18 Følger 1.0
Fagudvalgets sammensætning og sekretariatets arbejdsgruppe	Se afsnit 7 s. 6

Om Medicinrådet:

Medicinrådet er et uafhængigt råd, som udarbejder anbefalinger og vejledninger om lægemidler til de fem regioner.

Medicinrådet vurderer, om nye lægemidler og nye indikationer kan anbefales som standardbehandling og udarbejder fælles regionale behandlingsvejledninger.

Nye lægemidler vurderes i forhold til effekt, eksisterende behandling og pris. Det skal give lavere priser og lægemidler, der er til størst mulig gavn for patienterne.

De fælles regionale behandlingsvejledninger er vurderinger af, hvilke lægemidler der er mest hensigtsmæssige til behandling af patienter inden for et terapiområde og dermed grundlag for ensartet høj kvalitet for patienterne på tværs af sygehuse og regioner.

Indhold

1 Medicinrådets anbefaling

Ved utilstrækkelig effekt/ikke tolereret behandling med konventionelle syntetiske Disease Modifying Anti Rheumatic Drugs (csDMARDs) **anbefaler** Medicinrådet sarilumab som mulig standardbehandling til følgende populationer:

- Bionaive patienter med moderat til svær RA (i kombination med csDMARD).
- Patienter med moderat til svær RA, der skal skifte biologisk eller targeteret syntetisk behandling (i kombination med csDMARD).
- Bionaive patienter med moderat til svær RA, hvor behandling med csDMARDs ikke er en mulighed.
- Patienter med moderat til svær RA, som skal skifte biologisk eller targeteret syntetisk behandling, og hvor behandling med csDMARDs ikke er en mulighed.

De kliniske spørgsmål, som ligger til grund for anbefalingen, er, som følger:

1. Hvilken klinisk merværdi tilbyder sarilumab sammenlignet med tocilizumab i kombination med csDMARD til bionaive patienter med moderat til svær RA?
2. Hvilken klinisk merværdi tilbyder sarilumab sammenlignet med tocilizumab i kombination med csDMARD til patienter med moderat til svær RA, der skal skifte biologisk eller targeteret syntetisk behandling?
3. Hvilken klinisk merværdi tilbyder sarilumab sammenlignet med tocilizumab til bionaive patienter med moderat til svær RA, hvor behandling med csDMARDs ikke er en mulighed?
4. Hvilken klinisk merværdi tilbyder sarilumab sammenlignet med tocilizumab til patienter med moderat til svær RA, som skal skifte biologisk eller targeteret syntetisk behandling, og hvor behandling med csDMARDs ikke er en mulighed?

2 Introduktion

2.1 Om indikationen

RA er en kronisk sygdom, som er karakteriseret ved inflammatorisk respons i led, og som kan føre til ødelæggelse af disse.

2.2 Sagsbehandlingstid og proces for Medicinrådets vurdering

Sarilumab er behandlet i Medicinrådets 7-ugers proces.

Medicinrådet modtog den foreløbige ansøgning om sarilumab fra Sanofi-Aventis d. 13. februar 2018 og den endelige ansøgning (bilag 4) d. 1. juni 2018.

Medicinrådet har gennemført vurderingen af sarilumab på 7 uger og 4 dage opgjort fra modtagelse af den endelige ansøgning.

3 Medicinrådets vurdering af samlet klinisk merværdi

Medicinrådet vurderer, at sarilumab til patienter, der har haft utilstrækkelig effekt/ikke tolereret behandling med csDMARDs, giver:

- **Ingen klinisk merværdi** sammenlignet med tocilizumab i kombination med csDMARD til bionaive patienter med moderat til svær RA (meget lav evidenskvalitet).
- **Ingen klinisk merværdi** sammenlignet med tocilizumab i kombination med csDMARD til patienter med moderat til svær RA, der skal skifte biologisk eller targeteret syntetisk behandling (meget lav evidenskvalitet).
- **Ingen klinisk merværdi** sammenlignet med tocilizumab til bionaive patienter med moderat til svær RA, hvor behandling med csDMARDs ikke er en mulighed (meget lav evidenskvalitet).
- **Ingen klinisk merværdi** sammenlignet med tocilizumab til patienter med moderat til svær RA, som skal skifte biologisk eller targeteret syntetisk behandling, og hvor behandling med csDMARDs ikke er en mulighed (evidensens kvalitet kan ikke vurderes).

4 Høring

Sanofi-Aventis har valgt ikke at indsende et høringssvar.

5 Resumé af økonomisk beslutningsgrundlag

Ved behandling med sarilumab er omkostningerne per patient højere sammenlignet med tocilizumab s.c. (3.565 kr.) og lavere sammenlignet med tocilizumab i.v. (-9.201 kr.). Disse estimater er baseret på apotekernes indkøbspris (AIP). Sammenligner man derimod aftalepriser, er behandlingsomkostningerne for sarilumab lavere end for tocilizumab s.c.

Amgros vurderer, at en anbefaling af sarilumab som mulig standardbehandling vil medføre samlede meromkostninger på ca. 3,79 mio. kr. pr. år for alle populationer sammenlignet med tocilizumab s.c. (baseret på AIP). Analysens resultater påvirkes i altovervejende grad af lægemidlernes pris.

Amgros vurderer, at ansøger har indsendt en simpel analyse, som overordnet giver et acceptabelt estimat af omkostninger forbundet med sarilumab.

Amgros' beslutningsgrundlag og sundhedsøkonomiske analyse kan ses af bilag 1 og 2.

6 Overvejelser omkring alvorlighed/forsigtighed

Medicinrådet har ikke fundet anledning til at inddrage forhold vedrørende alvorlighed eller forsigtighed i anbefalingen.

7 Sammensætning af fagudvalg

Medicinrådets fagudvalg vedrørende gigtsygdomme

Formand	*Indstillet af*
Ulrik Tarp *Overlæge, dr.med.*	Lægevidenskabelige Selskaber og Dansk Reumatologisk Selskab
Medlemmer	*Udpeget af*
Claus Rasmussen *Overlæge, klinisk lektor*	Region Nordjylland
Hanne M. Lindegaard *Overlæge, klinisk lektor, ph.d.*	Region Syddanmark
Thomas Adelsten *Uddannelsesansvarlig overlæge*	Region Sjælland
Annemarie Lyng Svensson *Konstitueret overlæge, ph.d.*	Region Hovedstaden
Per Damkier *Professor, overlæge, ph.d.*	Dansk Selskab for Klinisk Farmakologi
Mikala Vasehus Holck *Klinisk farmaceut*	Dansk Selskab for Sygehusapoteksledelse
Dorte Vendelbo Jensen *Overlæge, sekretariatsleder*	DANBIO
Annette Schlemmer *Overlæge, MLP, lektor*	Dansk Reumatologisk Selskab
Anett Brøgger *Patient/patientrepræsentant*	Danske Patienter
En patient/patientrepræsentant	Danske Patienter

Medicinrådets sekretariat

Medicinrådet Dampfærgevej 27-29, 3. 2100 København Ø + 45 70 10 36 00 medicinraadet@medicinraadet.dk
Sekretariatets arbejdsgruppe: Jeppe Schultz Christensen (projekt- og metodeansvarlig) Jane Skov, Nicoline Kerzel Duel (projektgruppe) Charlotte Wulff Johansen (koordinator) Tenna Bekker (teamleder)

8 Bilag

Bilagsliste:

1) Amgros' beslutningsgrundlag
2) Amgros' sundhedsøkonomisk analyse
3) Vurdering af den kliniske merværdi af sarilumab
4) Ansøgers endelige ansøgning
5) Protokol for vurdering af den kliniske merværdi af sarilumab

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Beslutningsgrundlag til Medicinrådet

Dette dokument er Amgros' indstilling til Medicinrådet om vurdering af sarilumab (Kevzara) til mulig standardbehandling af behandling af moderat til svær, aktiv reumatoid artritis (RA) hos voksne patienter, som enten har haft utilstrækkelig respons på, eller som ikke tolererer en eller flere sygdomsmodificerende antireumatiske lægemidler (DMARDs). Indstillingen er baseret på en vurdering af lægemidlets meromkostninger sammenholdt med den kliniske merværdi.

Dato for Medicinrådsbeslutning	20-7-2018
Firma	Sanofi-Aventis
Lægemiddel	Sarilumab (Kevzara)
Indikation	Sarilumab (Kevzara) er i kombination med methotrexat (MTX) indiceret til behandling af moderat til svær, aktiv reumatoid artritis (RA) hos voksne patienter, som enten har haft utilstrækkelig respons på, eller som ikke tolererer en eller flere sygdomsmodificerende antireumatiske lægemidler (DMARDs)

Amgros' indstilling

- Det indstilles, at sarilumab (Kevzara) anbefales som mulig standardbehandling.

Overordnet konklusion

Medicinrådet har vurderet at sarilumab (Kevzara) til behandling af moderat til svær aktiv reumatoid artritis (RA) hos voksne patienter, som enten har haft utilstrækkelig respons på, eller som ikke tolererer en eller flere sygdomsmodificerende antireumatiske lægemidler (DMARDs), har ingen klinisk merværdi sammenlignet med tocilizumab (RoActemra).

Behandling med Sarilumab (Kevzara) er forbundet med lavere behandlingsomkostninger end tocilizumab (RoActemra), efter Amgros har indgået en aftale med Sanofi-Aventis om indkøb af sarilumab (Kevzara). Konklusionen er baseret på aftaleprisen for sarilumab (Kezara)

Tabel 1: Merværdi, meromkostninger og Amgros' anbefaling

Intervention	Komparator	Merværdi	Usikkerhed for klinisk merværdi	Amgros' konklusion om forhold mellem omkostninger og klinisk merværdi	indstilling til mulig standard-behandling

Sarilumab (Kevzara)	crizotinib (Xalkori)	Stor klinisk merværdi	Meget lav evidenskvalitet	Acceptabelt	Ja

Kontraktforhold

Amgros har indgået en rammeaftale med Leverandøren om en rabat på sarilumab (Kevzara). Aftalen gælder indtil 31.12.2018 med mulighed for forlængelse.

SARILUMAB (KEVZARA)

MODERAT TIL SVÆR, AKTIV REUMATOID ARTRITIS (RA)

AMGROS 29. juni 2018

Opsummering

Baggrund

Sarilumab (Kevzara) er i kombination med methotrexat (MTX) indiceret til behandling af moderat til svær, aktiv reumatoid artritis (RA) hos voksne patienter, som enten har haft utilstrækkelig respons på, eller som ikke tolererer en eller flere sygdomsmodificerende antireumatiske lægemidler (DMARDs). Sanofi-Aventis (herefter omtalt som ansøger) er markedsføringstilladelsesindehaver af sarilumab (Kevzara).

Analyse

Analysen estimerer de gennemsnitlige omkostninger pr. patient og de samlede budgetkonsekvenser for regionerne ved ibrugtagning af sarilumab (Kevzara) som mulig standardbehandling til patienter med af moderat til svær, aktiv reumatoid artritis (RA). I analyserne sammenlignes behandling med sarilumab (Kevzara) med behandling med tocilizumab (RoActemra).

I analyserne i denne afrapportering anvendes AIP på sarilumab (Kevzara) og tocilizumab (RoActemra).

Inkrementelle omkostninger og budgetkonsekvenser

Resultatet af omkostningsanalysen viser, at de gennemsnitlige omkostninger pr. patient i behandling med sarilumab (Kevzara) er 3.565 kr. (ved AIP) højere end de gennemsnitlige omkostninger pr. patient i behandling med tocilizumab (RoActemra) s.c., og 9.201 kr. lavere ned gennemsnitlige omkostninger pr. patient i behandling med tocilizumab (RoActemra) i.v.

Analysens resultater påvirkes i altovervejende grad af omkostningerne forbundet med anskaffelse af lægemidlerne. Resultaterne er derfor meget følsomme over for nuværende og fremtidige rabatter på AIP.

Amgros vurderer, at en anbefaling af sarilumab (Kevzara) som mulig standardbehandling vil betyde samlede meromkostninger på ca. 3,79 mio. kr. pr. år.

Konklusion

Overordnet konkluderer Amgros, at behandling med sarilumab (Kevzara) er forbundet med begrænsede meromkostninger sammenlignet med behandling med tocilizumab (RoActemra) s.c.

Liste over forkortelser

RA	reumatoid artritis
MTX	methotrexat
s.c.	Subkutan administration
i.v.	Intravenøs administration
DMARDs	Sygdomsmodificerende behandling (disease modifying anti rheumatic drugs)

INDHOLD

Liste over forkortelser

Ansøgning	
Lægemiddelfirma:	Sanofi-Aventis
Handelsnavn:	Kevzara
Generisk navn:	Sarilumab
Indikation:	Kevzara er i kombination med methotrexat (MTX) indiceret til behandling af moderat til svær, aktiv reumatoid artritis (RA) hos voksne patienter, som enten har haft utilstrækkelig respons på, eller som ikke tolererer en eller flere sygdomsmodificerende antireumatiske lægemidler (DMARDs).
ATC-kode:	L04AC14

Proces	
Ansøgning modtaget hos Amgros:	01-06-2018
Endelig rapport færdig:	19-06-2018
Sagsbehandlingstid fra endelig ansøgning:	18 dage
Arbejdsgruppe:	**Andreas Pagh Rasmussen** Asbjørn Lydert Hansen Asger Lindvig

Priser

Alle lægemiddelpriser i denne afrapportering er på AIP-niveau. Amgros har ofte aftaler om rabatter på de analyserede lægemidler. Derfor vil analyser på AIP-niveau ikke altid afspejle regionernes faktiske omkostninger til anskaffelse af lægemidlerne. Da rabatterne varierer betragteligt på tværs af lægemidler, vil prisforskellene i afrapporteringen, ikke altid afspejle de faktiske prisforskelle.

Anbefalingerne i Amgros' beslutningsgrundlag, som sendes sammen med denne afrapportering, bygger på regionernes faktiske anskaffelsespriser (SAIP).

1. BAGGRUND

Sarilumab (Kevzara) er i kombination med methotrexat (MTX) indiceret til behandling af moderat til svær, aktiv reumatoid artritis (RA) hos voksne patienter, som enten har haft utilstrækkelig respons på, eller som ikke tolererer en eller flere sygdomsmodificerende antireumatiske lægemidler (DMARDs). Sanofi-Aventis er markedsføringstilladelsesindehaver af sarilumab (Kevzara) og har indsendt en ansøgning til Medicinrådet om ibrugtagning af sarilumab (Kevzara) som mulig standardbehandling af RA på danske hospitaler. Medicinrådet har endeligt modtaget ansøgningen den 01. juni 2018. Som et led i denne ansøgning vurderer Amgros på vegne af Medicinrådet de økonomiske analyser, Sanofi-Aventis har sendt som en del af den samlede ansøgning til Medicinrådet. Denne rapport er Amgros' vurdering af de indsendte økonomiske analyser (herefter omtalt som analysen).

1.1 Problemstilling

Formålet med analysen er at estimere omkostningerne forbundet med behandling af RA i form af de gennemsnitlige omkostninger pr. patient og de samlede budgetkonsekvenser for regionerne ved anbefaling af sarilumab (Kevzara) som mulig standardbehandling. I analyserne sammenlignes behandling med sarilumab (Kevzara) med tocilizumab (RoActemra) som angivet i Medicinrådets protokol.

1.2 Patientpopulation

I Dansk reumatologisk kvalitets- og forskningsdatabase (DANBIO) var der ved udgangen af 2016 registreret 21.488 patienter i behandling for RA, hvoraf ca. 5.000 var i biologisk behandling. Antallet af RA patienter i biologisk behandling er stigende, således er antallet vokset med ca. 1.500 patienter siden 2010 [5–8], hvilket svarer til en gennemsnitlig stigning på ca. 250 bionaive patienter pr. år siden 2010. Der er før 2010 beskrevet en stigning på ca. 500 bionaive patienter pr. år [9], og det skønnes, at det egentlige tal ligger et sted imellem 250 og 500. Det anslås, at mindst 20 % af patienter i biologisk behandling vil skifte præparat i løbet af et år [10], hvilket hovedsageligt skyldes mangel på effekt eller uacceptable bivirkninger. Det vil sige, at ca. 1.000 (20 % af 5.000) af patienterne i biologisk behandling i 2016 vil have skiftet lægemiddel i løbet af et år(1).

De fleste patienter vil blive behandlet med sygdomsmodificerende behandling (disease modifying anti rheumatic drugs; DMARDs), herunder konventionelle syntetiske DMARDs (csDMARDs) alene eller i kombination med biologiske DMARDs. For nogle patienter vil biologisk monoterapi være eneste mulige behandling. Et nyligt studie baseret på data fra DANBIO viste, at 19 % af RA patienter var i biologisk monoterapi. Af disse var 70 % initieret på monoterapi med biologiske DMARDs, og 30 % havde tidligere været i kombinationsterapi med MTX.

Ansøger estimerer, på basis af DANBIO årsrapport 2016, at omkring 714 RA patienter hvert år behandles med IL-6 antistof (tocilizumab)(2).

Indikation

Sarilumab (Kevzara) gives sammen med MTX og er indiceret til behandling af moderat til svær, aktiv reumatoid artritis (RA) hos voksne patienter, som enten har haft utilstrækkelig respons på, eller som ikke tolererer en eller flere sygdomsmodificerende antireumatiske lægemidler (DMARDs).

Virkningsmekanisme

Sarilumab (Kevzara) er et IL-6 antistof.

Dosering

Sarilumab (Kevzara) administreres som 200 mg subkutan injektion én gang hver 2. uge i kombination med csDMARD eller som monoterapi. I tilfælde af neutropeni, trombocytopeni og forhøjede niveauer af leverenzymer reduceres dosis til 150 mg.

Komparator

Medicinrådet har defineret tocilizumab (RoActemra) s.c. 162 mg én gang ugentligt eller i.v. 8 mg/kg (dog højest 800 mg) hver 4. uge i kombination med csDMARD eller som monoterapi.

1.3 Medicinrådets kliniske spørgsmål

Medicinrådets protokol definerer fire kliniske spørgsmål for vurderingen af den kliniske merværdi af sarilumab (Kevzara):

P1: Hvilken klinisk merværdi tilbyder sarilumab sammenlignet med tocilizumab i kombination med csDMARD til bionaive patienter med moderat til svær RA?
P2: Hvilken klinisk merværdi tilbyder sarilumab sammenlignet med tocilizumab i kombination med csDMARD til patienter med moderat til svær RA, der skal skifte biologisk eller targeteret syntetisk behandling?
P3: Hvilken klinisk merværdi tilbyder sarilumab sammenlignet med tocilizumab til bionaive patienter med moderat til svær RA, hvor behandling med csDMARDs ikke er en mulighed?
P4: Hvilken klinisk merværdi tilbyder sarilumab sammenlignet med tocilizumab til patienter med moderat til svær RA, som skal skifte biologisk eller targeteret syntetisk behandling, og hvor behandling med csDMARDs ikke er en mulighed?

1.4 Tidshorisont

Indsendte analyse fra ansøger bygger på en tidshorisont på 1 år.

2. VURDERING AF INDSENDT ØKONOMISK ANALYSE

2.1 Model, metode og forudsætninger

I analysen estimeres de gennemsnitlige inkrementelle omkostninger pr. patient ved behandling med sarilumab (Kevzara) sammenlignet med behandling med tocilizumab (RoActemra). Analysen vurderes i følgende afsnit.

2.1.1 Modelbeskrivelse

Analysen estimerer de gennemsnitlige inkrementelle omkostninger pr. patient, som behandles med sarilumab (Kevzara) sammenlignet med tocilizumab (RoActemra) over en 1-årig periode. Der anvendes et begrænset samfundsperspektiv i analysen, herunder direkte omkostninger afholdt på hospitalerne for behandling af RA i form af anskaffelse og administration af lægemidler. Ansøger skriver i ansøgningen at omkostningsanalysen er fokuseret på omkostningselementer, der afviger mellem de to behandlingsregimer. Ansøger antager at der ikke er forskel mellem sarilumab (Kevzara) og tocilizumab (RoActemra) ift. baggrundsbehandling med csDMARD og antal patientbesøg på hospital mellem de subkutane lægemidler. Ansøger har inkluderet indirekte omkostninger i form af patientens tidsforbrug og transport forbundet med besøg på hospital.

Amgros' vurdering

Amgros vurderer, at analyseperspektivet for analysen er forsimplet. Amgros vurderer ligesom ansøger, at lægemiddelomkostningerne er den altoverskyggende omkostningsdriver for de inkrementelle omkostninger behandlingerne imellem.

2.1.2 Omkostninger

Det følgende afsnit om omkostninger redegør for hvordan og hvilke omkostninger ansøger har inkluderet i analysen. I gennemgangen fokuseres både på opgørelse af det anvendte ressourceforbrug og værdisætningen af dette.

Lægemidler

Alle analyser i denne ansøgning anvender AIP for sarilumab (Kevzara) og tocilizumab (RoActemra).

Da både sarilumab (Kevzara) og tocilizumab (RoActemra) gives i kombination metrotrexat (MTX) for P1-2, er omkostninger til MTX ikke indregnet. Da tocilizumab (RoActemra) kan administreres både intravenøst og subkutant indgår begge regimer i analysen.

De anvendte enhedspriser er angivet i tabellen nedenfor.

Tabel 1: Lægemiddelpriser, AIP, 04-05-2018

Behandlingsregime	Pakning	Pris pr. pakning, kr.
Sarilumab (Kevzara)	200 mg, 2 stk. S.C.	7.573,52
	200 mg, 1 stk. S.C.	3.786,76
Tocilizumab (RoActemra)	162 mg, 4 stk. S.C	7.299,28
	20 mg/ml IV. 20 ml.	4.720,11
	20 mg/ml IV. 10 ml.	2.372,25
	20 mg/ml IV. 4 ml.	955,85

Sarilumab (Kevzara) administreres som en subkutan dosis á 200 mg hver anden uge, svarende til 26 administrationer over 1 år.

Tocilizumab (RoActemra) gives enten subkutant 162 mg hver uge eller intravenøst 8 mg/kg hver 4. uge, svarende til hhv. 52 og 13 administrationer over 1 år. For dosisudregningen af tocilizumab (RoActemra) i.v. antager ansøger at en gennemsnitspatient vejer 73,9 kg, svarende til en samlet dosis pr. administration på 591 mg. Ansøger antager at dette fordeles på et hætteglas 200 mg og et med 400 mg.

Tabel 2: Gennemsnitlig dosis pr. patient pr. år

Behandlingsregime	Styrke	Administrationer	Pris pr. enhed	I alt
Sarilumab (Kevzara)	200 mg	26	3.786,76	98.455,76
Tocilizumab (RoActemra) s.c.	162 mg	52	1.824,82	94.890,64
Tocilizumab (RoActemra) i.v.	8 mg/kg*	13	7.092,36**	92.200,68**

*Gennemsnitlig vægt 73,9 kg. **Den samlede dosis per infusion er 591 mg fordeles på ét hætteglas med 200mg og ét med 400mg.

Amgros' vurdering

Doseringen af lægemidlerne er i tråd med lægemidlernes SmPC'er. Amgros vurderer at ansøgers tilgang er acceptabel.

Administration

Ansøger har estimeret en intravenøs administration med tocilizumab (RoActemra) til 922,66 kr. med henvisning til en analyse fra KORA fra 2015, der undersøger forskellen på administrationsomkostningerne mellem intravenøs og subkutan administration af biologiske lægemidler indenfor gastroenterologien(3). For de subkutane regimer antager ansøger at patienten gennemgår træning i injektionsteknik, og har værdisat træningen med 340,31 kr. som en engangsomkostning.

Tabel 3: Administrationsomkostninger pr. patient pr. år

Behandlingsregime	I.v. administration	Træning i injektionsteknik	Antal	I alt
Sarilumab (Kevzara)	-	340,31 kr.	1	340,31 kr.
Tocilizumab (RoActemra) s.c.	-	340,31 kr.	1	340,31 kr.
Tocilizumab (RoActemra) i.v.	922,66 kr.	-	13	11.994,58 kr.

Amgros' vurdering

Amgros vurderer at ansøgers tilgang er acceptabel.

Patientomkostninger

Ansøger antager at patienten har fire ambulante besøg, uanset valg af behandling, med en varighed af 20 minutter. For at undgå dobbeltælling af infusionstid og ambulantkontrol for intravenøst administreret tocilizumab (RoActemra) antager ansøger at tidsforbruget til ambulante kontrolbesøg er inkluderet i infusionstiden. Patientens rejsetid i forbindelse med hvert hospitalsbesøg antages at være 30 minutter. Transportafstanden antages at være 28 km. pr. besøg.
Ansøger har værdisat enhedsomkostningerne for transport til 3,53 kr./km og 180 kr./time.

Tabel 4: Patientomkostninger pr. patient pr. år

Behandlingsregime	Omkostninger ved infusion	Antal	Kontrolbesøg	Antal	I alt
Sarilumab (Kevzara)	-	-	248,24 kr.	4	992,96 kr.
Tocilizumab (RoActemra) s.c.	-	-	248,24 kr.	4	992,96 kr.
Tocilizumab (RoActemra) i.v.	368,84 kr.	13	-	-	4.794,92 kr.

2.2 Resultater

Amgros vurderer, at analysen er forsimplet, hvilket betyder at der kan være usikkerheder forbundet med estimeringen af de inkrementelle omkostninger behandlingerne imellem. Amgros vurderer dog ligesom ansøger, at lægemiddelomkostningerne er den altoverskyggende omkostningsdriver for de inkrementelle omkostninger behandlingerne imellem.

Resultaterne, der præsenteres i det følgende, bygger på indsendte model.

Resultatet af omkostningsanalysen viser, at de gennemsnitlige meromkostninger pr. patient i behandling med sarilumab (Kevzara) sammenlignet med behandling med tocilizumab (RoActemra) s.c. er på 3.565 kr. og -9.200 kr. sammenlignet med tocilizumab (RoActemra) i.v.

Tabellen nedenfor giver et overblik over størrelsen på de forskellige omkostningselementer for de forskellige behandlingsalternativer.

Tabel 5: Gennemsnitlige behandlingsomkostninger (udiskonterede), kr.

Omkostningselement	Sarilumab (Kevzara)	Tocilizumab (RoActemra) s.c.	Tocilizumab (RoActemra) i.v.
Lægemiddelomkostninger	98.455,76	94.890,64	92.200,68
Hospitalsomkostninger	340,31	340,31	11.994,58
Patientomkostninger	992,96	992,96	4.794,92
I alt	**99.789,03**	**96.223,91**	**108.990,18**
Difference	-	**3.565,12**	**-9.201,15**

Overordnet kan det konkluderes, at behandling med sarilumab (Kevzara) er forbundet med begrænsede meromkostninger sammenlignet med behandling med tocilizumab (RoActemra) s.c. og en mindre besparelse sammenlignet med tocilizumab (RoActemra) i.v.

2.2.1 Følsomhedsanalyser

Ansøger har indsendt følsomhedsanalyser for værdisætningen af infusionsomkostninger og for ændringer i den gennemsnitlige patientvægt. Begge følsomhedsanalyser påvirker udelukkende sammenligningen med tocilizumab (RoActemra) i.v. Følsomhedsanalysen for værdisætningen af infusionsomkostninger inkluderer et højt og et lavt estimat for omkostninger forbundet med i.v. infusion og træning i injektionsteknik, som illustreret i tabel 6. Følsomhedsanalysen for patientvægt anvender et højt estimat på 94 kg og et lavt estimat på 54 kg.

Tabel 6: Administrationsomkostninger i ansøgers følsomhedsanalyse, kr.

Omkostningselement	Base case	Lav	Høj
Omkostning pr. i.v. infusion	922,66	641,78	1.237,13
Træning i injektionsteknik	340,31	272,25	363,00

Ansøgers følsomhedsanalyse viser at behandling med sarilumab (Kevzara) ved et hhv. lavt og højt estimat for administrationsomkostning medfører en ændring i besparelsen fra 9.201 kr. i base casen til hhv. 5.459 og 13.216 kr. Ændres antagelsen omkring gennemsnitlig kropsvægt pr. patient, stiger besparelsen til 34.052 kr. hvis den gennemsnitlig vægt stiger til 94 kg. Antages kropsvægten at være 54 kg er behandling med sarilumab (Kevzara) forbundet med meromkostninger på 14.883 kr. sammenlignet med tocilizumab (RoActemra).

Tabel 7: Ansøgers følsomhedsanalyser, kr.

Følsomhedsanalyse	Base case
Base case	**-9.201,15**
Lav forskel i administrationsomkostning	-5.459,21
Høj forskel i administrationsomkostning	-13.216,49
Legemsvægt 94kg	-34.052,47
Legemsvægt 54 kg	14.883,30

3. BUDGETKONSEKVENSER

Budgetkonsekvenserne per år er baseret på antagelsen om, at lægemidlet vil blive anbefalet som standardbehandling. Man ser derfor på to scenarier:

A. Lægemidlet bliver anbefalet som standardbehandling af Medicinrådet til indikationen, som denne analyse omhandler
B. Lægemidlet bliver ikke anbefalet som standardbehandling

Budgetkonsekvenserne bliver differencen mellem budgetkonsekvenserne i de to scenarier.

3.1 Ansøgers estimater

3.1.1 Patientpopulation og markedsandel

Ansøger antager at i alt 714 patienter behandles med IL-6-antistof om året, baseret på DANBIOs 2016 årsrapport. Ansøger antager at 81 % er i kombinationsbehandling med csDMARD og 19 % er i monoterapi. Af patienterne i behandling med IL6 antistof antages 10% at være bionaive.

Det anslås således, at 81% af 714 patienter (578 patienter) er i kombinationsbehandling (patientgrupperne P1 og P2) og 19% er i monoterapi (136 patienter i grupperne P3 og P4). Af patienterne i behandling med IL-6-antistof antages 10% at være bio-naive, dvs. at grupperne P1 udgør 58 patienter og P3 udgør 14 patienter) og det resterende 90% at være bioerfarne (P2 således 521 patienter og P4 tilsvarende 122 patienter).

Tabel 8: Patientantal pr. population

	P1: Bionaive Komb. beh.	P2: Bioerfarne Komb. beh.	P3: Bionaive Monoterapi	P4: Bioerfarne Monoterapi
Antal patienter	58	521	14	122

3.1.2 Ansøgers estimat af budgetkonsekvenser

Ansøger antager, at såfremt sarilumab (Kevzara) anbefales af Medicinrådet som mulig standardbehandling, antages det, at 100 % af patienterne vil starte på sarilumab (Kevzara). Hvis sarilumab (Kevzara) *ikke* anbefales af Medicinrådet som mulig standardbehandling, antages det, at 100 % af patienterne vil fortsætte behandling med tocilizumab (RoActemra).

Sammenlignet med tocilizumab (RoActemra) s.c. estimeres budgetkonsekvenserne for at behandle med sarilumab (Kevzara) til at være 3,79 mio. kr. pr. år for alle populationer, tabel 9. Budgetkonsekvenserne pr. population er illustreret i tabel 10.

Tabel 9: Estimat af budgetkonsekvenser med og uden anbefaling, AIP.

	Total
Anbefaling	18.072.479
Anbefales ikke	14.284.097
Budgetkonsekvens	**3.788.382**

Tabel 10 Estimat af budgetkonsekvenser med og uden anbefaling for hver population, AIP.

	P1: Bionaive Komb. beh.	P2: Bioerfarne Komb. beh.	P3: Bionaive Monoterapi	P4: Bioerfarne Monoterapi
Anbefales	2.530.147	11.710.966	1.084.349	2.747.017
Anbefales ikke	1.999.774	9.256.095	857.046	2.171.183
Budgetkonsekvens	**530.373**	**2.454.872**	**227.303**	**575.834**

Amgros' vurdering af budgetkonsekvensanalyse

Amgros vurderer at af antallet at patienter, der vil modtage behandling med sarilumab (Kevzara) såfremt Medicinrådet anbefaler lægemidlet til mulig standardbehandling, og markedsoptaget er rimelige.

4. DISKUSSION

De præsenterede analyser er ikke foretaget på baggrund af aftalepriser, men på baggrund af AIP. Analysens resultater afspejler derfor ikke de reelle omkostninger, der er forbundet med anskaffelse af de analyserede lægemidler.

Analysens samlede resultater påvirkes i altovervejende grad af omkostningerne forbundet med anskaffelse af lægemidler. Nuværende og fremtidige rabatter på sarilumab (Kevzara), har derfor stor betydning for hvilken behandling, der er forbundet med de laveste omkostninger.

Overordnet set vurderer Amgros, at ansøger har indsendt en simpel analyse, som overordnet giver et acceptabelt estimat af omkostninger forbundet med behandlingen.

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Medicinrådets vurdering af klinisk merværdi af sarilumab til reumatoid artritis

Medicinrådets konklusion vedrørende klinisk merværdi

Ved utilstrækkelig effekt/ikke tolereret behandling med konventionelle syntetiske Disease Modifying Anti Rheumatic Drugs (csDMARDs) **anbefaler** Medicinrådet sarilumab som mulig standardbehandling til følgende populationer:

- **Ingen klinisk merværdi** sammenlignet med tocilizumab i kombination med csDMARD til bionaive patienter med moderat til svær RA.
- **Ingen klinisk merværdi** sammenlignet med tocilizumab i kombination med csDMARD til patienter med moderat til svær RA, der skal skifte biologisk eller targeteret syntetisk behandling.
- **Ingen klinisk merværdi** sammenlignet med tocilizumab til bionaive patienter med moderat til svær RA, hvor behandling med csDMARDs ikke er en mulighed.
- **Ingen klinisk merværdi** sammenlignet med tocilizumab til patienter med moderat til svær RA, som skal skifte biologisk eller targeteret syntetisk behandling, og hvor behandling med csDMARDs ikke er en mulighed.

Evidensens kvalitet vurderes for klinisk spørgsmål 1-3 at være meget lav, og kan for klinisk spørgsmål 4 ikke vurderes.

Handelsnavn	Kevzara
Generisk navn	Sarilumab
Firma	Sanofi-Aventis Denmark A/S
ATC-kode	L04AC14
Virkningsmekanisme	Sarilumab er et humant monoklonalt antistof (IgG1-subtype), der binder sig specifikt til både opløselige og membranbundne IL-6 receptorer (IL-6Rα) og hæmmer IL-6-medieret signalering.
Administration/dosis	Subkutant, 200 mg hver anden uge.
EMA-indikation	Sarilumab er i kombination med methotrexat (MTX) indiceret til behandling af moderat til svær, aktiv reumatoid artritis (RA) hos voksne patienter, som enten har haft utilstrækkelig respons på, eller som ikke tolererer en eller flere sygdomsmodificerende antireumatiske lægemidler (DMARDs). Sarilumab kan gives som monoterapi i tilfælde af intolerans over for MTX, eller når behandling med MTX er uhensigtsmæssig.
Godkendelsesdato Offentliggørelsesdato Dokumentnummer	24. juli 2018 24. juli 2018 Følger

Versionsnummer	1.0

Fagudvalgets sammensætning og sekretariatets arbejdsgruppe, se bilag 1

Definition af klinisk merværdi:

Medicinrådet kategoriserer lægemidlets kliniske merværdi i en af følgende kategorier:

Kategori 1. Stor merværdi: Vedvarende og stor forbedring i effektforhold der ikke tidligere er opnået med et relevant behandlingsalternativ. Eksempler herpå er sygdomsremission, markant stigning i overlevelsestid, langvarigt fravær af alvorlige sygdomssymptomer eller udtalt fravær af alvorlige bivirkninger.

Kategori 2. Vigtig merværdi: Markant forbedring, eksempelvis lindring af sygdomstilstand, moderat stigning i overlevelsestid, lindring af alvorlige symptomer, fravær af alvorlige bivirkninger og væsentligt fravær af andre bivirkninger.

Kategori 3. Lille merværdi: Moderat forbedring, f.eks. reduktion i ikkealvorlige sygdomssymptomer eller fravær af bivirkninger.

Kategori 4. Ingen merværdi: Ingen merværdi sammenlignet med standardbehandling/andre behandlinger.

Kategori 5. Negativ merværdi: Negativ merværdi sammenlignet med standardbehandling/andre behandlinger.

Kategori 6. Ikkedokumenterbar merværdi: Ikkedokumenterbar merværdi sammenlignet med standardbehandling/ andre behandlinger. Effektforskellen kan ikke kvantificeres ud fra det videnskabelige datagrundlag.

Om Medicinrådet:

Medicinrådet er et uafhængigt råd, som udarbejder anbefalinger og vejledninger om lægemidler til de fem regioner.

Medicinrådet vurderer, om nye lægemidler og nye indikationer kan anbefales som standardbehandling og udarbejder fælles regionale behandlingsvejledninger.

Nye lægemidler vurderes i forhold til effekt, eksisterende behandling og pris. Det skal give lavere priser og lægemidler, der er til størst mulig gavn for patienterne.

De fælles regionale behandlingsvejledninger er vurderinger af, hvilke lægemidler der er mest hensigtsmæssige til behandling af patienter inden for et terapiområde og dermed grundlag for ensartet høj kvalitet for patienterne på tværs af sygehuse og regioner.

Forkortelser

ACR50:	*American College of Rheumatology 50 % response*
bDMARD:	Biologisk *Disease Modifying Anti Rheumatic Drug*
CI:	Konfidensinterval
csDMARD:	Konventionelt syntetisk *Disease Modifiying Anti Rheumatic Drug*
DANBIO:	Dansk reumatologisk kvalitets- og forskningsdatabase
DMARD:	*Disease Modifying Anti Rheumatic Drug*
EMA:	Det Europæiske Lægemiddelagentur (*European Medicines Agency*)
EPAR:	*European Public Assessment Report*
EULAR:	*European League Against Rheumatism*
GRADE:	System til vurdering af evidens (*Grading of Recommendations Assessment, Development and Evaluation System*)
HAQ-DI	*Health Assessment Questionnaire Disability Index*
IV:	Intravenøs
MTX:	Methotrexat
OR:	Odds Ratio
QW:	Hver uge
Q2W:	Hver anden uge
Q4W:	Hver fjerde uge
RA:	Reumatoid artrit
RADS:	Rådet for Anvendelse af Dyr Sygehusmedicin
RCT:	Randomiseret kontrolleret forsøg (*Randomised Controlled Trial)*
RR:	Relativ Risiko
s.c.:	Subkutant
tsDMARD:	Targeteret syntetisk *Disease Modifying Anti Rheumatic Drug*
TNF:	*Tumor Necrosis Factor*
TSS:	*Total Sharp Score*

Indhold

1 Formål

Formålet med Medicinrådets vurdering af klinisk merværdi af sarilumab til reumatoid artritis (RA) er at vurdere den kliniske merværdi i forhold til et eller flere lægemidler til samme patientgruppe (komparatorer).

Ansøger har tilkendegivet en forventning om, at sarilumab giver "ingen klinisk merværdi" sammenlignet med komparator. Sarilumab er derfor behandlet i Medicinrådets 7-ugers proces. Med udgangspunkt i den kliniske merværdi og en omkostningsanalyse udarbejdet af Amgros vurderer Medicinrådet, om sarilumab skal anbefales som mulig standardbehandling.

2 Baggrund

Reumatoid artritis

RA er en systemisk og progredierende sygdom [1], der er karakteriseret ved inflammation i led og lednære strukturer og kan medføre leddestruktion. Sygdommen medfører ledsmerter, nedsat funktionsevne og en betydelig del af patienterne bliver helt eller delvist uarbejdsdygtige. Udover leddestruktion kan sygdommen medføre systemiske manifestationer og er forbundet med øget mortalitet, især pga. arteriosklerose og lungeinvolvering. Ætiologien er multifaktoriel, med miljøpåvirkninger (eksempelvis tobaksrygning) som risikofaktor samt en genetisk komponent.

Sygdommen klassificeres efter 2010 ACR/EULAR, kriterier defineret af American College of Rheumatology (ACR) og European League Against Rheumatism (EULAR) [2]. Klassifikationen er baseret på antal involverede led, autoimmun serologi, akutfaserespons og symptomvarighed.

RA forekommer globalt, men med geografisk og etnisk variation. I en nyere populationsbaseret dansk undersøgelse er incidensen mellem 32 og 35 pr. 100.000 og størst hos kvinder [3]. Sygdommen debuterer i alle aldre, men typisk mellem 50 og 70 år [4]. I Dansk reumatologisk kvalitets- og forskningsdatabase (DANBIO) var der ved udgangen af 2017 registreret 22.500 patienter i behandling for RA, hvoraf ca. 5.600 var i biologisk behandling [5].

Antallet af RA-patienter i biologisk behandling er stigende, således er antallet vokset med ca. 1.500 patienter siden 2010 [5–9], hvilket svarer til en gennemsnitlig stigning på ca. 250 bionaive patienter pr. år siden 2010. Der er før 2010 beskrevet en stigning på ca. 500 bionaive patienter pr. år [10], og det skønnes, at det egentlige tal ligger et sted imellem 250 og 500. Det anslås, at mindst 20 % af patienter i biologisk behandling vil skifte præparat i løbet af et år [11], hvilket hovedsageligt skyldes mangel på effekt eller uacceptable bivirkninger. Det vil sige, at ca. 1.000 (20 % af 5.000) af patienterne i biologisk behandling i 2016 vil have skiftet lægemiddel i løbet af et år.

Nuværende behandling

Der findes ingen kurativ behandling, men tidlig behandling kan bremse sygdommen og bedre prognosen. Behandlingen er principielt livslang og består af immunhæmmende medicin, der er delt op i symptomlindrende behandling (smertestillende behandling (NSAID)) og sygdomsmodificerende behandling (Disease Modifying Anti Rheumatic Drugs, DMARDs). Vigtige principper er tidlig og målrettet behandling for at forebygge leddestruktion. Behandlingen er en specialistopgave, der bør varetages af reumatologer.

Ved behandlingsopstart med DMARDs anvendes methotrexat (MTX) som førstevalg. Ved inadækvat respons kombineres dette præparat med andre konventionelle syntetiske DMARDs (csDMARDs), typisk salazopyrin og hydroxychloroquin (triple behandling). Hvis lav sygdomsaktivitet/remission ikke opnås, er næste behandlingsmulighed biologisk behandling/targeteret syntetisk behandling (bDMARDs/tsDMARDs) i kombination med MTX. De biologiske DMARDs opdeles i TNF-inhibitorer (adalimumab, certolizumab, etanercept, golimumab og infliximab) og biologiske lægemidler med andre virkningsmekanismer (rituximab, tocilizumab, sarilumab og abatacept). Dertil kommer de targeterede syntetiske DMARDS (tsDMARDs, baricitinib og tofacitinib). I den nuværende behandlingsvejledning fra Rådet for Anvendelse af Dyr Sygehusmedicin (RADS) indgår 8 bDMARDs [11].

De fleste patienter behandles med csDMARDs alene eller i kombination med bDMARDs eller tsDMARD. For nogle patienter er biologisk monoterapi eneste mulige behandling. Et nyligt studie baseret på data fra DANBIO [12] viste, at 19 % af RA-patienter var i biologisk monoterapi. Af disse var 70 % initieret på monoterapi med bDMARDs, og 30 % havde tidligere været i kombinationsterapi med MTX.

Anvendelse af det nye lægemiddel

Sarilumab er et humant monoklonalt antistof (IgG1-subtype), der binder sig specifikt til både opløselige og membranbundne IL-6 receptorer (IL-6Rα) og hæmmer IL-6-medieret signalering. Sarilumab administreres subkutant i en dosis af 200 mg hver anden uge og kan varetages i hjemmet af patienten selv. Sarilumab kan enten gives i kombination med MTX eller som monoterapi.

3 Metode

De præspecificerede metoder i protokollen er udarbejdet af Medicinrådet. Ansøgningen er valideret af Medicinrådets sekretariat.

Ansøger har anvendt og fulgt den præspecificerede metode jf. protokol, som blev godkendt i Medicinrådet den 15. marts 2018.

Ansøgers endelige ansøgning blev modtaget efter ændringer den 1. juni 2018. Sarilumab er behandlet i Medicinrådets 7-ugers proces, idet ansøger har tilkendegivet en forventning om, at sarilumab giver ingen klinisk merværdi sammenlignet med tocilizumab.

4 Litteratursøgning

Ansøger har gennemført en systematisk litteratursøgning som efterspurgt i protokollen, hvilket samlet resulterede i identifikation af fire studier af sarilumab og otte studier af tocilizumab. Disse studier er beskrevet under de relevante kliniske spørgsmål.

Ansøger har udover den systematiske litteratursøgning konsulteret Det Europæiske Lægemiddelagentur (EMA)s assessment report (EPAR) for sarilumab [13].

Fra evidens til kategori. Medicinrådet vurderer den kliniske merværdi af et lægemiddel ud fra den indsendte endelige ansøgning, evt. suppleret med andet materiale. I protokollen blev effektmålene angivet som "kritiske", "vigtige" og "mindre vigtige". I vurderingen af klinisk merværdi vægter de kritiske højest, de vigtige næsthøjest og de mindre vigtige indgår ikke.

Den kliniske merværdi kategoriseres først enkeltvis pr. effektmål, hvorefter der foretages en vurdering af den samlede kategori for lægemidlet på tværs af effektmålene. Kategoriseringen pr. effektmål foretages på baggrund af absolutte og relative værdier for det enkelte effektmål. Den relative effekt beskrives med et estimat og et konfidensinterval, der sammenholdes med generiske væsentlighedskriterier. Den absolutte effekt sammenholdes med den i protokollen beskrevne "mindste klinisk relevante forskel". Den endelige kategorisering af lægemidlets kliniske merværdi er en delvis kvalitativ proces, hvor der foretages en vurdering af det samlede datagrundlag på tværs af effektmålene.

Vurdering af evidensens kvalitet foretages med udgangspunkt i GRADE og udtrykker tiltroen til evidensgrundlaget for de enkelte effektstørrelser og den endelige kategori for klinisk merværdi. Evidensens kvalitet inddeles i fire niveauer: høj, moderat, lav og meget lav. GRADE-metoden er et internationalt anerkendt redskab til systematisk vurdering af evidens og udarbejdelse af anbefalinger. I denne vurdering er metoden anvendt til at vurdere evidensens kvalitet.

5 Databehandling

Nedenfor følger en overordnet beskrivelse af de anvendte metoder.

Databehandling i den endelige ansøgning
De statistiske analyser er udført af ansøger og valideret af Medicinrådets sekretariat.

Medicinrådet har ikke fundet anledning til at foretage ændringer af beregninger foretaget af ansøger eller supplere med yderligere beregninger.

I overensstemmelse med protokollen er alle resultater i vurderingen baseret på indirekte sammenligninger af sarilumab og tocilizumab.

Vurdering af datagrundlag
Samlet set betragtes det indleverede datagrundlag som tilstrækkeligt til at vurdere den kliniske merværdi af sarilumab som mulig standardbehandling af RA med følgende bemærkninger:

- For klinisk spørgsmål 1 er der ikke indleveret data til at udføre en komparativ analyse på effektmålet "alvorlige infektioner".
- For klinisk spørgsmål 2 er der kun indleveret data til komparativ analyse for følgende effektmål: mortalitet, behandlingsophør grundet uønskede hændelser, behandlingsophør grundet manglende effekt og alvorlige infektioner.
- For klinisk spørgsmål 3 er der ikke indleveret data til at udføre en komparativ analyse på effektmålet "TSS".
- For klinisk spørgsmål 4 foreligger ingen kliniske studier af hverken sarilumab eller komparator, men ansøger har udført en post hoc-analyse af data fra ONE-studiet.

6 Klinisk merværdi

6.1 Konklusion klinisk spørgsmål 1

Hvilken klinisk merværdi tilbyder sarilumab sammenlignet med tocilizumab i kombination med csDMARD til bionaive patienter med moderat til svær RA?

Fagudvalget vurderer, at sarilumab i kombination med csDMARD til bionaive patienter med RA giver **ingen klinisk merværdi** sammenlignet med tocilizumab.

6.1.1 Gennemgang af studier

Ansøger identificerede et klinisk studie bestående af to dele omhandlende sarilumab og fem kliniske studier omhandlende tocilizumab til besvarelse af klinisk spørgsmål 1. Nedenfor følger en beskrivelse af studiekarakteristika for de seks studier.

Karakteristika

Sarilumab

MOBILITY: Resultaterne fra MOBILITY-studiet er publiceret i henholdsvis 2014 og 2015 [14,15]. Studiet er et randomiseret, dobbeltblindet, placebokontrolleret multicenterstudie, der består af to dele - MOBILITY A og MOBILITY B. I MOBILITY A var patienter randomiseret til placebo eller 1 af 5 subkutane (s.c.) doser af sarilumab i kombination med methotrexat (MTX): 100 mg hver uge (qw), 150 mg qw, 100 mg hver anden uge (q2w), 150 mg q2w eller 200 mg q2w. I MOBILITY B var der to kohorter: Kohorte 1 var randomiseret på den samme måde som i MOBILITY A, og kun de, som blev randomiseret til placebo, 150 mg q2w eller 200 mg q2w sarilumab, fortsatte behandlingen i 52 uger. I Kohorte 2 blev patienterne randomiseret i forholdet 1:1:1 til placebo, sarilumab 150 mg q2w eller 200 mg q2w, i kombination med MTX. Analysen af primære endepunkter blev i MOBILITY A foretaget på data fra alle patienter, der blev randomiseret, mens sikkerhed blev analyseret på data fra alle patienter, som havde modtaget mindst én behandling. I MOBILITY B blev analyserne foretaget på data fra alle patienter, som blev randomiseret i Kohorte 2, og sikkerhedsanalyser blev foretaget på data fra alle patienter, der havde modtaget mindst én behandling og var randomiseret til placebo, sarilumab 150 mg q2w eller 200 mg q2w.

Tocilizumab

CHARISMA: Resultaterne fra CHARISMA-studiet er publiceret i 2006 [16]. Studiet er et dobbeltblindet, randomiseret, kontrolleret klinisk forsøg af tocilizumab i europæiske patienter med RA og utilstrækkelig respons på MTX monoterapi. Patienterne blev randomiseret til monoterapi (intravenøse (IV) infusioner af tocilizumab 2 mg/kg, 4 mg/kg eller 8 mg/kg hver fjerde uge (q4w) i kombination med placebo qw), kombinationsterapi (IV-infusioner af tocilizumab 2 mg/kg, 4 mg/kg eller 8 mg/kg q4w i kombination med en stabil dose af MTX), eller kontrolgruppe (placeboinfusioner q4w og stabil dosis af MTX). Effektanalyser blev foretaget på data fra alle patienter, der fik mindst én dosis og havde effektdata tilgængelige. Patienterne, som udgik af studiet pga. mangel på effekt, blev inkluderet i en nonresponders-analyse.

OPTION: Resultaterne fra OPTION-studiet er publiceret i 2008 [17]. Studiet er et randomiseret, dobbeltblindet fase 3-studie af sikkerhed og reduktion i symptomer ved behandling med tocilizumab vs. placebo, kombineret med MTX, hos patienter med moderat til svær RA. Patienter var randomiseret i en af tre arme – tocilizumab 4 mg/kg, 8 mg/kg eller placebo q4w i 24 uger i kombination med stabil dosis MTX. Patienterne, som ikke opnåede mindst 20 % forbedring fra baseline i hævede og ømme led ved uge 16, blev

tilbudt anden aktiv behandling (rescuebehandling). Effektanalyser blev foretaget på data fra alle som var randomiserede og fik mindst én dosis. Sikkerhedspopulationen bestod af alle randomiserede patienter, der fik mindst én dosis og havde mindst én vurdering af sikkerhed. Patienter, som udgik fra studiet før uge 24, de som fik rescuebehandling, og de der ikke havde endepunkter, som kunne måles i uge 24, var inkluderet i en nonresponders-analyse.

TOWARD: Resultaterne fra TOWARD-studiet er publiceret i 2008 [18]. Studiet er et randomiseret, dobbeltblindet, placebokontrolleret fase 3-studie. Patienterne blev randomiseret i forholdet 2:1 til tocilizumab 8 mg/kg eller placebo i kombination med DMARDs. Patienter, der ikke opnåede mindst 20 % forbedring i ømme og hævede led ved uge 16, fik tilbudt rescuebehandling. Effektanalyser blev foretaget på data fra alle randomiserede patienter, der fik mindst én dosis. Patienter, som ikke havde de krævede data ved et specifikt tidspunkt, de som trak sig tilbage fra studiet, eller de som fik tilbudt anden behandling, blev klassificeret som nonresponders. Sikkerhedsanalyser inkluderede alle patienter, som fik mindst én dosis og havde ≥ 1 vurdering af sikkerhed.

ROSE: Resultaterne fra ROSE-studiet er publiceret i 2012 [19]. Studiet er et randomiseret, dobbeltblindet, placebokontrolleret, multicenter fase 3b-studie, som har til formål at vurdere sikkerhed og effekt af tocilizumab vs. placebo i kombination af DMARDs, hos patienter med moderat til svær RA. Patienterne blev randomiseret i forholdet 2:1 til tocilizumab 8 mg/kg IV q4w plus stabil antirheumatisk terapi (bl.a. DMARD) eller placebo IV q4w plus DMARD. Patienter, der ikke opnåede mindst 20 % forbedring i ømme og hævede led ved uge 16, fik tilbudt rescuebehandling. Effektanalyser blev foretaget på data fra alle randomiserede patienter, som fik mindst én dosis. Sikkerhedspopulationen inkluderede alle patienter, som fik som mindst én dosis, og som havde mindst én vurdering af sikkerhed. Patienter der fik rescuebehandling, og de, som ikke havde de krævede data for at vurdere effekten i uge 24, var klassificeret som nonresponders.

LITHE: Resultaterne fra LITHE-studiet er publiceret i 2011 [20]. Studiet er et randomiseret, dobbeltblindet placebokontrolleret, fase 3-studie. Formålet med studiet var at vurdere effekt og sikkerhed af tocilizumab plus MTX vs. MTX alene i forebyggelse af strukturelle ledskader og forbedring af fysisk funktion hos patienter med moderat til svær RA. Patienterne blev randomiseret i forholdet 1:1:1 til IV tocilizumab 8 mg/kg, 4 mg/kg eller placebo qw4 i kombination med stabil dosis MTX. Patienter, der ikke opnåede mindst 20 % forbedring i ømme og hævede led ved uge 16, fik tilbudt anden behandling. Effektanalyser blev foretaget på data fra alle patienter, der fik mindst én dosis. Sikkerhedsanalyser blev foretaget hos alle patienter, som fik som mindst én dosis og havde ≥ 1 vurdering af sikkerhed.

Population

Populationerne i de to delstudier for sarilumab og fem studier for tocilizumab er præsenteret i tabellerne nedenfor.

Der er i tabel 1 kun opgivet de sarilumabstudiearme, der er relevante i vurderingen her, dvs. sarilumab 200 mg q2w. I tabel 2 er tocilizumabdosis i de beskrevne arme 8 mg/kg.

Tabel 1. Studiepopulationer i sarilumabstudier ved klinisk spørgsmål 1

SARILUMAB	**MOBILITY A (NCT01061736)**	**MOBILITY B (NCT01061736)**
Tidspunkt for gennemførelse af studiet	2010-2013	2010-2013
Sygdomsvarighed i år (gennemsnit ± SD eller range)	8,07 ± 8,62 (Placebo + MTX) 5,95 ± 6,18 (Sarilumab + MTX)	9,1 (0,3-44,0) (Placebo + MTX) 8,6 (0,3-34,2) (Sarilumab + MTX)
Alder (gennemsnit ± SD)	55,2 ± 12,5 (Placebo + MTX) 48,7 ± 12,4 (Sarilumab + MTX)	50,9 ± 11,2 (Placebo + MTX) 50,8 ± 11,8 (Sarilumab + MTX)
% Kvinder	73,1 (Placebo + MTX) 80,8 (Sarilumab + MTX)	81 (Placebo + MTX) 85 (Sarilumab + MTX)
Hævede led (gennemsnit ± SD)	17,45 ± 11,68 (Placebo + MTX) 16,63 ± 8,94 (Sarilumab + MTX)	16,7 ± 9,3 (Placebo + MTX) 16,8 ± 9,7 (Sarilumab + MTX)
DAS28-ESR (mean ± SD)	6,08 ± 0,86 (Placebo + MTX) 6,06 ± 0,90 (Sarilumab + MTX)	6,6 ± 0,9 (Placebo + MTX) 6,5 ± 1,0 (Sarilumab + MTX)

Tabel 2. Studiepopulationer i tocilizumabstudier ved klinisk spørgsmål 1

TOCILIZUMAB	**CHARISMA**	**OPTION (NCT00106548)**	**TOWARD (NCT00106574)**	**ROSE (NCT00531817)**	**LITHE (NCT00106535)**
Tidspunkt for gennemførelse af studiet	2006	2005-2007	2005-2007	2007-2011	2005-2012
Sygdomsvarighed i år (gennemsnit ± SD eller range)	11,2 (Placebo + MTX) 10,6 (Tocilizumab + MTX)	7,8 ± 7,2 (Placebo + MTX) 7,5 ± 7,3 (Tocilizumab + MTX)	9,8 ± 9,1 (Placebo + DMARDs) 9,8 ± 8,8 (Tocilizumab + DMARDs)	8,52 ± 9,05 (Placebo + DMARD) 8,62 ± 8,93 (Tocilizumab + DMARD)	9,0 ((0,5-44,3)) (Placebo + MTX) 9,3 ((0,6-48,8)) (Tocilizumab + MTX)
Alder (gennemsnit ± SD)	50,9 (Placebo + MTX) 50,1 (Tocilizumab + MTX)	50,6 ± 12,1 (Placebo + MTX) 50,8 ± 11,8 (Tocilizumab + MTX)	54 ± 13 (Placebo + DMARDs) 53 ± 13 (Tocilizumab + DMARDs)	55,8 ± 12,42 (Placebo + DMARD) 55,2 ± 12,06 (Tocilizumab + DMARD)	51,3 ± 12,4 (Placebo + MTX) 53,4 ± 11,7 (Tocilizumab + MTX)
% Kvinder	77,6 (Placebo + MTX) 78,0 (Tocilizumab + MTX)	77,9 (Placebo + MTX) 85,4 (Tocilizumab + MTX)	84 Placebo + DMARDs) 81 (Tocilizumab + DMARDs)	82,9 (Placebo + DMARD) 79,5 (Tocilizumab + DMARD)	83 (Placebo + MTX) 82 (Tocilizumab + MTX)
Hævede led (gennemsnit ± SD)	16 (Placebo + MTX) 15 (Tocilizumab + MTX)	20,7 ± 11,7 (Placebo + MTX) 19,5 ± 11,3 (Tocilizumab + MTX)	18,7 ± 10,8 (Placebo + DMARDs) 19,7 ± 11,6 (Tocilizumab + DMARDs)	19,9 ± 12,1 (Placebo + DMARD) 19,7 ± 12,4 (Tocilizumab + DMARD)	16,6 ± 9,2 (Placebo + MTX) 17,3 ± 9,5 (Tocilizumab + MTX)
DAS28-ESR (mean ± SD)	6,75 (Placebo + MTX)	6,8 ± 0,9 (Placebo + MTX)	6,6 ± 1,0 (Placebo + DMARDs)	6,55 ± 1,01 (Placebo + DMARD)	6,5 ± 1,0 (Placebo + MTX)

	6,47 (Tocilizumab + MTX)	6,8 ± 0,9 (Tocilizumab + MTX)	6,7 ± 1,0 (Tocilizumab + DMARDs)	6,53 ± 1,03 (Tocilizumab + DMARD)	6,6 ± 1,0 (Tocilizumab + MTX)

Fagudvalget finder, at der for samtlige studier ikke er nogen betydende forskelle i baselinekarakteristika mellem studiearmene. Fagudvalget vurderer, at patientkarakteristika i studierne ikke afviger væsentligt fra den danske patientpopulation, men fremhæver dog, at RA-patienter med 16-20 hævede led er sjældent forekommende i Danmark.

6.1.2 Resultater og vurdering

Resultater og vurdering af de effektmål, som fagudvalget har præspecificeret som hhv. kritiske og vigtige, følger nedenfor.

Mortalitet (kritisk)

Der var ingen dødsfald i studiets opfølgningstid, og det er dermed ikke muligt at vurdere, hvorvidt sarilumab har merværdi i forhold til tocilizumab (komparator) på dette effektmål.

American College of Rheumatology 50 % respons (ACR50) (kritisk)

De anvendte data for dette effektmål er rapporteret efter 24 ugers opfølgningstid for sarilumab og tocilizumab.

Tabel 3. Vurdering af klinisk merværdi: ACR50

	Forhåndsdefineret grundlag for vurdering		Resultater
Absolutte forskelle	15 procentpoint		-14 procentpoint [-26;5]
Relative forskelle	Stor merværdi	LL > 1,33	
	Vigtig merværdi	LL > 1,11	
	Lille merværdi	LL > 1,00	
	Ingen merværdi	LL < 1,00	0,68 [0,41;1,10]
	Negativ merværdi	UL < 1,00	
Evidensens kvalitet	Meget lav		

UL: Upper confidence limit (øvre konfidensgrænse)
LL: Lower confidence limit (nedre konfidensgrænse)
Første kolonne indeholder de i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen. Anden kolonne indeholder data fra ansøgning, som indgår i Medicinrådets vurdering.

Den absolutte forskel mellem sarilumab og komparator er mindre end den forhåndsdefinerede mindste klinisk relevante forskel. Fagudvalget bemærker, at den absolutte forskel nærmer sig en negativ klinisk merværdi. Tilsvarende indikerer estimatet for den relative forskel negativ merværdi, men opnår ikke statistisk signifikans, da konfidensintervallet indeholder 1,00. Samlet har sarilumab **ingen klinisk merværdi** sammenlignet med tocilizumab vedrørende det kritiske effektmål ACR50.

Behandlingsophør grundet uønskede hændelser (kritisk)

De anvendte data for dette effektmål er rapporteret efter 52 ugers opfølgningstid for sarilumab og tocilizumab.

Tabel 4. Vurdering af klinisk merværdi: Behandlingsophør grundet uønskede hændelser

	Forhåndsdefineret grundlag for vurdering		Resultater
Absolutte forskelle	5 procentpoint		0 procentpoint [-5;11]
Relative forskelle	Stor merværdi	UL < 0,75	
	Vigtig merværdi	UL < 0,90	
	Lille merværdi	UL < 1,00	
	Ingen merværdi	UL > 1,00	1,01 [0,44;2,31]
	Negativ merværdi	LL > 1,00	
Evidensens kvalitet	Meget lav		

UL: Upper confidence limit (øvre konfidensgrænse)
LL: Lower confidence limit (nedre konfidensgrænse)
Første kolonne indeholder de i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen. Anden kolonne indeholder data fra ansøgning, som indgår i Medicinrådets vurdering.

Både absolutte og relative forskelle indikerer, at sarilumab har **ingen klinisk merværdi** i forhold til tocilizumab vedrørende dette effektmål.

Behandlingsophør grundet manglende effekt (vigtig)

De anvendte data for dette effektmål er rapporteret efter 52 ugers opfølgningstid, for sarilumab og tocilizumab.

Tabel 5. Vurdering af klinisk merværdi: Behandlingsophør grundet manglende effekt

	Forhåndsdefineret grundlag for vurdering		Resultater
Absolutte forskelle	10 procentpoint		6 procentpoint [0;46]
Relative forskelle	Stor merværdi	UL < 0,75	
	Vigtig merværdi	UL < 0,90	
	Lille merværdi	UL < 1,00	
	Ingen merværdi	UL > 1,00	
	Negativ merværdi	LL > 1,00	12,18 [1,60;92,82]
Evidensens kvalitet	Meget lav		

UL: Upper confidence limit (øvre konfidensgrænse)
LL: Lower confidence limit (nedre konfidensgrænse)
Første kolonne indeholder de i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen. Anden kolonne indeholder data fra ansøgning, som indgår i Medicinrådets vurdering.

Den absolutte forskel mellem sarilumab og komparator er mindre end den forhåndsdefinerede mindste klinisk relevante forskel. Estimatet for den relative forskel er statistisk signifikant og viser en negativ

merværdi da nedre konfidensgrænse overstiger 1,00. Fagudvalget tillægger den absolutte forskel størst vægt, hvorfor sarilumab vurderes at have **ingen klinisk merværdi** sammenlignet med tocilizumab vedrørende dette effektmål.

Alvorlige infektioner (vigtig)

Ansøger har ikke indleveret data på dette effektmål, hvorfor den kliniske merværdi kategoriseres som **ikkedokumenterbar.**

Total Sharp Score (TSS) (vigtig)

De anvendte data for dette effektmål er rapporteret efter 52 ugers opfølgningstid for sarilumab og tocilizumab.

Tabel 6. Vurdering af klinisk merværdi: TSS

	Forhåndsdefineret grundlag for vurdering		Resultater
Absolutte forskelle	10 procentpoint		19 procentpoint [2;38]
Relative forskelle	Stor merværdi	LL > 1,33	
	Vigtig merværdi	LL > 1,11	
	Lille merværdi	LL > 1,00	1,21 [1,03;1,43]
	Ingen merværdi	LL <1,00	
	Negativ merværdi	UL < 1,00	
Evidensens kvalitet	Meget lav		

UL: Upper confidence limit (øvre konfidensgrænse)
LL: Lower confidence limit (nedre konfidensgrænse)
Første kolonne indeholder de i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen. Anden kolonne indeholder data fra ansøgning, som indgår i Medicinrådets vurdering.

Den absolutte forskel mellem sarilumab og komparator overstiger den forhåndsdefinerede mindste klinisk relevante forskel. Tilsvarende indikerer estimatet for den relative forskel en lille merværdi, da nedre konfidensgrænse overstiger 1,00. Samlet har sarilumab **lille klinisk merværdi** sammenlignet med tocilizumab vedrørende TSS.

Health Assessment Questionnaire Disability Index (HAQ-DI) (vigtig)

De anvendte data for dette effektmål er rapporteret efter både 24 og 52 ugers opfølgningstid for sarilumab og tocilizumab. Fagudvalget har valgt at fokusere på resultaterne ved 52 uger. Ansøger har rapporteret resultater for andelen af patienter, der opnår en ændring på ≥ 0,30, hvilket er en større ændring end protokollen definerede (≥ 0,20). Fagudvalget anser det rapporterede som et mere ambitiøst effektmål, der kan erstatte det efterspurgte.

Tabel 7. Vurdering af klinisk merværdi: HAQ-DI

	Forhåndsdefineret grundlag for vurdering		Resultater
Absolutte forskelle	15 procentpoint		33 procentpoint [11;63]
Relative forskelle	Stor merværdi	LL > 1,33	
	Vigtig merværdi	LL > 1,11	1,53 [1,18;2,00]
	Lille merværdi	LL > 1,00	
	Ingen merværdi	LL < 1,00	
	Negativ merværdi	UL < 1,00	
Evidensens kvalitet	Meget lav		

UL: Upper confidence limit (øvre konfidensgrænse)
LL: Lower confidence limit (nedre konfidensgrænse)
Første kolonne indeholder de i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen. Anden kolonne indeholder data fra ansøgning, som indgår i Medicinrådets vurdering.

Den absolutte forskel mellem sarilumab og komparator overstiger den forhåndsdefinerede mindste klinisk relevante forskel. Tilsvarende indikerer estimatet for den relative forskel en vigtig merværdi, da nedre konfidensgrænse overstiger 1,11. Samlet har sarilumab **vigtig klinisk merværdi** sammenlignet med tocilizumab vedrørende HAQ-DI.

6.1.3 Evidensens kvalitet

Evidensens kvalitet for klinisk spørgsmål 1 er samlet set vurderet som værende **meget lav**, da der nedgraderes et niveau for "indirectness" (grundet indirekte sammenligninger) og to niveauer for "imprecision", da konfidensintervallerne for flere effektmål (herunder det kritiske effektmål ACR50) er så brede, at de både indeholder en positiv og en negativ merværdi.

6.1.4 Konklusion for klinisk spørgsmål 1

Fagudvalget vurderer, at sarilumab i kombination med csDMARD til bionaive patienter med RA giver **ingen klinisk merværdi** sammenlignet med tocilizumab. Fagudvalget lægger vægt på, at merværdikategorierne for de enkelte effektmål ikke peger entydigt i én retning. En samlet vurdering er, at der ikke er tendens til forskelle mellem sarilumab og komparator i én retning (se tabel 8). Fagudvalget bemærker derudover, at ansøger ikke har leveret data på det vigtige effektmål "alvorlige infektioner".

Tabel 8. Oversigt over merværdi for kritiske og vigtige effektmål for klinisk spørgsmål 1.

Effektmål	**Vigtighed**	**Merværdi**
Mortalitet	Kritisk	Ikkedokumenterbar
American College of Rheumatology 50 % response, ACR50	Kritisk	Ingen
Behandlingsophør grundet uønskede hændelser	Vigtig	Ingen
Behandlingsophør grundet manglende effekt	Vigtig	Ingen
Alvorlige infektioner	Vigtig	Ikkedokumenterbar
Total Sharp Score, TSS	Vigtig	Lille
Health Assessment Questionnaire Disability Index, HAQ-DI	Vigtig	Vigtig
Samlet	-	**Ingen**

6.2 Konklusion klinisk spørgsmål 2

Hvilken klinisk merværdi tilbyder sarilumab sammenlignet med tocilizumab i kombination med csDMARD til patienter med moderat til svær RA, der skal skifte biologisk eller targeteret syntetisk behandling?

Fagudvalget vurderer, at sarilumab i kombination med csDMARD til patienter med RA, der skal skifte behandling, har **ingen klinisk merværdi** sammenlignet med tocilizumab.

6.2.1 Gennemgang af studier

Ansøger identificerede ét klinisk studie omhandlende sarilumab og to kliniske studier omhandlende tocilizumab til besvarelse af klinisk spørgsmål 2. Nedenfor følger en beskrivelse af studiekarakteristika.

Karakteristika

Sarilumab

TARGET: Resultaterne fra TARGET-studiet er publiceret i 2017 [21]. Studiet er baseret på et randomiseret, dobbeltblindet, parallel- og placebokontrolleret design. I studiet blev patienterne randomiseret i forholdet 1:1:1 til en af tre behandlinger: s.c. sarilumab 150 mg, 200 mg eller placebo – alle tre arme q2w og i kombination med csDMARD i 24 uger. Primære effekt- og sikkerhedsanalyser blev foretaget på data fra alle randomiserede patienter, der modtog mindst én dosis sarilumab.

Tocilizumab

RADIATE: Resultaterne fra RADIATE-studiet er publiceret i 2008 [22]. Studiet er et randomiseret, dobbeltblindet fase 3-studie af sikkerhed og reduktion i symptomer ved behandling med tocilizumab vs. placebo i kombination med MTX i patienter med moderat til svær aktivt RA. Patienterne var randomiserede til tocilizumab IV 8 mg/kg, 4 mg/kg eller placebo IV q4w i kombination med stabil dosis MTX. Andre DMARDs var ikke tilladt. Patienter, der ikke opnåede mindst 20 % forbedring i ømme og hævede led, fik tilbudt anden aktiv behandling. Analysen af primære endepunkter blev foretaget på data fra alle patienter, der fik mindst én dosis. Sikkerhedsdata bestod af de af ovennævnte population, der havde mindst én vurdering af sikkerhed.

NCT01242488: Resultaterne fra studiet er publiceret i 2014 [23]. Studiet er et randomiseret, dobbeltblindet, placebokontrolleret fase 2b-studie. Studiet sammenligner effekt og sikkerhed af olokizumab administreret s.c. i 12 uger til patienter med RA, som tidligere havde utilstrækkelig effekt af anti-TNF-terapi, med tocilizumab eller placebo. Patienterne blev randomiseret til 1 af 9 behandlingsarme: placebo, olokizumab (60, 120 eller 40 mg) q4w eller q2w, eller 8 mg/kg tocilizumab q4w. Effekt blev analyseret i randomiserede patienter, som fik mindst én dosis og havde mindst én vurdering af effekt. Sikkerhedsanalyser blev foretaget ved patienter, der fik mindst én eller delvis dosis.

Population

Populationerne i de to studier er præsenteret i tabellen nedenfor.

Der er kun opgivet den sarilumabstudiearm, der er relevant i vurderingen her, dvs. sarilumab 200 mg q2w. Tocilizumabdosis er i de beskrevne arme 8 mg/kg q4w.

Tabel 9. Studiepopulationer ved klinisk spørgsmål 2

	TARGET (NCT01709578)	**RADIATE (NCT00106522)**	**Olokizumab (NCT01242488)**
Tidspunkt for gennemførelse af studiet	2012-2015	2005-2007	2010-2012
Sygdomsvarighed i år (gennemsnit ± SD) (ved olokizumab: median)	12,0 ± 10,0 (Placebo + csDMARD) 12,7 ± 9,6 (Sarilumab + csDMARD)	11,4 ± 9,2 (Placebo + MTX) 12,6 ± 9,3 (Tocilizumab + MTX)	7,45 (Placebo + MTX) 10,55 (Tocilizumab + MTX)
Alder (gennemsnit ± SD)	51,9 ± 12,4 (Placebo + csDMARD) 52,9 ± 12,9 (Sarilumab + csDMARD)	53,4 ± 13,3 (Placebo + MTX) 53,9 ± 12,7 (Tocilizumab + MTX)	58,18 (Placebo + MTX) 56,58 (Tocilizumab + MTX)
% Kvinder	85,1 (Placebo + csDMARD) 82,1 (Sarilumab + csDMARD)	79 (Placebo + MTX) 84 (Tocilizumab + MTX)	77,3 (Placebo + MTX) 86,0 (Tocilizumab + MTX)
Hævede led (gennemsnit ± SD) (Ved olokizumab: median, min.-maks.)	20,2 ± 11,3 (Placebo + csDMARD) 20,0 ± 11,9 (Sarilumab + csDMARD)	18,9 ± 11,1 (Placebo + MTX) 18,9 ± 10,9 (Tocilizumab + MTX)	13,17 (4,0-44,7) (Placebo + MTX) 12,38 (6,0-32,0) (Tocilizumab + MTX)
DAS28-ESR (mean ± SD)	6,2 ± 0,9 (Placebo + csDMARD) 6,3 ± 1,0 (Sarilumab + csDMARD)	6,80 ± 1,06 (Placebo + MTX) 6,79 ± 0,93 (Tocilizumab + MTX)	5,69 (Placebo + MTX) 5,72 (Tocilizumab + MTX)

Fagudvalget finder, at der for de to studier ikke er nogen betydende forskelle i baselinekarakteristika mellem studiearmene. Fagudvalget vurderer, at patientkarakteristika i studierne ikke afviger væsentligt fra den danske patientpopulation, men fremhæver dog, at RA-patienter med 16-20 hævede led er sjældent forekommende i Danmark.

6.2.2 Resultater og vurdering

Resultater og vurdering af de effektmål, som fagudvalget har præspecificeret som hhv. kritiske og vigtige, følger nedenfor.

Mortalitet (kritisk)

En enkelt patient i placeboarmen af TARGET-studiet døde i studiets opfølgningstid, og det er dermed ikke muligt at vurdere, hvorvidt sarilumab har merværdi i forhold til tocilizumab (komparator) på dette effektmål.

American College of Rheumatology 50 % respons (ACR50) (kritisk)

Ansøger har ikke indleveret data på dette effektmål, hvorfor den kliniske merværdi kategoriseres som **ikkedokumenterbar.**

Behandlingsophør grundet uønskede hændelser (kritisk)

De anvendte data for dette effektmål er rapporteret efter 24 ugers opfølgningstid for sarilumab og tocilizumab.

Tabel 10. Vurdering af klinisk merværdi: Behandlingsophør grundet uønskede hændelser

	Forhåndsdefineret grundlag for vurdering		Resultater
Absolutte forskelle	5 procentpoint		5 procentpoint [3;30]
Relative forskelle	Stor merværdi	UL < 0,75	
	Vigtig merværdi	UL < 0,90	
	Lille merværdi	UL < 1,00	
	Ingen merværdi	UL > 1,00	0,54 [0,01;20,78]
	Negativ merværdi	LL > 1,00	
Evidensens kvalitet	Meget lav		

UL: Upper confidence limit (øvre konfidensgrænse)
LL: Lower confidence limit (nedre konfidensgrænse)
Første kolonne indeholder de i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen. Anden kolonne indeholder data fra ansøgning, som indgår i Medicinrådets vurdering.

Den absolutte forskel mellem sarilumab og komparator opnår netop den forhåndsdefinerede mindste klinisk relevante forskel og indikerer derfor en negativ merværdi. Estimatet for den relative forskel indikerer dog ingen merværdi, da øvre konfidensgrænse overstiger 1,00. Samlet vurderer fagudvalget, at sarilumab har **ingen klinisk merværdi** sammenlignet med tocilizumab vedrørende dette effektmål.

Behandlingsophør grundet manglende effekt (vigtig)

De anvendte data for dette effektmål er rapporteret efter 24 ugers opfølgningstid for sarilumab og tocilizumab.

Tabel 11. Vurdering af klinisk merværdi: Behandlingsophør grundet manglende effekt

	Forhåndsdefineret grundlag for vurdering		Resultater
Absolutte forskelle	10 procentpoint		-2 procentpoint [-2;30]
Relative forskelle	Stor merværdi	UL < 0,75	
	Vigtig merværdi	UL < 0,90	
	Lille merværdi	UL < 1,00	
	Ingen merværdi	UL > 1,00	2,04 [0,29;14,23]
	Negativ merværdi	LL > 1,00	
Evidensens kvalitet	Meget lav		

UL: Upper confidence limit (øvre konfidensgrænse)
LL: Lower confidence limit (nedre konfidensgrænse)
Første kolonne indeholder de i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen. Anden kolonne indeholder data fra ansøgning, som indgår i Medicinrådets vurdering.

Den absolutte forskel mellem sarilumab og komparator opnår ikke den forhåndsdefinerede mindste klinisk relevante forskel. Estimatet for den relative forskel indikerer ligeledes ingen merværdi, da øvre konfidensgrænse overstiger 1,00. Samlet har sarilumab **ingen klinisk merværdi** sammenlignet med tocilizumab vedrørende dette effektmål.

Alvorlige infektioner (vigtig)

De anvendte data for dette effektmål er rapporteret efter 24 ugers opfølgningstid for sarilumab og tocilizumab.

Tabel 12. Vurdering af klinisk merværdi: Alvorlige infektioner

	Forhåndsdefineret grundlag for vurdering		Resultater
Absolutte forskelle	10 procentpoint		-1 procentpoint [-4;24]
Relative forskelle	Stor merværdi	UL < 0,75	
	Vigtig merværdi	UL < 0,90	
	Lille merværdi	UL < 1,00	
	Ingen merværdi	UL > 1,00	0,67 [0,07;6,29]
	Negativ merværdi	LL > 1,00	
Evidensens kvalitet	Meget lav		

UL: Upper confidence limit (øvre konfidensgrænse)
LL: Lower confidence limit (nedre konfidensgrænse)
Første kolonne indeholder de i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen. Anden kolonne indeholder data fra ansøgning, som indgår i Medicinrådets vurdering.

Den absolutte forskel mellem sarilumab og komparator opnår ikke den forhåndsdefinerede mindste klinisk relevante forskel. Estimatet for den relative forskel indikerer ligeledes ingen merværdi, da øvre

konfidensgrænse overstiger 1,00. Samlet har sarilumab **ingen klinisk merværdi** sammenlignet med tocilizumab vedrørende alvorlige infektioner.

Total Sharp Score (TSS) (vigtig)

Ansøger har ikke indleveret data på dette effektmål, hvorfor den kliniske merværdi kategoriseres som **ikkedokumenterbar.**

Health Assessment Questionnaire Disability Index (HAQ-DI) (vigtig)

Ansøger har ikke indleveret data på dette effektmål, hvorfor den kliniske merværdi kategoriseres som **ikkedokumenterbar.**

6.2.3 Evidensens kvalitet

Evidensens kvalitet for klinisk spørgsmål 2 er samlet set vurderet som værende **meget lav**, da der nedgraderes ét niveau for "indirectness" (grundet indirekte sammenligninger) og to niveauer for "imprecision", da konfidensintervallerne for alle effektmål er så brede, at de både indeholder en positiv og en negativ merværdi.

6.2.4 Konklusion for klinisk spørgsmål 2

Fagudvalget vurderer, at sarilumab i kombination med csDMARD til bioerfarne patienter med RA har **ingen klinisk merværdi** sammenlignet med tocilizumab. Fagudvalget bemærker, at ansøger ikke har leveret data på et kritisk effektmål (ACR50) og to vigtige (TSS og HAQ-DI). Samlet vurderer fagudvalget, at sarilumab har ingen klinisk merværdi sammenlignet med tocilizumab.

Tabel 13. Oversigt over merværdi for kritiske og vigtige effektmål for klinisk spørgsmål 2.

Effektmål	Vigtighed	Merværdi
Mortalitet	Kritisk	Ikkedokumenterbar
American College of Rheumatology 50 % response, ACR50	Kritisk	Ikkedokumenterbar
Behandlingsophør grundet uønskede hændelser	Vigtig	Ingen
Behandlingsophør grundet manglende effekt	Vigtig	Ingen
Alvorlige infektioner	Vigtig	Ingen
Total Sharp Score, TSS	Vigtig	Ikkedokumenterbar
Health Assessment Questionnaire Disability Index, HAQ-DI	Vigtig	Ikkedokumenterbar
Samlet	**-**	**Ingen**

6.3 Konklusion klinisk spørgsmål 3

Hvilken klinisk merværdi tilbyder sarilumab sammenlignet med tocilizumab til bionaive patienter med moderat til svær RA, hvor behandling med csDMARDs ikke er en mulighed?

Fagudvalget vurderer, at sarilumab som monoterapi til bionaive patienter med RA har **ingen klinisk merværdi** sammenlignet med tocilizumab.

6.3.1 Gennemgang af studier

Ansøger identificerede ét klinisk studie omhandlende sarilumab og ét klinisk studie omhandlende tocilizumab til besvarelse af klinisk spørgsmål 3. Nedenfor følger en beskrivelse af studiekarakteristika.

Karakteristika

Sarilumab

MONARCH: Resultaterne fra MONARCH-studiet er publiceret i 2017 [24]. Studiet er et randomiseret, dobbeltblindet, double-dummy, aktivt kontrolleret fase 3 superiority forsøg, der vurderer effekt og sikkerhed af sarilumab monoterapi vs. adalimumab monoterapi ved patienter med RA. Patienterne var randomiseret centralt til enten at modtage sarilumab s.c. 200 mg q2w + placebo q2w eller adalimumab 40 s.c. 40 mg q2w + placebo i 24 uger. De patienter i sarilumabarmen, der ikke opnåede mindst 20 % bedring i ømme og hævede led ved uge 16, blev tilladt at modtage en dosis adalimumab eller matchende placebo. Effektanalyser i ITT-populationen bestod af alle randomiserede patienter, dvs. også patienter med øget dosis efter uge 16.

Tocilizumab

ADACTA: Resultaterne fra ADACTA-studiet er publiceret i 2013 [25]. Studiet er et multicenter, randomiseret, blindet fase 4-studie. Patienterne blev randomiseret i forholdet 1:1 til tocilizumab 8 mg/kg q4w plus placebo eller adalimumab 40 mg q2w plus placebo. Patienter, der ikke opnåede mindst 20 % forbedring i hævede led og ømme led ved uge 16, blev tilbudt en anden behandling. Sikkerhedspopulation inkluderer alle patienter, der fik mindst én dosis tocilizumab eller adalimumab og havde mindst én vurdering af sikkerhed. Effektanalyser blev foretaget på data fra patienter, der fik mindst én dosis tocilizumab eller adalimumab og havde mindst én vurdering af effekt.

Population

Populationerne i de to studier er præsenteret i tabellen nedenfor.

Tabel 14. Studiepopulationer ved klinisk spørgsmål 3

	MONARCH (NCT02332590)	**ADACTA (NCT01119859)**
Tidspunkt for gennemførelse af studiet	2015-2020 (forventet)	2010-2012
Sygdomsvarighed i år (gennemsnit ± SD)	6,6 ± 7,8 (Adalimumab) 8,1 ± 8,1 (Sarilumab)	7,3 ± 8,1 (Tocilizumab) 6,3 ± 6,9 (Adalimumab)
Alder (gennemsnit ± SD)	53,6 ± 11,9 (Adalimumab) 50,9 ± 12,6 (Sarilumab)	54,4 ± 13,0 (Tocilizumab) 53,3 ± 12,4 (Adalimumab)
% Kvinder	81,1 (Adalimumab) 85,3 (Sarilumab)	79,1 (Tocilizumab) 82,1 (Adalimumab)
Hævede led (gennemsnit ± SD)	17,5 ± 10,3 (Adalimumab) 18,6 ± 10,7 (Sarilumab)	11,3 ± 5,3 (Tocilizumab) 12,4 ± 5,4 (Adalimumab)
DAS28-ESR (mean ± SD)	6,8 ± 0,8 (Adalimumab) 6,8 ± 0,8 (Sarilumab)	6,7 ± 0,9 (Tocilizumab) 6,8 ± 0,9 (Adalimumab)

Fagudvalget finder, at der for de to studier ikke er nogen betydende forskelle i baselinekarakteristika mellem studiearmene. Fagudvalget vurderer, at patientkarakteristika i studierne ikke afviger væsentligt fra den danske patientpopulation, men fremhæver dog at RA-patienter med 16-20 hævede led er sjældent forekommende i Danmark.

6.3.2 Resultater og vurdering

Resultater og vurdering af de effektmål, som fagudvalget har præspecificeret som hhv. kritiske og vigtige, følger nedenfor.

Mortalitet (kritisk)

I MONARCH-studiet omkom én patient i sarilumabgruppen. Dødsårsagen (aortadissektion) var ikke relatereret til behandlingen. I ADACTA-studiet omkom to patienter i tocilizumabgruppen. Det ene dødsfald var muligvis relateret til behandlingen, men dødsårsagen var ukendt.

American College of Rheumatology 50 % respons (ACR50) (kritisk)

De anvendte data for dette effektmål er rapporteret efter 24 ugers opfølgningstid for sarilumab og tocilizumab.

Tabel 15. Vurdering af klinisk merværdi: ACR50

	Forhåndsdefineret grundlag for vurdering		Resultater
Absolutte forskelle	15 procentpoint		-5 procentpoint [-19;17]
Relative forskelle	Stor merværdi	LL > 1,33	
	Vigtig merværdi	LL > 1,11	
	Lille merværdi	LL > 1,00	
	Ingen merværdi	LL < 1,00	0,90 [0,60;1,35]
	Negativ merværdi	UL < 1,00	
Evidensens kvalitet	Meget lav		

UL: Upper confidence limit (øvre konfidensgrænse)
LL: Lower confidence limit (nedre konfidensgrænse)
Første kolonne indeholder de i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen. Anden kolonne indeholder data fra ansøgning, som indgår i Medicinrådets vurdering.

Den absolutte forskel mellem sarilumab og komparator er mindre end den forhåndsdefinerede mindste klinisk relevante forskel. Tilsvarende indikerer estimatet for den relative forskel ingen merværdi, da konfidensintervallet inkluderer 1,00. Samlet har sarilumab **ingen klinisk merværdi** sammenlignet med tocilizumab vedrørende det kritiske effektmål ACR50.

Behandlingsophør grundet uønskede hændelser (kritisk)

De anvendte data for dette effektmål er rapporteret efter 52 ugers opfølgningstid for sarilumab og tocilizumab.

Tabel 16. Vurdering af klinisk merværdi: Behandlingsopgør grundet uønskede hændelser

	Forhåndsdefineret grundlag for vurdering		Resultater
Absolutte forskelle	5 procentpoint		0 procentpoint [-4;11]
Relative forskelle	Stor merværdi	UL < 0,75	
	Vigtig merværdi	UL < 0,90	
	Lille merværdi	UL < 1,00	
	Ingen merværdi	UL > 1,00	0,94 [0,29;3,03]
	Negativ merværdi	LL > 1,00	
Evidensens kvalitet	Meget lav		

UL: Upper confidence limit (øvre konfidensgrænse)
LL: Lower confidence limit (nedre konfidensgrænse)
Første kolonne indeholder de i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen. Anden kolonne indeholder data fra ansøgning, som indgår i Medicinrådets vurdering.

Både absolutte og relative effektmål indikerer, at sarilumab har **ingen klinisk merværdi** i forhold til tocilizumab vedrørende dette effektmål.

Behandlingsophør grundet manglende effekt (vigtig)

De anvendte data for dette effektmål er rapporteret efter 52 ugers opfølgningstid for sarilumab og tocilizumab.

Tabel 17. Vurdering af klinisk merværdi: Behandlingsopgør grundet manglende effekt

	Forhåndsdefineret grundlag for vurdering		Resultater
Absolutte forskelle	10 procentpoint		0 procentpoint [-4;25]
Relative forskelle	Stor merværdi	UL < 0,75	
	Vigtig merværdi	UL < 0,90	
	Lille merværdi	UL < 1,00	
	Ingen merværdi	UL > 1,00	1,00 [0,15;6,70]
	Negativ merværdi	LL > 1,00	
Evidensens kvalitet	Meget lav		

UL: Upper confidence limit (øvre konfidensgrænse)
LL: Lower confidence limit (nedre konfidensgrænse)
Første kolonne indeholder de i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen. Anden kolonne indeholder data fra ansøgning, som indgår i Medicinrådets vurdering.

Både absolutte og relative effektmål indikerer, at sarilumab har **ingen klinisk merværdi** i forhold til tocilizumab vedrørende dette effektmål.

Alvorlige infektioner (vigtig)

De anvendte data for dette effektmål er rapporteret efter 24 ugers opfølgningstid for sarilumab og tocilizumab.

Tabel 17. Vurdering af klinisk merværdi: Alvorlige infektioner

	Forhåndsdefineret grundlag for vurdering		Resultater
Absolutte forskelle	10 procentpoint		1 procentpoint [-3;36]
Relative forskelle	Stor merværdi	UL < 0,75	
	Vigtig merværdi	UL < 0,90	
	Lille merværdi	UL < 1,00	
	Ingen merværdi	UL > 1,00	1,17 [0,17;10,77]
	Negativ merværdi	LL > 1,00	
Evidensens kvalitet	Meget lav		

UL: Upper confidence limt (øvre konfidensgrænse)
LL: Lower confidence limit (nedre konfidensgrænse)
Første kolonne indeholder de i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen. Anden kolonne indeholder data fra ansøgning, som indgår i Medicinrådets vurdering.

Den absolutte forskel mellem sarilumab og komparator er mindre end den forhåndsdefinerede mindste klinisk relevante forskel. Tilsvarende indikerer estimatet for den relative forskel ingen merværdi, da konfidensintervallet inkluderer 1,00. Samlet har sarilumab **ingen klinisk merværdi** sammenlignet med tocilizumab vedrørende alvorlige infektioner.

Total Sharp Score (TSS) (vigtig)

Ansøger har ikke indleveret data på dette effektmål, hvorfor den kliniske merværdi kategoriseres som **ikkedokumenterbar.**

Health Assessment Questionnaire Disability Index (HAQ-DI) (vigtig)

De anvendte data for dette effektmål er rapporteret efter 24 ugers opfølgningstid for sarilumab og tocilizumab.

Tabel 18. Vurdering af klinisk merværdi: HAQ-DI

	Forhåndsdefineret grundlag for vurdering		Resultater
Absolutte forskelle	15 procentpoint		7 procentpoint [-7;27]
Relative forskelle	Stor merværdi	LL > 1,33	
	Vigtig merværdi	LL > 1,11	
	Lille merværdi	LL > 1,00	
	Ingen merværdi	LL < 1,00	1,13 [0,87;1,47]
	Negativ merværdi	UL < 1,00	
Evidensens kvalitet	Meget lav		

UL: Upper confidence limit (øvre konfidensgrænse)
LL: Lower confidence limit (nedre konfidensgrænse)
Første kolonne indeholder de i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen. Anden kolonne indeholder data fra ansøgning, som indgår i Medicinrådets vurdering.

Den absolutte forskel mellem sarilumab og komparator er mindre end den forhåndsdefinerede mindste klinisk relevante forskel. Tilsvarende indikerer estimatet for den relative forskel ingen merværdi, da konfidensintervallet inkluderer 1,00. Samlet har sarilumab **ingen klinisk merværdi** sammenlignet med tocilizumab vedrørende HAQ-DI.

6.3.3 Evidensens kvalitet

Evidensens kvalitet for klinisk spørgsmål 1 er samlet set vurderet som værende **meget lav**, da der nedgraderes for "indirectness" (grundet indirekte sammenligninger) og to niveauer for "imprecision", da konfidensintervallerne for alle effektmål er så brede, at de både indeholder en positiv og en negativ merværdi.

6.3.4 Konklusion for klinisk spørgsmål 3

Fagudvalget vurderer, at sarilumab som monoterapi til bionaive patienter med RA har ingen klinisk merværdi sammenlignet med tocilizumab. Fagudvalget lægger vægt på, at merværdikategorierne for de enkelte effektmål ikke peger entydigt i én retning. Fagudvalget bemærker derudover, at ansøger ikke har leveret data på det vigtige effektmål "TSS".

Fagudvalget er bekymret for det eksisterende evidensgrundlag, men er bekendt med resultaterne fra et direkte sammenlignende studie mellem sarilumab og adalimumab (TNF-hæmmer) i monoterapi, som indgår i ansøgningen [24]. Studiet viser overordnet, at sarilumab har god effekt sammenlignet med adalimumab på blandt andet ACR50 og en sammenlignelig bivirkningsprofil. Adalimumab og tocilizumab er ligestillet i den nuværende RADS-behandlingsvejledning for RA. Studiet supplerer således de eksisterende data og underbygger fagudvalgets vurdering af sarilumab sammenlignet med tocilizumab.

På baggrund af ovenstående vurderer fagudvalget, at sarilumab har ingen klinisk merværdi sammenlignet med tocilizumab.

Tabel 19. Oversigt over merværdi for kritiske og vigtige effektmål for klinisk spørgsmål 3.

Effektmål	Vigtighed	Merværdi
Mortalitet	Kritisk	Ikkedokumenterbar
American College of Rheumatology 50 % response, ACR50	Kritisk	Ingen
Behandlingsophør grundet uønskede hændelser	Vigtig	Ingen
Behandlingsophør grundet manglende effekt	Vigtig	Ingen
Alvorlige infektioner	Vigtig	Ingen
Total Sharp Score, TSS	Vigtig	Ikkedokumenterbar
Health Assessment Questionnaire Disability Index, HAQ-DI	Vigtig	Ingen
Samlet	**-**	**Ingen**

6.4 Konklusion klinisk spørgsmål 4

Hvilken klinisk merværdi tilbyder sarilumab sammenlignet med tocilizumab til patienter med moderat til svær RA, som skal skifte biologisk eller targeteret syntetisk behandling, og hvor behandling med csDMARDs ikke er en mulighed?

Fagudvalget vurderer, at sarilumab som monoterapi til patienter med RA, som skal skifte behandling, har **ingen klinisk merværdi** sammenlignet med tocilizumab.

6.4.1 Gennemgang af studier

Der foreligger ikke kliniske studier af denne population.

6.4.2 Resultater og vurdering

Ansøger har vedlagt en post hoc-analyse fra ONE-studiet, der endnu ikke er publiceret, men hvis primære resultater dog indgår i EPAR'en for sarilumab [13] . Analysen sammenligner de 38 patienter, som var bioerfarne, med den øvrige studiepopulation. Studiet havde ikke styrke til at danne grundlag for denne analyse, så sikre konklusioner kan ikke drages. Nedenfor er indsat en tabel over effekten af sarilumab i de to populationer.

Tabel 20. Effekt af sarilumab i post hoc-analyse

Effektmål	ONE - bionaive N = 94	ONE - bioerfarne N = 38	Mindste klinisk relevante forskel
Mortalitet	0	0	
ACR50	53 %	50 %	15 procentpoint
Behandlingsophør grundet bivirkninger	5 %	13 %	5 procentpoint
Behandlingsophør grundet manglende effekt	-	-	10 procentpoint
Alvorlige infektioner	0 %	0 %	5 procentpoint
HAQ-DI; ændring ≥ 0,22	71 %	61 %	15 procentpoint

Baseret på den tilgængelige dokumentation er det ikke muligt at tildele sarilumab en klinisk merværdi på dette spørgsmål. Fagudvalget vurderer dog, at der ikke er noget, der taler for, at den kliniske merværdi af

sarilumab versus tocilizumab til bioerfarne patienter adskiller sig fra merværdien til bionaive patienter (klinisk spørgsmål 3). Derfor mener fagudvalget, baseret på en klinisk vurdering, at sarilumab har **ingen klinisk merværdi** for denne population.

6.4.3 Evidensens kvalitet

Da der ikke foreligger kliniske studier foruden den upublicerede post hoc-analyse, og fagudvalgets kategorisering er baseret på en klinisk vurdering, kan evidensens kvalitet ikke vurderes for klinisk spørgsmål 4.

6.4.4 Konklusion for klinisk spørgsmål 4

Fagudvalget vurderer, at sarilumab som monoterapi til patienter med RA, som skal skifte behandling, giver **ingen klinisk merværdi** sammenlignet med tocilizumab (evidensens kvalitet kan ikke vurderes).

7 Andre overvejelser

Fagudvalget kunne have ønsket et bedre evidensgrundlag end det tilgængelige. Ansøger har ikke kunnet levere data på flere effektmål, heriblandt ACR50 (kritisk) for klinisk spørgsmål 1, og alle resultater er baseret på indirekte sammenligninger. Det ringe evidensgrundlag skyldes til dels den valgte komparator, som ifølge Medicinrådets proces for vurdering af lægemidler, der ikke har klinisk merværdi, er valgt af ansøger.

Fagudvalget har derfor ikke stor tiltro til evidensen, men lægger vægt på at sarilumab og tocilizumab har samme virkningsmekanisme (IL-6 hæmmer) og må forventes at have lignende effekt i en direkte sammenligning. Derudover bemærker fagudvalget, at der findes en direkte sammenligning mellem sarilumab og adalimumab i monoterapi, og at sarilumab viser god effekt og sikkerhed i dette studie. Adalimumab er ligestillet med tocilizumab i den gældende lægemiddelrekommandation.

På trods af den dårlige evidens mener fagudvalget derfor at kunne vurdere den kliniske merværdi af sarilumab sammenlignet med tocilizumab som følger.

8 Fagudvalgets vurdering af samlet klinisk merværdi og samlet evidensniveau

Fagudvalget vurderer, at sarilumab til patienter med moderat til svær reumatoid artrit der har utilstrækkelig effekt/ikke tolereret behandling med csDMARDs har:

- **Ingen klinisk merværdi** sammenlignet med tocilizumab i kombination med csDMARD til bionaive patienter med moderat til svær RA.
- **Ingen klinisk merværdi** sammenlignet med tocilizumab i kombination med csDMARD til patienter med moderat til svær RA, der skal skifte biologisk eller targeteret syntetisk behandling.
- **Ingen klinisk merværdi** sammenlignet med tocilizumab til bionaive patienter med moderat til svær RA, hvor behandling med csDMARDs ikke er en mulighed.
- **Ingen klinisk merværdi** sammenlignet med tocilizumab til patienter med moderat til svær RA, som skal skifte biologisk eller targeteret syntetisk behandling, og hvor behandling med csDMARDs ikke er en mulighed.

Evidensens kvalitet vurderes for klinisk spørgsmål 1-3 at være meget lav, og kan for klinisk spørgsmål 4 ikke vurderes.

9 Rådets vurdering af samlet klinisk merværdi og samlet evidensniveau

Medicinrådet vurderer, at sarilumab til patienter med moderat til svær reumatoid artrit der har utilstrækkelig effekt/ikke tolereret behandling med csDMARDs har:

- **Ingen klinisk merværdi** sammenlignet med tocilizumab i kombination med csDMARD til bionaive patienter med moderat til svær RA.
- **Ingen klinisk merværdi** sammenlignet med tocilizumab i kombination med csDMARD til patienter med moderat til svær RA, der skal skifte biologisk eller targeteret syntetisk behandling.
- **Ingen klinisk merværdi** sammenlignet med tocilizumab til bionaive patienter med moderat til svær RA, hvor behandling med csDMARDs ikke er en mulighed.
- **Ingen klinisk merværdi** sammenlignet med tocilizumab til patienter med moderat til svær RA, som skal skifte biologisk eller targeteret syntetisk behandling, og hvor behandling med csDMARDs ikke er en mulighed.

Evidensens kvalitet vurderes for klinisk spørgsmål 1-3 at være meget lav og kan for klinisk spørgsmål 4 ikke vurderes.

10 Relation til eksisterende behandlingsvejledning

Medicinrådet har besluttet at udarbejde en fælles regional behandlingsvejledning for terapiområdet reumatoid artrit. Her vil man bl.a. tage stilling til, hvilken plads sarilumab har i forhold til andre lægemidler til behandling af sygdommen. Behandlingsvejledningen forventes godkendt i efteråret 2018.

Indtil behandlingsvejledningen foreligger, vurderer fagudvalget, at det vil være hensigtsmæssigt at benytte tocilizumab før sarilumab, da den kliniske erfaring med dette lægemiddel er større.

Medicinrådet anbefaler, at regionerne, indtil den fælles regionale behandlingsvejledning er godkendt, vælger det lægemiddel, der er forbundet med de laveste omkostninger.

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12 Bilag 1: Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende gigtsygdomme

Formand	*Indstillet af*
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Application for the assessment of clinically added value of Kevzara for rheumatoid arthritis

Contents

1 Basic information

TABLE 1-1 CONTACT INFORMATION

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TABLE 1-2 OVERVIEW OF THE PHARMACEUTICAL

Proprietary name	Kevzara®
Generic name	sarilumab
Marketing authorization holder in Denmark	sanofi-aventis groupe, 54 rue La Boétie, 75008 Paris, France
ATC code	L04AC14
Pharmacotherapeutic group	L Antineoplastic and immunomodulating agents L04 Immunosuppressants L04AC Interleukin inhibitors
Active substance	Sarilumab, a recombinant human monoclonal antibody of the IgG1 isotype that with high affinity binds both membranous bound and soluble forms of the IL-6Rα
Pharmaceutical form	Solution for injection
Mechanism of action	Sarilumab binds specifically to both soluble and membrane-bound interleukin(IL)-6 receptors (sIL-6Rα and mIL-6Rα) and inhibits IL-6-mediated signaling. IL-6 is a pleiotropic cytokine that stimulates diverse cellular responses such as proliferation, differentiation, survival and apoptosis and can activate hepatocytes to release acute-phase proteins, C-reactive protein (CRP) and serum amyloid A. Elevated levels of IL-6 are found in the synovial fluid of patients with rheumatoid arthritis (RA) and play an important role in both the pathologic inflammation and joint destruction that are hallmarks of RA [1].
Dosage regimen	The recommended dose is 200 mg once every 2 weeks (q2w) administered as a subcutaneous (SC) injection. Reduction of the dose to 150 mg q2w is recommended for management of neutropenia, thrombocytopenia and liver enzyme elevations. The injection can be self-administered using a single-dose pre-filled pen or syringe. Kevzara is stable out of the refrigerator for 14 days and should not be stored above 25 °C.
Therapeutic indication relevant for assessment (as	Kevzara in combination with methotrexate (MTX) is indicated for the treatment of moderately to severely active RA in adult patients who have responded inadequately to, or who are intolerant to one or more disease modifying anti

defined by the European Medicines Agency, EMA)	rheumatic drugs (DMARDs). Kevzara can be given as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate.
Other approved therapeutic indications	None
Will dispensing be restricted to hospitals?	Yes, expected to be restricted to hospitals
Combination therapy and/or co-medication	In combination with MTX or as monotherapy
Packaging – types, sizes/number of units, and concentrations	Kevzara is available as 200 mg and 150 mg pre-filled pen and as 200 mg pre-filled syringe.
Orphan drug designation	No

2 Abbreviations

ACR20	20% improvement in American College of Rheumatology (ACR) criteria
ACR50	50% improvement in American College of Rheumatology (ACR) criteria
ACR70	70% improvement in American College of Rheumatology (ACR) criteria
AE	Adverse event
bDMARD	Biological DMARD
CCP	Cyclic citrullinated peptide
CI	Confidence interval
COX2	Cyclooxygenase-2
CRP	C-reactive protein
csDMARD	Conventional synthetic DMRARD
DAS28	Disease Activity Score in 28 joints
DMARD	Disease-modifying antirheumatic drug
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FACIT-F	Functional assessment of chronic illness therapy-fatigue
HAQ-DI	The disability index (DI) of the Health Assessment Questionnaire (HAQ)
hsCRP	High-sensitivity C-reactive protein
IL	Interleukin
ITT	Intention-to-treat
IV	Intravenous(ly)
LOCF	Last observation carried forward
MCID	Minimal clinically important difference
MTX	Methotrexate
NSAID	Nonsteroidal anti-inflammatory drug
PRO	Patient reported outcome
qw	Once weekly
q2w	Once every 2 weeks
q4w	Once every 4 weeks
RA	Rheumatoid arthritis
RF	Rheumatoid factor

SC	Subcutaneous(ly)
SF-36	Short form-36
SJC	Swollen joint count
SHS	Modified Sharp/van der Heijde score
TJC	Tender joint count
tsDMARD	Targeted synthetic DMARD
TNF	Tumor necrosis factor
TSS	Total Sharp Score
VAS	Visual analogue scale
vs	Versus

3 Summary

Sarilumab, the active substance of Kevzara, is a recombinant human monoclonal antibody of the IgG1 isotype that with very high affinity binds both membranous bound and soluble forms of the IL-6Rα and thereby inhibits IL-6-mediated signaling. Kevzara in combination with MTX is indicated for the treatment of moderately to severely active RA in adult patients who have responded inadequately to, or who are intolerant to one or more DMARDs. Kevzara can be given as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate. In clinical practice in Denmark, the patient population defined in the approved EMA indication consists of 4 populations: bio-naïve patients and bio-experienced patients, and with Kevzara used either as monotherapy or in combination with MTX.

The systematic literature search for this application identified 4 sarilumab publications and 8 tocilizumab publications, which were included. In addition, 3 relevant sarilumab studies, which remains to be published, were identified in the EPAR for Kevzara.

In both bio-naïve and bio-experienced patients treated with sarilumab in combination with csDMARDs, the absolute differences between sarilumab and placebo groups were clinically relevant (i.e., above the MCID) and statistically significant for the efficacy outcomes ACR50 and HAQ-DI. In one trial, treatment discontinuation due to AEs in the sarilumab groups was clinically relevant and statistically significantly larger than for placebo.

In the comparative analyses of sarilumab vs tocilizumab performed for bio-naïve patients treated with combination therapy, the effect ratios for TSS and HAQ-DI were 1.21 and 1.53, respectively, in favour of sarilumab, with the absolute differences in responder rates between the sarilumab and tocilizumab groups being clinically relevant. Treatment discontinuation due to lack of effect was statistically significantly higher with sarilumab compared to tocilizumab, however, the difference was not clinically relevant. No other clinically relevant or statistically significant differences were found between sarilumab and tocilizumab.

For bio-experienced patients treated with combination therapy, the absolute difference between sarilumab and tocilizumab reached the MCID of 5% for discontinuations due to AE in the comparative analysis, but the difference was not statistically significant. No other clinically relevant or statistically significant differences were found in this population.

For bio-naïve patients treated with monotherapy, no clinically relevant or statistically significant differences between sarilumab and tocilizumab were found in the comparative analyses for any of the safety or efficacy outcomes.

Treatment with sarilumab monotherapy in bio-experienced patients was assessed based on a subgroup analysis of a currently unpublished safety study. The available data indicate that the efficacy and safety outcomes are comparable to those observed with monotherapy in bio-naïve patients. This is further supported by subgroup analyses of sarilumab therapy in combination with csDMARDs where no differences between bio-naïve and bio-experienced patients have been reported. A recent publication from a pan-European register collaboration, confirms the clinical utility of IL-6 inhibition in bDMARD exposed patients.

The long-term efficacy of sarilumab has been demonstrated in patients treated with sarilumab in combination with csDMARDs where the proportion of patients with ACR50 response was maintained for up to 5 years and the proportion with no radiographic progression (TSS) was maintained for up to 3 years.

Thus, based on the available data, the efficacy and safety profile of sarilumab is comparable to that of tocilizumab in both bio-naïve and bio-experienced patients and both in combination with MTX and when used as monotherapy. The main differences between Kevzara and subcutaneous RoActemra are the dosing frequency, out of fridge stability, and availability of dose strengths and administration devices.

Overall, across the four populations relevant for clinical practice in Denmark, no added clinical value of Kevzara compared to RoActemra has been found.

4 Literature search

A systematic literature search was performed in PubMed and in Cochrane Library by two independent researchers. The inclusion and exclusion criteria for the search and selection are provided in Table 7-1 and the databases and search strategy are summarized in Table 7-2. A total of 87 references were identified in PubMed and 374 in Cochrane Library. After removal of conference abstracts and duplicate results, 148 references were left. The identified literature was screened and assessed by two independent researchers based on the PICOs (patients, intervention, comparator, outcomes) described in the assessment protocol for Kevzara and additional defined inclusion and exclusion criteria (Table 7-1). Based on review on the title and abstract level, 126 references were excluded. For 1 reference, the full-text could not be retrieved, and the article was excluded. However, since the article was based on the 1-year data from the LITHE study, the data was most likely published elsewhere. Full-text screening was performed for 20 publications, of which 8 were excluded based on the full-text read. A Prisma flow diagram of the selection process is provided in Figure 7-1. A complete list of references excluded after full-text screening, including the reasons for excluding each reference, is provided in Table 7-3. No disagreements were noted during the search and selection process.

Based on a request from the Danish Medicines Council to use the Cochrane RCT filter instead of publication type to filter for randomized controlled trials, an updated PubMed search was performed on 28 May 2018. The search found 193 references in addition to the 87 references originally identified (see Table 7-2). These were screened by two independent researchers using the same criteria as described above. All 193 references were excluded based on title and abstract and no disagreements were noted during the search and selection process. A Prisma flow diagram for the additional search is available in Figure 7-2.

After selection of relevant articles, data were extracted into a project-specific Microsoft Excel table by one researcher and a second researcher independently checked the data extraction for accuracy and completeness. Any disagreements were resolved by consensus. Data were only extracted for outcomes where the absolute numbers of patients (responders and total population) were reported. If only the proportion of responders were reported, and it was either model based or it was not possible to determine

the total number of subjects used as the denominator, the outcome (or in one case the entire publication) was excluded.

In addition to the articles found with the described search strategy, EMA's scientific assessment reports (EPARs) were retrieved for both sarilumab [1] and tocilizumab [2,3].

Five additional sarilumab studies were identified in the EPAR for Kevzara. The reason for excluding data from these studies from this application are summarized in Table 4-1.

TABLE 4-1 EXCLUDED SARILUMAB STUDIES

Trial name	NCT number	Reason for exclusion
Single-dose study to describe the pharmacodynamics (PD) and safety of sarilumab (REGN88/SAR153191) and tocilizumab in adults with rheumatoid arthritis (RA) (6R88-RA-1309)	02097524	The study was a phase 1, single-dose, open-label study with the main purpose to describe the pharmacodynamic effects, safety and pharmacokinetics of a single dose of sarilumab. Tocilizumab was included as comparator arm.
A multicenter, randomized, open-label, parallel-group usability study of the sarilumab auto-injector device and a prefilled syringe in patients with moderate to severe active rheumatoid arthritis who are candidates for anti-IL6R therapy (EASY)	02057250	The study was an uncontrolled, open-label, phase 3 trial testing 2 different devices (auto-injector device and pre-filled syringe) for delivery of sarilumab.
An open-label, randomized, parallel group study assessing the immunogenicity and safety of sarilumab administered as monotherapy in patients with active rheumatoid arthritis (ONE)	02121210	The study was an uncontrolled, open-label, phase 3 trial testing 2 different doses of sarilumab as monotherapy with the main objective to assess the immunogenicity of sarilumab. Since a subgroup of the study population had prior bDMARD use, the results of a *post-hoc* subgroup analysis are relevant for clinical question 3.4 and thus described narratively in section 5.5
A randomized, double-blind, double-dummy study assessing the safety and tolerability of sarilumab and tocilizumab in patients with rheumatoid arthritis who are inadequate responders to or intolerant of TNF antagonists (ASCERTAIN)	01768572	The study is unpublished and no data is available in the EPAR. However, since the data are relevant for clinical question 3.2, the overall conclusions of the study are mentioned narratively in section 5.3
A multi-center, uncontrolled extension study evaluating efficacy and safety of SAR153191 in patients with active rheumatoid arthritis (RA) (EXTEND)	01146652	Data available in the EPAR and in a recent publication is presented in section 5.6 in order to describe the long-term efficacy and safety of sarilumab to the extent possible.

4.1 Relevant studies

The relevant studies included in this application for the assessment of each clinical question, as defined in the assessment protocol, are listed in Table 4-2.

TABLE 4-2 RELEVANT STUDIES INCLUDED IN THE ASSESSMENT

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question[1]
Sarilumab studies				
Sarilumab, a fully human monoclonal antibody against IL-6Rα in patients with rheumatoid arthritis and an inadequate response to methotrexate: efficacy and safety results from the randomised SARIL-RA-MOBILITY Part A trial. Huizinga TW et al. Ann Rheum Dis. 2014 [4]	A randomized, double-blind, placebo-controlled, multicenter, two-part, dose ranging and confirmatory study with an operationally seamless design, evaluating efficacy and safety of SAR153191 on top of methotrexate (MTX) in patients with active rheumatoid arthritis who are inadequate responders to MTX therapy (MOBILITY Part A)	01061736	March 2010 to May 2011	3.1
Sarilumab plus methotrexate in patients with active rheumatoid arthritis and inadequate response to methotrexate: results of a phase III study. Genovese MC et al. Arthritis Rheumatol. 2015 [5]	A randomized, double-blind, placebo-controlled, multicenter, two-part, dose ranging and confirmatory study with an operationally seamless design, evaluating efficacy and safety of SAR153191 on top of methotrexate (MTX) in patients with active rheumatoid arthritis who are inadequate responders to MTX therapy (MOBILITY Part B)	01061736	07-Mar-2011 to 08-Oct-2013 (first patient in to last patient out)	3.1
Sarilumab and nonbiologic disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis and inadequate response or intolerance to tumor necrosis factor inhibitors. Fleischmann R et al. Arthritis Rheumatol. 2017 [6]	A randomized, double-blind, parallel, placebo-controlled study assessing the efficacy and safety of sarilumab added to non-biologic DMARD therapy in patients with rheumatoid arthritis who are inadequate responders to or intolerant of TNF-α antagonists (TARGET)	01709578	October 2012 to March 2015 (first patient in to last patient out)	3.2
Efficacy and safety of sarilumab monotherapy versus adalimumab monotherapy for the treatment of patients with active rheumatoid arthritis (MONARCH): a randomised, double-blind, parallel-group phase III trial. Burmester GR et al. Ann Rheum Dis. 2017 [7]	A randomized, double-blind, parallel-group study assessing the efficacy and safety of sarilumab monotherapy versus adalimumab monotherapy in patients with rheumatoid arthritis (MONARCH)	02332590	11-Feb-2015 to 20-Jan-2016 (first patient in to last patient treated)	3.3

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question[1]
Tocilizumab studies				
Double-blind randomized controlled clinical trial of the interleukin-6 receptor antagonist, tocilizumab, in European patients with rheumatoid arthritis who had an incomplete response to methotrexate. Maini RN et al. Arthritis Rheum. 2006 [8]	The Chugai humanized anti-human recombinant interleukin-6 monoclonal antibody (CHARISMA) study	Not available	14-May-2001 to 03-Sep-2002 (first patient in to last patient out)	3.1
Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. Smolen JS et al. Lancet. 2008 [9]	A randomized, double-blind study of safety and reduction in signs and symptoms during treatment with tocilizumab versus placebo, in combination with methotrexate, in patients with moderate to severe rheumatoid arthritis (OPTION)	00106548	16-Feb-2005 to 13-Nov-2006 (first patient in to last patient out)	3.1
Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: the tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. Genovese MC et al. Arthritis Rheum. 2008 [10]	A randomized, double-blind study of the effect of tocilizumab on reduction in signs and symptoms in patients with moderate to severe active rheumatoid arthritis and inadequate response to DMARD therapy (TOWARD)	00106574	24-Mar-2005 to Feb-2007 (first patient in to last patient out [estimated from last patient in])	3.1
Efficacy of tocilizumab in patients with moderate to severe active rheumatoid arthritis and a previous inadequate response to disease-modifying antirheumatic drugs: the ROSE study. Yazici Y et al. Ann Rheum Dis. 2012 [11]	A randomized, double-blind, parallel-group study to evaluate the safety and efficacy of tocilizumab versus placebo in combination with DMARDs in patients with moderate to severe active rheumatoid arthritis (ROSE)	00531817	October 2007 to March 2011 (dates from clinicaltrials.gov)	3.1
Tocilizumab inhibits structural joint damage in rheumatoid arthritis patients with inadequate responses to methotrexate: results from the double-blind treatment phase of a randomized placebo-controlled trial of tocilizumab safety and prevention of structural joint damage at one year. Kremer JM et al. Arthritis Rheum. 2011 [12]	A randomized, double-blind study of safety and prevention of structural joint damage during treatment with tocilizumab versus placebo, in combination with methotrexate, in patients with moderate to severe rheumatoid arthritis (LITHE)	00106535	December 2004 to February 2008 (collection of 1-year data in study)	3.1

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question[1]
IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. Emery P et al. Ann Rheum Dis. 2008 [13]	A randomized, double-blind study of safety and reduction in signs and symptoms during treatment with tocilizumab versus placebo, in combination with methotrexate, in patients with moderate to severe active rheumatoid arthritis and inadequate response to anti-TNF therapy (RADIATE)	00106522	May 2005 to November 2007 (dates from clinicaltrials.gov)	3.2
Efficacy and safety of olokizumab in patients with rheumatoid arthritis with an inadequate response to TNF inhibitor therapy: outcomes of a randomised Phase IIb study. Genovese MC et al. Ann Rheum Dis. 2014. [14]	Randomized, double-blind, placebo-controlled, dose ranging study with an active comparator to evaluate the efficacy and safety of CDP6038 administered subcutaneously for 12 weeks to subjects with rheumatoid arthritis having previously failed TNF-blocker therapy	01242488	November 2010 to June 2012	3.2[2]
Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial. Gabay C et al. Lancet. 2013 [15]	A multi-center, randomized, blinded, parallel-group study of the reduction of signs and symptoms during monotherapy treatment with tocilizumab 8 mg/kg intravenously versus adalimumab 40 mg subcutaneously in patients with rheumatoid arthritis (ADACTA)	01119859	19-May-2010 to 21-Jun-2011 (enrolment)	3.3

[1]multiple clinical questions are defined in the assessment protocol. The numbers refer to the section number in the protocol.

[2]tocilizumab was used as a comparator in this study, and data for the tocilizumab and placebo arms are extracted for this application

4.2 Main characteristics of included studies

All included studies were randomized, placebo-controlled, double-blind studies. The main characteristics of each of the studies are summarized in appendix 7.2. The following tables are provided:

5 Clinical questions

Section 5.1 summarizes the outcomes and assessments performed as well as the availability of outcomes for each study and clinical question. The 4 clinical questions included in the assessment protocol are answered separately in sections 5.2 to 5.5. Maintenance of effect is described in section 5.6.

5.1 Outcomes and assessments

The 7 outcomes to be evaluated for each clinical question, according to the assessment protocol for Kevzara from the Danish Medicines Council, are shown in Table 5-1 together with the pre-defined MCID for each outcome.

TABLE 5-1 OUTCOMES AND MCIDS DEFINED IN THE ASSESSMENT PROTOCOL FOR KEVZARA

Outcome	Importance	Definition and unit	MCID between groups
Mortality	Critical	Proportion of patients	-
ACR50	Critical	Proportion of patients with an improvement of at least 50% according to the ACR criteria, which is defined as a clinically relevant improvement	15%-points
Treatment discontinuation due to AE	Critical	Proportion of patients who discontinued study treatment or was withdrawn from the study due to AE	5%-points
Treatment discontinuation due to lack of effect	Important	Proportion of patients who was withdrawn from the study due to lack of effect	10%-points
Serious infections	Important	Proportion of patients with a serious infection (serious AE)	5%-points
TSS, no progression	Important	Proportion of patients with no progression in TSS	10%-points
HAQ-DI; change ≥0.22	Important	Proportion of patients with a change from baseline in HAQ-DI score of ≥0.22, which is defined as a clinically relevant response	15%-points

ACR, American College of Rheumatology; AE, adverse event; HAQ-DI, Health Assessment Questionnaire, Disability Index; MCID, minimal clinically important difference, expressed as the difference between groups in %-points events/responders; TSS, total sharp score

Not all outcomes were reported in all studies. Table 5-2 provides an overview of which outcomes are available for the assessment of each clinical question. While the safety outcomes were available in most of the publications, ACR50 and HAQ-DI was only available in part of the studies due to methodological issues (see Table 5-2). TSS was only accessed in two 1-year studies relevant for clinical question 3.1. No publications relevant for clinical question 3.4 were found.

The statistical methods used for estimation of absolute and relative differences in effect for both results per study and for the comparative analyses are described in appendix 7.3.

TABLE 5-2 OVERVIEW OF OUTCOMES AND STUDIES AVAILABLE FOR EACH CLINICAL QUESTION

Outcome	Studies relevant for clinical question 3.1[1]	Studies relevant for clinical question 3.2[1]	Studies relevant for clinical question 3.3[1]	Comments
Mortality	MOBILITY A MOBILITY B CHARISMA OPTION TOWARD ROSE LITHE	TARGET RADIATE Olokizumab study	MONARCH ADACTA	
ACR50	MOBILITY A MOBILITY B OPTION	TARGET Olokizumab study	MONARCH ADACTA	In most of the articles, this outcome was only reported as % responders and not as number of responders. Since the proportion of responders was either model based and/or it was not possible to determine the total number of subjects used as the denominator, data for this outcome were not extracted in these cases. For MOBILITY, 24-week data were extracted in addition to the 52-week data to be able to make comparative analysis vs OPTION
Treatment discontinuation due to AE	MOBILITY A MOBILITY B CHARISMA OPTION TOWARD ROSE LITHE	TARGET RADIATE	MONARCH ADACTA	
Treatment discontinuation due to lack of effect	MOBILITY A MOBILITY B CHARISMA OPTION ROSE LITHE	TARGET RADIATE	MONARCH ADACTA	

Outcome	Studies relevant for clinical question 3.1[1]	Studies relevant for clinical question 3.2[1]	Studies relevant for clinical question 3.3[1]	Comments
Serious infections	MOBILITY A MOBILITY B CHARISMA OPTION TOWARD ROSE	TARGET RADIATE Olokizumab study	MONARCH ADACTA	
TSS, no progression	MOBILITY B LITHE			In MOBILITY, TSS was assessed using the modified Sharp/van der Heijde scoring while the Genant-modified Sharp score was used in the LITHE study. The indirect comparison performed adjusts for background differences between studies, including minor differences in scoring algorithms, see appendix 7.3
HAQ-DI; change ≥0.22	MOBILITY B	TARGET	MONARCH ADACTA	In some of the studies, this outcome was not assessed (MOBILITY A, CHARISMA, OPTION, LITHE, ROSE, Olokizumab study) while other studies (TOWARD, RADIATE) only reported this outcome as % responders and not as number of responders. Since the proportion of responders was either model based and/or it was not possible to determine the total number of subjects used as the denominator, data for this outcome were not extracted where only the proportion of responders was reported
HAQ-DI; change ≥0.30	MOBILITY B OPTION LITHE	TARGET	MONARCH	In the OPTION (24-week data) and LITHE (52-week data) studies, only this cut-off for clinical relevance was used. Thus, data for this outcome were also extracted for the MOBILITY study to be able to make comparative analyses. The outcome is considered relevant with this higher cut-off for clinical relevance since it requires a greater treatment effect, and is thus an even stronger efficacy outcome

[1]multiple clinical questions are defined in the assessment protocol. The numbers refer to the section number in the protocol.

5.2 Clinical question 3.1

What added clinical value does sarilumab offer compared to tocilizumab in combination with csDMARD for bio-naïve patients with moderate to severe RA?

Population

Patients with moderate to severe disease activity despite treatment with csDMARDs.

Intervention

Sarilumab, subcutaneously (SC) 200 mg every 2 weeks (q2w) in combination with csDMARD.

Comparator

Tocilizumab, SC 162 mg once weekly (qw) or IV 8 mg/kg (maximum 800 mg) every 4th week (q4w) in combination with csDMARD.

5.2.1 Presentation of relevant studies

One relevant clinical study with sarilumab was identified. The MOBILITY study was a randomized, double-blind, placebo-controlled, multicenter study evaluating efficacy and safety of sarilumab on top of MTX in patients with active RA who were inadequate responders to MTX therapy. MOBILITY was designed as an operationally seamless phase 2/3 study where part A was a phase 2b dose-selection study [4] and part B was the pivotal phase 3 study [5]. Details of the study design are provided in Table 7-4. Study treatment was 12 weeks (part A) or 52 weeks (part B) sarilumab in combination with MTX (10-25 mg/week). In part A, 5 different SC dosage regimens were tested (100 mg qw, 150 mg qw, 100 mg q2w, 150 mg q2w, or 200 mg q2w) and in part B, 2 different doses (150 mg q2w and 200 mg q2w) were tested. Only the results for 200 mg q2w are included in this application.

A total of 5 randomized, placebo-controlled, double-blind tocilizumab studies, relevant for clinical question 3.1, were identified: CHARISMA [8], OPTION [9], TOWARD [10], ROSE [11] and LITHE [12].

CHARISMA was a phase 2b, 16-week, dose-ranging study in patients with active RA and with inadequate response to MTX. The study included 7 arms (IV tocilizumab monotherapy 2 mg/kg, 4 mg/kg or 8 mg/kg q4w, IV tocilizumab 2 mg/kg, 4 mg/kg or 8 mg/kg q4w in combination with stable MTX, or placebo q4w in combination with stable MTX). Only results for 8 mg/kg q4w in combination with MTX are included in this application, since a control (placebo) arm was only available for this treatment regimen. Details of the study design are provided in Table 7-7.

TOWARD and ROSE were phase 3 studies in patients with moderate to severe active RA, testing IV tocilizumab 8 mg/kg q4w in combination with stable DMARDs, which were primarily MTX (used by 74-87% of the patients). The duration of treatment was 24 weeks in both studies. Details of the study designs are provided in Table 7-9 and Table 7-10, respectively.

OPTION and LITHE were likewise phase 3 studies, testing IV tocilizumab 4 mg/kg and 8 mg/kg q4w in combination with stable MTX in patients with moderate to severe active RA. The duration of treatment was 24 weeks in OPTION and 104 weeks in LITHE. In the LITHE study patients could switch to open-label treatment during the 2nd year; thus, only the 52-week results from the double-blind part of the study are included in this application. Furthermore, only results for 8 mg/kg q4w are included for both studies. Details of the study designs are provided in Table 7-8 and Table 7-11, respectively.

The patient populations studied were similar across studies. The patients had moderate to severe RA, the majority were women (73-85%), with a mean age of 49-56 years and a mean duration of RA ranging from 6.0 to 9.8 years. An exception was the CHARISMA study, where the mean duration of disease in all groups was less than 1 year. In all studies, part of the patients had previously been exposed to bDMARDs, ranging from 5-9% of the patients in the OPTION study to 38% in the ROSE study. For most of the studies, it was stated that previous anti-TNF non-responders were excluded from participation. Additional details on the baseline characteristics are provided in Table 7-4, Table 7-7, Table 7-8, Table 7-9, Table 7-10 and Table 7-11.

5.2.2 Results per study

In MOBILITY B, 1 of 424 patients in the 200 mg sarilumab group and 2 of 427 patients in the placebo group died during the 52-week study period (p=0.575). No patients died during the 12 weeks study period in the 200 mg sarilumab or placebo groups in MOBILITY A.

In MOBILITY A, 21 of 52 patients (40%) in the 200 mg sarilumab group achieved an ACR50 response at week 12, compared to 8 of 52 (15%) in the placebo group (p=0.008). In MOBILITY B, a total of 182 of 399 patients (46%) in the 200 mg sarilumab group achieved an ACR50 response at week 24, compared to 66 of 398 (17%) in the placebo group (p<0.001). At week 52, the corresponding number of responders were 171 of 399 (43%) in the 200 mg sarilumab group and 72 of 398 (18%) in the placebo group (p<0.001).

In MOBILITY A, 4 of 51 patients (8%) in the 200 mg sarilumab group discontinued treatment due to AE during the 12 weeks study, compared to 2 of 51 (4%) in the placebo group (p=0.411). The safety analyses of MOBILITY B included a few additional patients from cohort 1 (randomized before dose selection) who were randomized to the doses selected for the phase 3 study and thus continued in the study after dose selection. These patients were not included in the efficacy analyses of part B. Hence, there is a slight discrepancy in the total number of patients in the reporting of safety versus efficacy outcomes. In MOBILITY B, a total of 59 of 424 patients (14%) in the 200 mg sarilumab dose group discontinued treatment due to AE during the 52 weeks double-blind period of the study, compared to 20 of 427 patients (5%) in the placebo group (p<0.001). Discontinuations were generally attributable to infections, neutropenia and increased transaminase levels [5].

In MOBILITY A, 1 of 51 patients (2%) in the 200 mg sarilumab group were withdrawn from the study due to lack of effect, compared to 2 of 51 (4%) in the placebo group (p=0.566). In MOBILITY B, the corresponding numbers after the 52-week study were 6 of 399 patients (2%) in the 200 mg sarilumab group, compared to 3 of 398 (1%) in the placebo group (p=0.326).

In MOBILITY A, no patients in either group experienced serious infections during the 12-week study. In MOBILITY B, 17 of 424 patients (4%) in the 200 mg sarilumab group experienced serious infections during the 52-week study, compared to 10 of 427 (2%) in the placebo group (p=0.171). No severe, systemic opportunistic infections were reported. The most frequently reported opportunistic infection was herpes zoster (8 cases distributed evenly across the 3 treatment groups studied) [5].

Radiographic progression was assessed by the modified Sharp/van der Heijde scoring (SHS) system in MOBILITY B. A total of 222 of 398 patients (56%) in the 200 mg sarilumab group had no radiographic progression at week 52, compared to 154 of 398 patients (39%) in the placebo group (p<0.001).

In MOBILITY B, a total of 231 of 399 patients (58%) in the 200 mg sarilumab group achieved a change from baseline of ≥0.22 points in the HAQ-DI score at week 24, compared to 156 of 398 (39%) in the placebo

group (p<0.001). At week 52, the corresponding number of responders were 212 of 399 patients (53%) in the sarilumab 200 mg group and 131 of 398 (33%) in the placebo group (p<0.001).

The absolute differences between active and placebo groups for all outcomes and all studies are summarized and benchmarked against the minimal clinically important difference (MCID) in Table 5-3. For the efficacy and quality of life outcomes (ACR50, TSS, HAQ-DI), the effect of 200 mg sarilumab compared to placebo was statistically significantly different from placebo and well above the MCID. For the safety outcomes (discontinuation due to AE, discontinuation due to lack of effect, serious infections), the difference between 200 mg sarilumab and placebo were well below the MCID, apart from discontinuations due to AEs in the 52-week MOBILITY B study, where the absolute difference between 200 mg sarilumab and placebo was 9%.

For the tocilizumab studies, the absolute differences observed between the tocilizumab and placebo groups were comparable to those observed for sarilumab for both the efficacy and safety outcomes.

Further details on the results per study are included in appendix 7.4 where the following tables are relevant for clinical question 3.1:

Table 7-15 Results per study – MOBILITY study part A
Table 7-16 Results per study – MOBILITY study part B
Table 7-19 Results per study – CHARISMA study
Table 7-20 Results per study – OPTION study
Table 7-21 Results per study – TOWARD study
Table 7-22 Results per study – ROSE study
Table 7-23 Results per study – LITHE study

TABLE 5-3 SUMMARY OF TREATMENT EFFECT VS PLACEBO PER STUDY FOR CLINICAL QUESTION 3.1

Outcome	Absolute difference in proportion of patients meeting outcome (active – placebo group)								MCID for difference between groups[1]
	MOBILITY A (week 12)	MOBILITY B (week 24)	MOBILITY B (week 52)	CHARISMA (week 16)	OPTION (week 24)	TOWARD (week 24)	ROSE (week 24)	LITHE (week 52)	
Mortality	0%		0%	0%	0%	0%	0%	0%	-
ACR50	25%*	29%**	25%**		33%**				15%-points
Treatment discontinuation due to AE	4%		9%**	4%	3%	2%	3%	5%*	5%-points
Treatment discontinuation due to lack of effect	-2%		1%	-10%	-1%		0%	-3%*	10%-points
Serious infections	0%		2%	6%	2%	1%	2%		5%-points
TSS, no progression			17%**					14%**	10%-points
HAQ-DI; change ≥0.22		19%**	20%**						15%-points
HAQ-DI; change ≥0.30		18%**	21%**		17%**			10%	15%-points

ACR, American College of Rheumatology; AE, adverse event; HAQ-DI, Health Assessment Questionnaire, Disability Index; MCID, minimal clinically important difference, expressed as the difference between groups in %-points events/responders; TSS, total sharp score

Blank fields: outcome is not reported

*p<0.05; **p<0.001

[1]as defined in the assessment protocol for Kevzara

Source: Table 7-15, Table 7-16, Table 7-19, Table 7-20, Table 7-21, Table 7-22 and Table 7-23

5.2.3 Comparative analyses

Comparative analyses were performed for all outcomes that were available for the same treatment duration for both sarilumab and tocilizumab. Thus, only results from 3 studies could be included in the comparative analysis: MOBILITY B (week 24 and week 52), OPTION (week 24) and LITHE (week 52). The comparative analyses of sarilumab versus tocilizumab are summarized in Table 5-4.

At week 24, the ACR50 responder rate was 14% lower after treatment with sarilumab compared to tocilizumab (Table 5-4). The difference was mainly due to a higher placebo response in the MOBILITY B study compared to the OPTION study (17% vs 11%). However, the difference was not statistically significant (p=0.117) and slightly below clinical relevance (MCID=15%). Week 52 data for ACR50 were not available in the LITHE study, however, when looking at the ACR50 responder rates provided in the Scientific Discussion for RoActemra [3], the absolute difference was approximately 26% (8 mg/kg tocilizumab 36%, placebo 10%), similar to the absolute difference for sarilumab of 25% (200 mg sarilumab 43%, placebo 18%) after 52 weeks (see Table 5-3).

The comparative analysis of TSS showed a statistically significant (p=0.023) absolute difference of 19% in favor of sarilumab, well above the MCID of 10%-points in responder rates between treatment groups. The corresponding relative difference was 1.21 (95% CI: 1.03, 1.43).

For HAQ-DI, only results for a change of ≥0.30 from baseline were available for the comparative analysis. After 24 weeks, there was no difference between sarilumab and tocilizumab. However, after 52 weeks, a statistically significant absolute difference (sarilumab – tocilizumab) of 33% was found, well above the MCID of 15%-points in responder rates between groups. The corresponding relative difference was 1.53 (95% CI: 1.18, 2.00) in favor of sarilumab.

For the safety outcomes, no differences were found between sarilumab and tocilizumab for mortality or treatment discontinuation due to AE. Serious infections could not be assessed since the LITHE study only reported these per 100 patient years of exposure and it was not possible to use these numbers for the comparative analysis. For treatment discontinuation due to lack of effect, there was a statistically significant (p=0.016) absolute difference of 6% in favor of tocilizumab and a corresponding relative difference of 12.12 (95% CI: 1.59, 92.35). The 6% difference between treatments is; however, not assessed as clinically relevant according to the pre-defined MCID of 10%.

In summary, after 52 weeks of treatment, a larger proportion of patients experienced a positive treatment response for the important outcomes TSS and HAQ-DI after sarilumab treatment compared to tocilizumab treatment, for both outcomes the difference in responder rates was clinically relevant. However, no clinically relevant differences were found between the treatments for other outcomes.

Thus, since no differences between the treatments were observed for the critical outcomes it is assessed that overall, there is no added clinical value of Kevzara compared to RoActemra.

TABLE 5-4 SUMMARY OF COMPARATIVE ANALYSES FOR CLINICAL QUESTION 3.1

Outcome	Comparative analysis (sarilumab vs tocilizumab)			
	Absolute difference (95% CI) (proportion of patients (%))	MCID[1]	Relative difference (95% CI) Risk/effect ratio	*P* value
Mortality (week 52)[2]	-1 (-1, 4)	-	0.26 (0.01, 4.82)	0.363
ACR50 (week 24)[3]	-14 (-26, 5)	15%	0.68 (0.41, 1.10)	0.117
Treatment discontinuation due to AE (week 52)[2]	0 (-5, 11)	5%	1.01 (0.44, 2.31)	0.985
Treatment discontinuation due to lack of effect (week 52)[2]	6 (0, 46)	10%	12.18 (1.60,92.82)	0.016
TSS, no progression (week 52)[2]	19 (2, 38)	10%	1.21 (1.03, 1.43)	0.023
HAQ-DI; change ≥0.30 (week 24)[3]	-5 (-15, 10)	15%	0.87 (0.62, 1.23)	0.447
HAQ-DI; change ≥0.30 (week 52)[2]	33 (11, 63)	15%	1.53 (1.18, 2.00)	0.002

ACR, American College of Rheumatology; AE, adverse event; HAQ-DI, Health Assessment Questionnaire, Disability Index; MCID, minimal clinically important difference, expressed as the difference between groups in %-points events/responders; TSS, total sharp score

[1]as defined in the assessment protocol for Kevzara

[2]MOBILITY Part B 52-weeks data vs LITHE; comparisons were only performed between studies and outcomes with the same duration

[3]MOBILITY Part B 24-weeks data vs OPTION; comparisons were only performed between studies and outcomes with the same duration

Source: Table 7-27

5.3 Clinical question 3.2

What added clinical value does sarilumab offer compared to tocilizumab in combination with csDMARD for patients with moderate to severe RA who have to change biological or tsDMARD treatment?

Population

Patients in csDMARD-treatment with moderate to severe disease activity despite treatment with bDMARDs or tsDMARDs.

Intervention

Sarilumab, SC 200 mg q2w in combination with csDMARD.

Comparator

Tocilizumab, SC 162 mg qw or IV 8 mg/kg (maximum 800 mg) q4w in combination with csDMARD.

5.3.1 Presentation of relevant studies

Two studies relevant for clinical question 3.2 were identified.

TARGET was a 3-arm, randomized, multicenter, double-blind, placebo-controlled, parallel group, phase 3 study in patients with moderately to severely active RA and a history of inadequate response to or intolerance of anti-TNF treatment. The patients were treated for 24 weeks with SC sarilumab 150 mg, sarilumab 200 mg or placebo q2w in combination with stable background csDMARD treatment, which was primarily MTX (used by 85-87% of the patients). Only results for the 200 mg sarilumab and placebo groups are included in this application. Details of the study design are provided in Table 7-5.

RADIATE was a randomized, double-blind, placebo-controlled, parallel group, phase 3 study in patients with moderate to severe active RA and inadequate response to anti-TNF therapy. Patients were treated for 24 weeks with IV tocilizumab 8 mg/kg, 4 mg/kg or placebo q4w in combination with stable MTX. Only data for the 8 mg/kg and placebo groups are included in this application. Details of the study design are provided in Table 7-12.

An additional study included tocilizumab as an active comparator to olokizumab. The study was a dose-ranging, double-blind, placebo and active-controlled, multicenter, randomized, phase 2b study. Patients were randomized to 1 of 9 treatment arms; olokizumab (60, 120 or 240 mg) q4w or q2w, placebo q4w or q2w, or 8 mg/kg tocilizumab q4w. All patients received a stable dose of MTX concomitantly. Randomization was stratified according to the number of prior failed TNF inhibitors (1 vs 2 or more). Only data for the tocilizumab group and corresponding placebo group are included in this application. Details of the study design are provided in Table 7-13.

The patient populations in the 3 studies were similar. The majority of patients were women (77-86%), with a mean age of 52-58 years and a mean duration of RA ranging from 7.5 to 12.7 years. In the TARGET study, 75-77% of patients reported previous use of 1 anti-TNF treatment; in the RADIATE study 42-50% of patients reported previous use of 1 anti-TNF treatment and 32-44% of patients reported previous use of 2 anti-TNF treatments, and in the olokizumab study 55-58% of patients reported previous use of 1 anti-TNF treatment and 42-46% reported previous use of at least 2 anti-TNF treatments. Additional details on the baseline characteristics are provided in Table 7-5, Table 7-12 and Table 7-13.

In addition to these studies, the safety profile of sarilumab has further been investigated in a multicenter randomized, double-blind, double-dummy, parallel-group, three-arm, 24-week, phase 3 study in patients with moderate to severe RA who were inadequate responders or intolerant to anti-TNF treatment. The objective was to assess the safety and tolerability of sarilumab and tocilizumab in the same study. Patients were randomized in a 1:1:2 ratio to SC injections of sarilumab 150 mg or 200 mg q2w or IV infusion of tocilizumab q4w starting at 4 mg/kg and with the option to increase to 8 mg/kg, if needed (based on Investigator's discretion), in combination with csDMARD background therapy. The primary study results of the ASCERTAIN study were included in the Marketing Authorization Application for Kevzara; however, as no data were included in the EPAR for Kevzara and the study remains to be published, data from the study could not be included in this application.

5.3.2 Results per study

During the 24-week TARGET study, no patients in the 200 mg sarilumab group died while 1 patient died in the placebo group (p=0.561).

In TARGET, 75 of 184 (41%) in the 200 mg sarilumab group achieved an ACR50 response at week 24, compared to 33 of 181 (18%) in the placebo group (p<0.001).

Study treatment was discontinued due to AE in 17 of 184 (9%) in the 200 mg sarilumab group, compared to 8 of 181 (4%) in the placebo group (p=0.076), while 2 of 184 patients (1%) in the 200 mg sarilumab group and 5 of 181 patients (3%) in the placebo group discontinued treatment due to lack of effect (p=0.261).

Serious infections were experienced by 2 patients (1%) in each group (p=0.987) during the TARGET study.

For HAQ-DI, 103 of 184 (56%) in the 200 mg sarilumab group achieved a change from baseline of ≥0.22 points at week 24, compared to 64 of 181 (35%) in the placebo group (p<0.001), while 87 of 184 patients

(47%) in the 200 mg sarilumab group achieved a change from baseline of ≥0.30, compared to 57 of 181 (31%) in the placebo group (p=0.003).

The absolute differences between active and placebo groups for all outcomes in both studies are summarized and benchmarked against the MCID in Table 5-5. For ACR50 and both definitions of a clinically relevant change in HAQ-DI, the effect of 200 mg sarilumab compared to placebo was statistically significant and greater than the MCID. For discontinuation due to lack of effect and serious infections, the difference between 200 mg sarilumab and placebo were well below the MCID, while the absolute difference between 200 mg sarilumab and placebo was 5% for discontinuation due to AE, similar to the MCID, however the difference was not statistically significant.

It was not possible to extract data for the efficacy outcomes for tocilizumab from the RADIATE study. However, responder rates for ACR50 were provided in the publication [13], with an absolute difference between active and placebo of approximately 25% (8 mg/kg tocilizumab 28.8% and placebo 3.8%), similar to the difference for sarilumab (see Table 5-5). Likewise, the responder rates for an improvement in HAQ-DI score ≥0.22 from baseline were provided in a publication [16], with an absolute difference between tocilizumab and placebo of approximately 34% (8 mg/kg tocilizumab 66.2% and placebo 32.3%). These data were, however, not extracted for this application since it was not possible to determine if the responder rates were adjusted and/or what the denominator had been for calculating the responder rates. For the safety outcomes, the absolute differences in both the proportion of patients discontinued due to lack of efficacy and the proportion of patients discontinued due to AE were lower for tocilizumab compared to sarilumab.

The differences between tocilizumab and placebo for the outcomes reported in the olokizumab study were comparable to the differences between sarilumab and placebo.

TSS was not assessed in any of the studies.

TABLE 5-5 SUMMARY OF TREATMENT EFFECT VS PLACEBO PER STUDY FOR CLINICAL QUESTION 3.2

Outcome	Absolute difference in proportion of patients meeting outcome (active – placebo group)			MCID for difference between groups[1]
	TARGET (week 24)	RADIATE (week 24)	Olokizumab study (week 12)	
Mortality	-1%	0%	-2%	-
ACR50	23%**		20%	15%-points
Treatment discontinuation due to AE	5%	1%		5%-points
Treatment discontinuation due to lack of effect	-2%	-10%*		10%-points
Serious infections	0%	1%	3%	5%-points
HAQ-DI; change ≥0.22	21%**			15%-points
HAQ-DI; change ≥0.30	16%*			15%-points

ACR, American College of Rheumatology; AE, adverse event; HAQ-DI, Health Assessment Questionnaire, Disability Index; MCID, minimal clinically important difference, expressed as the difference between groups in %-points events/responders
Blank fields: outcome is not reported
*p<0.05; **p<0.001
[1]as defined in the assessment protocol for Kevzara
Source: Table 7-17, Table 7-24 and Table 7-25

Further details on the results per study are included in appendix 7.4 where the following tables are relevant for clinical question 3.2:

Table 7-17 Results per study – TARGET study
Table 7-24 Results per study – RADIATE study
Table 7-25 Results per study – Olokizumab study

5.3.3 Comparative analyses

Comparative analyses were performed for the outcomes that were available in both studies, i.e. only for the safety outcomes. The comparative analyses of sarilumab versus tocilizumab are summarized in Table 5-6. The absolute difference between sarilumab and tocilizumab for treatment discontinuation due to AE was 5%, similar to the MCID, however the difference was not statistically significant. No other clinically relevant or statistically significant differences were found.

TABLE 5-6 SUMMARY OF COMPARATIVE ANALYSES FOR CLINICAL QUESTION 3.2

Outcome	Comparative analysis (sarilumab vs tocilizumab)			
	Absolute difference (95% CI) (proportion of patients (%))	MCID[1]	Relative difference (95% CI) Risk ratio	*P* value
Mortality (week 24)[2]	0 (-1, 11)	-	0.54 (0.01, 20.78)	0.739
Treatment discontinuation due to AE (week 24) [2]	5 (-3, 30)	5%	1.83 (0.54, 6.18)	0.331
Treatment discontinuation due to lack of effect (week 24) [2]	2 (-2, 30)	10%	2.04 (0.29, 14.23)	0.470
Serious infections (week 24)[2]	-1 (-4, 24)	5%	0.67 (0.07, 6.29)	0.728

MCID, minimal clinically important difference, expressed as the difference between groups in %-points events/responders
ACR50 and HAQ-DI were not included in the comparative analyses, since only relative numbers were published
[1]as defined in the assessment protocol for Kevzara
[2]TARGET vs RADIATE; comparisons were only performed between studies and outcomes with the same duration
Source: Table 7-28

In addition to this, the overall conclusions of the ASCERTAIN study were that no clinically meaningful differences in safety parameters were observed between sarilumab and tocilizumab, and within the limitations of this safety study, which was not designed to evaluate the comparative efficacy of sarilumab and tocilizumab, efficacy responses were likewise similar between the treatment groups [1].

Thus, no added clinical value of Kevzara compared to RoActemra was found in this population.

5.4 Clinical question 3.3

What added clinical value does sarilumab offer compared to tocilizumab to bio-naïve patients with moderate to severe RA where treatment with csDMARDs is not an option?

Population

Patients with RA and moderate to severe disease activity who have not yet received treatment with bDMARDs or tsDMARDs and where treatment with csDMARDs is not an option.

Intervention

Sarilumab, SC 200 mg q2w.

Comparator

Tocilizumab, SC 162 mg qw or IV 8 mg/kg (maximum 800 mg) q4w.

5.4.1 Presentation of relevant studies

Two studies relevant for clinical question 3.3 were identified.

The MONARCH study was a randomized, multicenter, parallel-group, double-blind, double-dummy study assessing the efficacy and safety of sarilumab monotherapy versus adalimumab monotherapy in patients with active RA who were either intolerant of, inappropriate candidates for continued treatment with, or inadequate responders to MTX [7]. Patients were treated for 24 weeks with sarilumab 200 mg q2w or adalimumab 40 mg q2w in a double-dummy design. Prior use of bDMARDs was not allowed.

The ADACTA study was a randomized, multicenter, parallel-group, double-blind, phase 4 study assessing the efficacy and safety of tocilizumab monotherapy versus adalimumab monotherapy in patients with RA who were intolerant of MTX or where continued treatment with MTX was considered inappropriate [15]. Patients were treated for 24 weeks with IV tocilizumab 8 mg/kg q4w plus SC placebo q2w or SC adalimumab 40 mg q2w plus IV placebo q4w. Prior use of bDMARDs was not allowed.

The patient populations in the 2 studies were similar. The majority of patients were women (79-85%), with a mean age of 51-54 years and a mean duration of RA ranging from 6.3 to 8.1 years. Additional details on the baseline characteristics are provided in Table 7-6 and Table 7-14.

5.4.2 Results per study

In MONARCH, 1 patient in the sarilumab group and no patients in the adalimumab group died during the 24-week study (p=0.570).

A total of 84 of 184 patients (46%) in the sarilumab group achieved an ACR50 response at week 24, compared to 55 of 185 (30%) in the adalimumab group (p=0.002).

One patient was randomized but not treated in the adalimumab group and was therefore not included in the safety population. Study treatment was discontinued due to AE in 11 of 184 patients (6%) in the sarilumab group, compared to 13 of 184 (7%) in the adalimumab group, while 2 of 184 patients (1%) in the sarilumab group and 4 of 185 patients (2%) in the placebo group discontinued treatment due to lack of effect (p=0.424).

Serious infections were experienced by 2 out of 184 patients (1%) in each group (p=1.000) during the MONARCH study.

For HAQ-DI, 124 of 184 patients (67%) in the sarilumab group achieved a change from baseline of ≥0.22 points in the HAQ-DI score at week 24, compared to 100 of 185 (54%) in the adalimumab group (p=0.009), while 114 of 184 patients (62%) in the sarilumab group achieved a change from baseline of ≥0.30, compared to 88 of 185 (48%) in the placebo group (p=0.006).

The absolute differences between test and control groups for all outcomes in both studies are summarized and benchmarked against the MCID in Table 5-7. For ACR50, the absolute effect of sarilumab compared to

adalimumab was well above the MCID. For both definitions of a clinically relevant change in HAQ-DI, the differences between sarilumab and adalimumab were statistically significant, but below the MCID for responders between treatment groups. For discontinuation due to AE, discontinuation due to lack of effect and serious infections, the difference between sarilumab and placebo were well below the MCID. All results for tocilizumab were similar.

TSS was not assessed in any of the studies.

TABLE 5-7 SUMMARY OF TREATMENT EFFECT VS PLACEBO PER STUDY FOR CLINICAL QUESTION 3.3

Outcome	Absolute difference in proportion of patients meeting outcome (active – placebo group)		MCID for difference between groups[1]
	MONARCH (week 24)	ADACTA (week 24)	
Mortality	1%	1%	-
ACR50	16%*	19%**	15%-points
Treatment discontinuation due to AE	-1%	-1%	5%-points
Treatment discontinuation due to lack of effect	-1%	-4%	10%-points
Serious infections	0%	-1%	5%-points
HAQ-DI; change ≥0.22	13%*	5%	15%-points
HAQ-DI; change ≥0.30	14%*		15%-points

ACR, American College of Rheumatology; AE, adverse event; HAQ-DI, Health Assessment Questionnaire, Disability Index; MCID, minimal clinically important difference, expressed as the difference between groups in %-points events/responders
Blank fields: outcome is not reported
*p<0.05; **p<0.001
[1]as defined in the assessment protocol for Kevzara
Source: Table 7-18 and Table 7-26

Further details on the results per study are included in appendix 7.4 where the following tables are relevant for clinical question 3.3:

Table 7-18 Results per study – MONARCH
Table 7-26 Results per study – ADACTA study

5.4.3 Comparative analyses

Comparative analyses were performed for the outcomes that were available in both studies. The comparative analyses of sarilumab versus tocilizumab are summarized in Table 5-8. Overall, no statistically significant or clinically relevant differences between sarilumab and tocilizumab were found and hence, no added clinical value of Kevzara compared to RoActemra.

TABLE 5-8 SUMMARY OF COMPARATIVE ANALYSES FOR CLINICAL QUESTION 3.3

Outcome	Comparative analysis (sarilumab vs tocilizumab)			
	Absolute difference (95% CI) (proportion of patients (%))	MCID[1]	Relative difference (95% CI) Risk/effect ratio	*P* value
Mortality (week 24)[2]	-1 (-2, 31)	-	0.67 (0.02,17.82)	0.809
ACR50 (week 24)[2]	-5 (-19, 17)	15%	0.90 (0.60, 1.35)	0.619
Treatment discontinuation due to AE (week 24)[2]	0 (-4, 11)	5%	0.94 (0.29, 3.03)	0.918
Treatment discontinuation due to lack of effect (week 24)[2]	0 (-4, 25)	10%	1.00 (0.15, 6.70)	1.000
Serious infections (week 24)[2]	1 (-3, 36)	5%	1.17 (0.13,10.77)	0.892
HAQ-DI; change ≥0.22 (week 24)[2]	7 (-7, 27)	15%	1.13 (0.87, 1.47)	0.354

ACR, American College of Rheumatology; AE, adverse event; HAQ-DI, Health Assessment Questionnaire, Disability Index; MCID, minimal clinically important difference, expressed as the difference between groups in %-points events/responders
[1]as defined in the assessment protocol for Kevzara
[2]MONARCH vs ADACTA; comparisons were only performed between studies and outcomes with the same duration
Source: Table 7-29

5.5 Clinical question 3.4

What added clinical value does sarilumab offer compared to tocilizumab for patients with moderate to severe RA who have to change biological or tsDMARD treatment and where treatment with csDMARDs is not an option?

Population

Patients with RA and moderate to severe disease activity despite treatment with bDMARDs or tsDMARDs and where treatment with csDMARDs is not an option.

Intervention

Sarilumab, SC 200 mg q2w.

Comparator

Tocilizumab, SC 162 mg qw or IV 8 mg/kg (maximum 800 mg) q4w.

5.5.1 Presentation of relevant studies

No studies have been conducted with sarilumab to evaluate safety and efficacy in this population. However, in one sarilumab monotherapy study (the ONE study) a small subgroup of in total 38 patients (28.8% of the study population) have had bDMARD exposure prior to enrolment. The primary study results of the ONE study were included in the Marketing Authorization Application for Kevzara; however, as only the overall conclusions without details of the data were included in the EPAR for Kevzara and the study remains to be published, the study data could not be included in this application. However, in order to provide data for this patient population, as requested in the protocol for this application, we have conducted a descriptive *post hoc* analysis of the available outcomes in the bDMARD exposed vs bDMARD naïve patients enrolled in the ONE study.

ONE was an open-label, multicenter, randomized, parallel group, phase 3 study assessing the immunogenicity and safety of sarilumab administered as monotherapy for 24 weeks. The study included patients with moderate to severe RA who were candidates for treatment with a biologic as monotherapy, i.e. patients who have had prior intolerance of or inadequate response to DMARDs. Patients were stratified by region and prior bDMARD exposure and were randomized in a 1:1 ratio to sarilumab monotherapy 150 mg or 200 mg q2w. For the purpose of the *post hoc* analysis, data from the 150 mg and 200 mg arms were pooled to increase the number of patients in the analysis, which is considered reasonable since the efficacy responses were similar between the 2 dose groups [1]. For continuous outcomes (DAS28 and ACR50 components), no missing data imputation was performed but responder status was determined using available data, and patients were classified as non-responders for all time points beyond the time point of discontinuation of study treatment.

In the ONE study, 80.3% of the total study population (N=132) were women, the mean age was 52.4 years and the mean duration of RA was 10.5 years (range 0.3 to 38.6). A total of 20 patients with prior bDMARD exposure were enrolled in the 150 mg arm (30.8%) and 18 patients in the 200 mg arm (26.9%), while a total of 45 bDMARD naïve patients were enrolled in the 150 mg arm (69.2%) and 49 in the 200 mg arm (73.1%).

5.5.2 Results per study

No deaths occurred during the ONE study.

In the ONE study, 19 of 38 (50%) bDMARD exposed patients achieved an ACR50 response at week 24, compared to 50 of 94 (53%) patients in the bDMARD naïve subgroup. In support of this, DAS28-CRP remission rates (<2.6) were comparable between bDMARD exposed vs bDMARD naïve patients (42% in both groups).

Study treatment was discontinued due to AE in 5 of 38 (13%) of the bDMARD exposed patients, compared to 5 of 94 (5%) in the bDMARD naïve subgroup. In total, only 2 patients in the 150 mg sarilumab arm and none in the 200 mg arm discontinued treatment due to lack of effect; hence this outcome was not further analyzed in the bDMARD subgroups.

No serious infections occurred in the study.

For HAQ-DI, 23 of 38 (61%) bDMARD exposed patients achieved a change from baseline of ≥0.22 points at week 24, compared to 67 of 94 (71%) patients in the bDMARD naïve subgroup. The absolute difference in responder rates between the 2 subgroups is below the pre-specified MCID of 15%. Furthermore, the responder rate for change from baseline of ≥0.22 points in HAQ-DI in the MONARCH study is comparable (67% in the 200 mg sarilumab group, see Table 7-18). This indicates, that there is no clinically meaningful difference in HAQ-DI response between patients with prior bDMARD use and bio-naïve patients treated with sarilumab monotherapy.

For treatment discontinuation due to AE, the discontinuation rate in bDMARD exposed patients exceeded the pre-specified MCID on 5% as opposed to bDMARD naïve patients. However, due to the limited number of events, this finding needs to be interpreted with caution. Moreover, in the 200 mg sarilumab group, only a single patient of 18 (6%) bDMARD exposed patients discontinued treatment due to AE, compared to 4 of 49 (8%) bDMARD naïve patients.

For other outcomes (ACR50 and HAQ-DI), the absolute differences between bDMARD exposed vs bDMARD naïve patients were below the pre-specified MCID ranges, indicating no clinically meaningful differences between patients with prior bDMARD use and bio-naïve patients.

5.5.3 Comparative analyses

Overall the data from the ONE study suggest that sarilumab monotherapy in prior bDMARD exposed patients provides clinical outcomes comparable to those observed in bDMARD naïve patients in the MONARCH study (Table 5-9). The higher discontinuation rate due to AE in the bDMARD exposed patients should be interpreted with caution, since the rate is based on a limited number of events and since, in the 200 mg sarilumab group, only a single patient of 18 (6%) bDMARD exposed patients discontinued treatment due to AE, compared to 4 of 49 (8%) bDMARD naïve patients.

The similar clinical response in prior bDMARD exposed and bDMARD naïve patients is supported by data from the MOBILITY study where sarilumab in combination with MTX resulted in improvements in clinical efficacy (including ACR20, ACR50 and ACR70 response rates) of similar magnitude in patients with and without previous bDMARD exposure [4,5] and independent of the number of prior bDMARDs used [4].

However, since the ONE study was not designed to evaluate safety or efficacy in bDMARD exposed vs bDMARD naïve patients it is not possible to draw firm conclusions on this *post hoc* analysis. Further studies are warranted to confirm the safety and efficacy of sarilumab in bDMARD exposed patients.

No tocilizumab studies were identified in this patient population that fulfills the literature selection criteria (Table 7-1). However, a recent publication from a pan-European register collaboration confirms the clinical utility of IL-6 inhibition in bDMARD exposed patients [17].

Overall, since no published clinical studies in this population are available, it is not possible to conclude on the clinical value of Kevzara compared to RoActemra.

TABLE 5-9 SUMMARY OF TREATMENT EFFECT OF SARILUMAB MONOTHERAPY IN BIO-NAÏVE AND PREVIOUSLY BIO-EXPOSED PATIENTS

Outcome	bDMARD naïve		bDMARD exposed	MCID for difference between groups[1]
	MONARCH (week 24) Sarilumab q2w	ONE (week 24) Sarilumab q2w monotherapy	ONE (week 24) Sarilumab q2w monotherapy	
Mortality	1%	0%	0%	-
ACR50	46%	53%	50%	15%-points
Treatment discontinuation due to AE	6%	5%	13%	5%-points
Treatment discontinuation due to lack of effect	1%			10%-points
Serious infections	1%	0%	0%	5%-points
HAQ-DI; change ≥0.22	67%*	71%	61%	15%-points
HAQ-DI; change ≥0.30	62%*			15%-points

ACR, American College of Rheumatology; AE, adverse event; HAQ-DI, Health Assessment Questionnaire, Disability Index; MCID, minimal clinically important difference, expressed as the difference between groups in %-points events/responders
Blank fields: outcome is not reported
[1]as defined in the assessment protocol for Kevzara
Source: Table 7-18

5.6 Long-term efficacy and safety of sarilumab

The EXTEND study is a multicenter, multinational, open-label, uncontrolled long-term study with the primary objective to evaluate sarilumab long-term safety and the secondary objective to assess sarilumab efficacy in patients with RA.

The study has enrolled patients from the initial phase 3 studies: MOBILITY Part A and B (rollover, N=1283 patients), TARGET (rollover, N=454 patients), ASCERTAIN (rollover, N=168 patients) and ONE (rollover, N=111 patients). Additionally, 7 patients were enrolled from the ACT11575 study, which was terminated early. Thus, the overall safety patient population in EXTEND was N=2023 ([sarilumab plus DMARD safety population, N=1912] + [monotherapy safety population, N=111]).

Upon entry into EXTEND, all patients received sarilumab 200 mg q2w in combination with a stable dose of their csDMARDs, except for patients from the ONE study who received sarilumab monotherapy. As in the lead-in studies, the sarilumab dose could be reduced to 150 mg q2w for certain laboratory abnormalities. The treatment duration for a patient in EXTEND is at least 264 weeks from the first sarilumab administration in the study. In addition, patients may continue to be treated beyond 264 weeks until sarilumab is commercially available or until 2020 at the latest, when the study will be closed. The study is still ongoing, but data is included in the EPAR up to 264 weeks for some patients (cut-off date 25 January 2016).

The available efficacy data from the EPAR are summarized in Table 5-10 and Table 5-11. The proportion of patients with ACR50 response and DAS28 remission was maintained up to 264 weeks for patients treated with sarilumab plus csDMARDs and up to 48 weeks for patients treated with sarilumab monotherapy. However, in all groups the proportion of patients with ACR50 response and DAS28 remission increased profoundly after the switch to open-label treatment in the EXTEND study (Table 5-10). Thus, the results of this long-term study have to be evaluated with caution as the placebo effect in the data has to be taken into consideration.

For radiographic progression of bone damage, data from the EXTEND study showed that the proportion of patients with no progression was maintained for up to 100 weeks for patients treated with 200 mg sarilumab q2w in combination with MTX (Table 5-11). Furthermore, in the group of patients that was followed for up to 3 years, the proportion of patients with no progression was also maintained [1].

Safety outcomes were not reported separately for the EXTEND study in the EPAR. However, a recent publication has reported safety data exclusively for the patients from MOBILITY who were enrolled into the EXTEND study [18]. During the 52-week EXTEND study, the treatment discontinuation rate due to AEs was 8-9% (in patients randomized to placebo and 200 mg sarilumab in the MOBILITY study), and treatment discontinuation due to lack of efficacy was 1-2%. Across the entire 2-year period, serious infections occurred at a rate of 4.6 events per 100 patient-years, and no additional deaths were reported during the first year of the EXTEND study. Overall, the recently published 2-year safety observations from the EXTEND study are consistent with the safety profile of sarilumab in other studies of shorter duration and with the long-term safety of both IV and SC tocilizumab [19,20].

TABLE 5-10 SUMMARY OF LONG-TERM EFFICACY OF SARILUMAB (ACR50 AND DAS28 REMISSION)[1]

Week	Sarilumab + DMARD[2]		Sarilumab monotherapy[3]	
	Proportion (n/N) with ACR50 response[4]	Proportion (n/N) with DAS28 remission[5]	Proportion (n/N) with ACR50 response[4]	Proportion (n/N) with DAS28 remission[5]
0	43.4% (824/1897)	30.4% (569/1873)	58.6% (65/11)	46.4% (51/110)
24	60.5% (1078/1782)	50.6% (899/1778)	64.2% (70/109)	59.6% (65/109)
48	62.6% (1037/1656)	53.6% (887/1654)	73.3% (22/30)	53.3% (16/30)
96	65.4% (749/1145)	57.8% (658/1139)		
144	65.6% (391/596)	56.4% (335/594)		
192	69.1% (141/204)	60.6% (123/203)		
216	72.1% (132/183)	63.3% (114/180)		
240	71.2% (89/125)	68.5% (85/124)		
264	58.1% (25/43)	59.0% (23/39)		

ACR, American College of Rheumatology; DAS28, Disease Activity Score in 28 joints

[1]Safety population from the EXTEND study. Data are pooled for the 150 mg and 200 mg q2w doses

[2]Patients rolled over from the MOBILITY part A and B, TARGET, ASCERTAIN and ACT11575 studies

[3]Patients rolled over from the ONE study

[4]The number represents subset of the total number of patients who had the response. The denominator is the number of patients in the treatment group who had the parameter assessed

[5]DAS28 remission defined as DAS28-CRP<2.6

Source: EPAR for Kevzara [1]

TABLE 5-11 SUMMARY OF LONG-TERM EFFICACY OF SARILUMAB (TSS, NO PROGRESSION)[1]

	Proportion (n/N) with no progression in mTSS[2]	
	Placebo (N=398)	Sarilumab 200 mg q2w + MTX (N=399)
Week 52	40.4% (115/285)	65.0% (180/277)
OR (95% CI) vs placebo[3]		2.79 (1.98, 3.94)
p-value vs placebo[4]		<0.0001
Week 100	44.2% (126/285)	60.6% (168/277)
OR (95% CI) vs placebo[3]		1.96 (1.40, 2.75)
p-value vs placebo[4]		<0.0001

mTSS, modified total Sharp score

[1]Data from the EXTEND study for patients originally randomized into MOBILITY Part 2, cohort 2. Data are from the EPAR [1]. Numbers in the publication [18] are slightly different since all available data were used as observed and linear extrapolation of radiographic data was applied if a radiograph was performed before the scheduled 1- or 2-year assessment

[2]Patients with change ≤0 in modified total Sharp score. Percentages were calculated using the number of ITT patients with available progression status at the corresponding time as the denominator. Data collected after treatment discontinuation or starting rescue medication were used as observed. Linear extrapolation was used to impute missing scores

[3]Mantel-Haenszel estimate

[4]CMH test stratified by prior biologic use and region

Source: EPAR for Kevzara [1]

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17. Lauper K, Nordström DC, Pavelka K, Hernández MV, Kvien TK, Kristianslund EK, Santos MJ, Rotar Ž, Iannone F, Codreanu C, Lukina G, Gale SL, Sarsour K, Luder Y, Courvoisier DS, Gabay C. Comparative effectiveness of tocilizumab versus TNF inhibitors as monotherapy or in combination with conventional synthetic disease-modifying antirheumatic drugs in patients with rheumatoid arthritis after the use of at least one biologic disease-modifying antirheumatic drug: analyses from the pan-European TOCERRA register collaboration. Ann Rheum Dis. 2018 May 5. [Epub ahead of print].
18. Genovese MC, van Adelsberg J, Fan C, Graham NMH, van Hoogstraten H, Parrino J, Mangan EK, Spindler A, Huizinga TWJ, van der Heijde D; EXTEND study investigators. Two years of sarilumab in patients with rheumatoid arthritis and an inadequate response to MTX: safety, efficacy and radiographic outcomes. Rheumatology (Oxford). 2018 May 9. [Epub ahead of print]
19. Nishimoto N, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, Azuma J. Long-term safety and efficacy of tocilizumab, an anti-IL-6 receptor monoclonal antibody, in monotherapy, in patients with rheumatoid arthritis (the STREAM study): evidence of safety and efficacy in a 5-year extension study. Ann Rheum Dis. 2009 Oct;68(10):1580-4.
20. Kivitz A, Wallace T, Olech E, Borofsky M, Devenport J, Pei J, Michalska M. Long-term safety and efficacy of subcutaneously administered tocilizumab for adult rheumatoid arthritis: A multicenter phase 3b long-term extension study. Rheumatol Ther. 2016 Dec;3(2):291-304.

7 Appendices

7.1 Literature search

TABLE 7-1 INCLUSION AND EXCLUSION CRITERIA FOR SCREENING AND ASSESSMENT

Inclusion criteria	**Population:** Moderate to severe rheumatoid arthritis, DMARD-experienced patients, adults ≥18 years old **Interventions:** Sarilumab or tocilizumab **Comparators:** Placebo, adalimumab **Outcomes:** mortality, ACR50, treatment discontinuation due to AE, treatment discontinuation due to lack of efficacy, serious infections, TSS, HAQ-DI **Settings (if applicable):** Not defined **Study design:** Randomized controlled trial, double-blind **Language restrictions:** English **Other search limits or restrictions applied:** Trials only
Exclusion criteria	**Population:** MTX naïve, juvenile RA **Intervention(s):** Sarilumab in other doses than 200 mg q2w, tocilizumab in other doses than 162 qw or 8 mg/kg q4w **Comparator(s):** MTX, other cDMARDs **Outcomes:** Biomarkers only, concomitant disease **Settings (if applicable):** Studies performed exclusively outside of Europe or USA/Canada **Study design:** Open-label, uncontrolled, phase 1 and phase 2a studies **Language restrictions:** Not English **Other search limits or restrictions applied:** None

TABLE 7-2 DATABASES AND SEARCH STRATEGY

Database	Date of search	Time period covered	Number of search results	Applied search strings
PubMed via https://www.ncbi.nlm.nih.gov/pubmed/advanced	28MAY2018	No limits applied	190[1]	(((((((("tocilizumab" OR "tocilizumab"[Supplementary Concept] OR "atlizumab" OR "actemra" OR "sarilumab" OR "sarilumab"[Supplementary Concept] OR "kevzara")))) AND ((arthritis, rheumatoid [MeSH Terms] OR (rheumatoid[Text Word] AND arthritis[Text Word])))) AND ((((("Randomized Controlled Trial"[pt] OR "Controlled Clinical Trial"[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR "Clinical Trials as Topic"[mh:noexp] OR randomly[tiab] OR trial[ti]) NOT ("Animals"[mh] NOT "Humans"[mh])))))) NOT ((((((("tocilizumab" OR "tocilizumab"[Supplementary Concept] OR "atlizumab" OR "actemra" OR "sarilumab" OR "sarilumab"[Supplementary Concept] OR "kevzara")))) AND ((arthritis, rheumatoid [MeSH Terms] OR (rheumatoid[Text Word] AND arthritis[Text Word])))) AND (("controlled clinical trial"[Publication Type] OR "randomized controlled trial"[Publication Type]))))
PubMed via https://www.ncbi.nlm.nih.gov/pubmed/advanced	27MAR2018 and 16APR2018	No limits applied	87[2]	("tocilizumab" OR "tocilizumab"[Supplementary Concept] OR "atlizumab" OR "actemra" OR "sarilumab" OR "sarilumab"[Supplementary Concept] OR "kevzara") AND ("randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type]) AND (arthritis, rheumatoid [MeSH Terms] OR (rheumatoid [Text Word] AND arthritis [Text Word]))
Cochrane Library via http://cochranelibrary-wiley.com/cochranelibrary/search/advanced	17APR2018 and 23APR2018	No limits applied	374	("tocilizumab" OR "atlizumab" OR "actemra" OR "sarilumab" OR "kevzara") AND ((arthritis, rheumatoid [MeSH Terms] OR (rheumatoid [Text Word] AND arthritis [Text Word])) Results were limited to trials only

[1]Based on feedback from the Danish Medicines Council, an updated search was performed using the Cochrane RCT filter: ((("Randomized Controlled Trial"[pt] OR "Controlled Clinical Trial"[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR "Clinical Trials as Topic"[mh:noexp] OR randomly[tiab] OR trial[ti]) NOT ("Animals"[mh] NOT "Humans"[mh])) instead of filtering by publication type only ("randomized controlled trial"[pt] OR "controlled clinical trial"[pt]). The search performed only retrieved the difference between the original PubMed search and the updated search

[2]When repeating the original PubMed search on 28 May 2018, a total of 90 search results were found. These 3 extra references were screened in addition to the 190 references found as the difference between using the original and the updated search terms

FIGURE 7-1 PRISMA FLOW CHART FOR ORIGINAL LITERATURE SEARCH

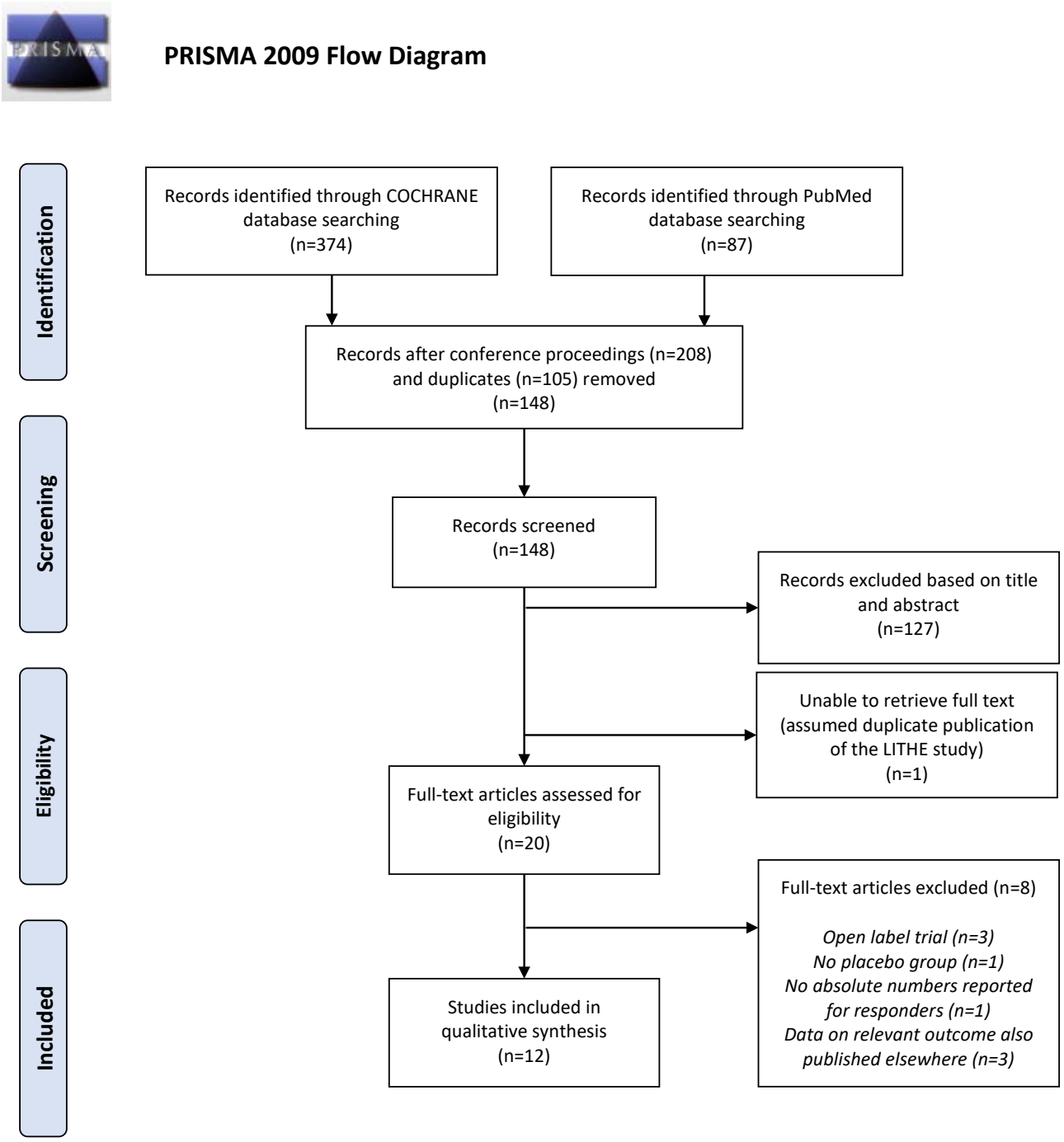

FIGURE 7-2 PRISMA FLOW CHART FOR UPDATED PUBMED LITERATURE SEARCH

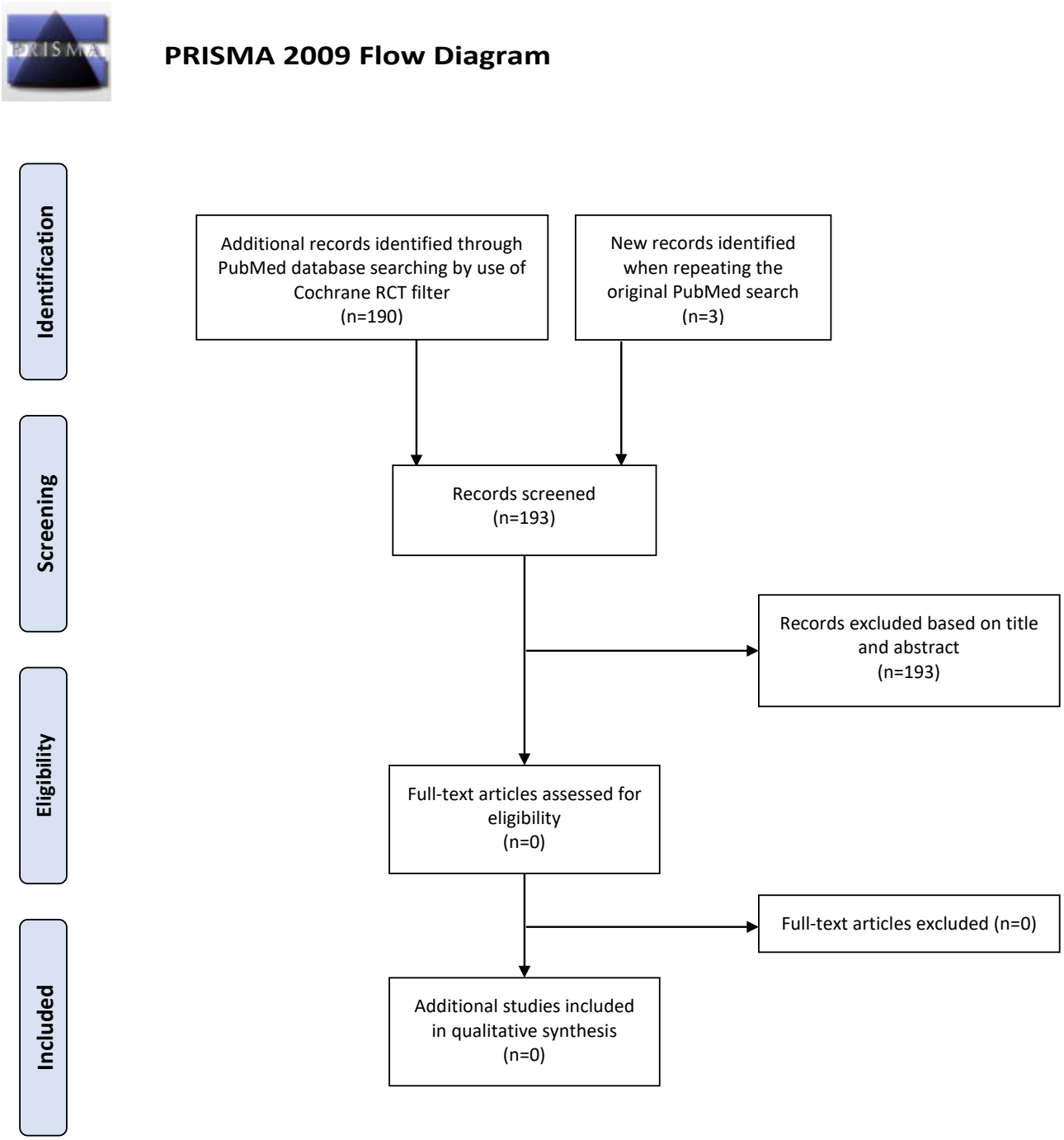

TABLE 7-3 EXCLUDED LITERATURE

Reference	Reason for exclusion
Excluded after full text screening	
Abdulkader OAF, Qushmaq K, Aljishi F. Tocilizumab efficacy and safety in rheumatoid arthritis patients after inadequate response to disease-modifying anti-rheumatic drugs or anti-tumor necrosis factor. Annals of Saudi medicine. 2016;36(3):190-196	Open-label, single arm study. Performed in 3 centers in Saudi Arabia only.
Fleischmann RM, Halland AM, Brzosko M, Burgos-Vargas R, Mela C, Vernon E, Kremer JM. Tocilizumab inhibits structural joint damage and improves physical function in patients with rheumatoid arthritis and inadequate responses to methotrexate: LITHE study 2-year results. J Rheumatol. 2013 Feb;40(2):113-26.	Open-label study. 2-year data of LITHE study. After the first year, patients on placebo or low dose tocilizumab could switch to open-label high dose tocilizumab treatment, which most patients did.
Kaneko Y, Atsumi T, Tanaka Y, Inoo M, Kobayashi-Haraoka H, Amano K, Miyata M, Murakawa Y, Yasuoka H, Hirata S, Nagasawa H, Tanaka E, Miyasaka N, Yamanaka H, Yamamoto K, Takeuchi T. Comparison of adding tocilizumab to methotrexate with switching to tocilizumab in patients with rheumatoid arthritis with inadequate response to methotrexate: 52-week results from a prospective, randomised, controlled study (SURPRISE study). Ann Rheum Dis. 2016 Nov;75(11):1917-1923.	Uncontrolled, open-label study. Intervention was switch to tocilizumab or add-on tocilizumab to MTX.
Nishimoto N, Hashimoto J, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, Murata N, van der Heijde D, Kishimoto T. Study of active controlled monotherapy used for rheumatoid arthritis, an IL-6 inhibitor (SAMURAI): evidence of clinical and radiographic benefit from an x ray reader-blinded randomised controlled trial of tocilizumab. Ann Rheum Dis. 2007 Sep;66(9):1162-7.	Tocilizumab tested versus cDMARD, no placebo group included. Japanese patients only.
Strand V, Burmester GR, Ogale S, Devenport J, John A, Emery P. Improvements in health-related quality of life after treatment with tocilizumab in patients with rheumatoid arthritis refractory to tumour necrosis factor inhibitors: results from the 24-week randomized controlled RADIATE study. Rheumatology (Oxford). 2012 Oct;51(10):1860-9.	Only proportion of responders, not absolute numbers, reported for HAQ-DI. Since it was not clear if the reported proportions were adjusted, the article was excluded.
Strand V, Kosinski M, Chen CI, Joseph G, Rendas-Baum R, Graham NM, van Hoogstraten H, Bayliss M, Fan C, Huizinga T, Genovese MC. Sarilumab plus methotrexate improves patient-reported outcomes in patients with active rheumatoid arthritis and inadequate responses to methotrexate: results of a phase III trial. Arthritis Res Ther. 2016 Sep 6;18:198.	Does not include any relevant data for the application that has not already been published elsewhere (HAQ-DI reported in Genovese et al, Arthritis Rheum 2015)
Strand V, Michalska M, Birchwood C, Pei J, Tuckwell K, Finch R, Gabay C, Kavanaugh A, Jones G. Impact of tocilizumab monotherapy on patient-reported outcomes in patients with rheumatoid arthritis from two randomised controlled trials. RMD open. 2017;3(2)	Does not include any relevant data for the application that has not already been published elsewhere (HAQ-DI reported in Gabay et al, Lancet 2013)
Strand V, Reaney M, Chen C-I, Proudfoot CWJ, Guillonneau S, Bauer D, Mangan E, Graham NMH, Hoogstraten H, Lin Y, Pacheco-Tena C, Fleischmann R. Sarilumab improves patient-reported outcomes in rheumatoid arthritis patients with inadequate response/intolerance to tumour necrosis factor inhibitors. RMD open. 2017;3(1):e000416	Does not include any relevant data for the application that has not already been published elsewhere (HAQ-DI reported in Fleischmann et al, Arthritis Rheumatol 2017)

Reference	Reason for exclusion
Full-text not retrieved	
Halland A-M. Tocilizumab inhibits structural joint damage in rheumatoid arthritis patients with inadequate responses to methotrexate at one year - The LITHE study. European musculoskeletal review. 2012;7(2):108-111	Unable to retrieve full-text. 1-year data from the LITHE study, also reported elsewhere (Kremer et al, Arthritis Rheum 2011)

7.2 Main study characteristics of included studies

7.2.1 MOBILITY study

TABLE 7-4 MAIN STUDY CHARACTERISTICS – MOBILITY STUDY PART A AND B

Trial name (official title from clinicaltrials.gov)	A randomized, double-blind, placebo-controlled, multicenter, two-part, dose ranging and confirmatory study with an operationally seamless design, evaluating efficacy and safety of SAR153191 on top of methotrexate (MTX) in patients with active rheumatoid arthritis who are inadequate responders to MTX therapy (MOBILITY).
NCT number	NCT01061736
Objective	Primary objectives *Part A (dose-ranging study)* • To demonstrate that sarilumab on top of MTX was effective on reduction of signs and symptoms of rheumatoid arthritis at 12 weeks. • To select one or more dose regimens to be evaluated in the pivotal part B study *Part B (phase 3, pivotal study)* To demonstrate that sarilumab added to MTX was effective in: • reduction of signs and symptoms of rheumatoid arthritis at 24 weeks • inhibition of progression of structural damage at 52 weeks • improvement in physical function at 16 weeks Secondary objectives included *Part B* • To demonstrate that sarilumab added to MTX was effective in induction of a major clinical response at 52 weeks • To assess the safety of sarilumab added to MTX
Publications – title, author, journal, year	Sarilumab, a fully human monoclonal antibody against IL-6Rα in patients with rheumatoid arthritis and an inadequate response to methotrexate: efficacy and safety results from the randomised SARIL-RA-MOBILITY Part A trial. Huizinga TW et al. Ann Rheum Dis. 2014 [4]. Sarilumab plus methotrexate in patients with active rheumatoid arthritis and inadequate response to methotrexate: results of a phase III study. Genovese MC et al. Arthritis Rheumatol. 2015 [5]. Sarilumab plus methotrexate improves patient-reported outcomes in patients with active rheumatoid arthritis and inadequate responses to methotrexate: results of a phase III trial. Strand V et al. Arthritis Res Ther. 2016 (excluded, no additional relevant data).
Study type and design	The MOBILITY study was a multicenter, randomized, double-blind, placebo-controlled study. MOBILITY was designed as an operationally seamless phase 2/3 study (part A and part B). Randomization was performed centrally, with allocation generated by interactive voice response system, stratified by region and prior use of biologic agents. All patients and investigators were blinded to the study treatments. Assessment of tender and swollen joints were performed by an assessor independent from the investigator and blinded from the patient's data.

	MTX had to be stable ≥6 weeks prior to screening. All other DMARDs were discontinued prior to the study. Patients, who completed the 12-week/52-week treatment period and were eligible, could enter an open-label long-term extension study. In part A, patients were randomized to placebo or 1 of 5 SC doses of sarilumab (100 mg qw, 150 mg qw, 100 mg q2w, 150 mg q2w, or 200 mg q2w). In part B, 2 cohorts of patients were enrolled. In cohort 1 (randomized prior to the phase 3 dose selection), the randomization scheme was identical to part A. After the phase 3 dose selection, patients in cohort 1 randomized to placebo or sarilumab 150 mg or 200 mg q2w continued the 52-week study, while patients randomized to the other 3 treatment arms were not continued. In cohort 2 (randomized after dose selection), patients were randomized (1:1:1) to receive placebo, sarilumab 150 mg q2w or sarilumab 200 mg q2w, in combination with weekly MTX. In part B, patients who did not achieve ≥20% improvement from baseline in swollen or tender joint counts by week 16 were offered rescue therapy.
Follow-up time	The total study duration for a participant was 16-22 weeks (Part A) and 56-62 weeks (Part B) broken down as follows: • *Screening*: Up to 4 weeks • *Treatment*: 12 weeks (Part A) and 52 weeks (Part B) • *Follow-up*: 6 weeks (if not continuing in the long-term extension study)

Population (inclusion and exclusion criteria) (from clinicaltrials.gov)	<u>Inclusion criteria</u>
	
	• Diagnosis of rheumatoid arthritis ≥3 months duration
	• Active disease defined as:
	  o at least 8/68 tender joints and 6/66 swollen joints
	  o hs-CRP >6 mg/L
	  o continuous treatment with MTX for at least 12 weeks prior to baseline visit and on stable dose for at least 6 weeks prior to screening visit
	
	Part B only
	
	• Bone erosion based on documented X-ray prior to first study drug intake or
	• Anti-CCP positive or
	• RF positive
	
	<u>Exclusion criteria</u>
	
	• Age <18 years or >75 years
	• Treatment with DMARDs other than MTX within 4 weeks or 12 weeks prior to screening (depending on DMARDs)
	• Past history of non-response to prior TNF or biologic treatment
	• Any past or current biologic agents for the treatment of RA within 3 months
	• Use of parenteral glucocorticoids or intraarticular glucocorticoids within 4 weeks prior to screening visit
	• Use of oral glucocorticoid greater than 10 mg/day or equivalent/day, or a change in dosage within 4 weeks prior to baseline visit

Intervention	<u>Part A, dose-ranging study (phase 2b)</u> Placebo SC (n=52), sarilumab SC 100 mg qw (n=50), 150 mg qw (n=50), 100 mg q2w (n=51), 150 mg q2w (n=51) or 200 mg q2w (n=52) in combination with a stable dose of MTX (10-25 mg/week).

	Part B (phase 3) *Cohort 1:* placebo SC (n=30) or sarilumab SC 100 mg qw (n=29), 150 mg qw (n=27), 100 mg q2w (n=28), 150 mg q2w (n=30) or 200 mg q2w (n=28) in combination with a stable dose of MTX (10-25 mg/week). *Cohort 2:* placebo SC (n=398), sarilumab SC 150 mg q2w (n=400) or 200 mg q2w (n=399) in combination with a stable dose of MTX (10-25 mg/week). Oral corticosteroids (≤ 10mg/day prednisone or equivalent) and NSAIDs/COX2 inhibitors in stable dose were permitted. All patients received folic acid according to local regulations.

Primary and secondary endpoints	Primary endpoints
	
	Part A
	
	• Proportion of patient achieving ACR20 response at week 12
	
	Part B
	
	• Proportion of patients achieving ACR20 response at week 24
	• Change from baseline in HAQ-DI at Week 16
	• Change from baseline in van Der Heijde modified TSS at week 52
	
	Secondary endpoints included
	
	Part B
	
	• Proportion of patients achieving a major clinical response (ACR 70 maintained for ≥6 consecutive months)
	• Radiographic progression (change from baseline):
	  o Erosion score at 24 and 52 weeks
	  o Joint space narrowing at 24 and 52 weeks
	  o TSS at 24 weeks
	  o Proportion with no radiographic progression
	• ACR50 and ACR 70 response at weeks 24 and 52

Method of analysis	Part A All efficacy endpoints were analyzed in the ITT population which included all randomized patients and was analyzed according to the treatment group allocated by randomization. Patients who discontinued treatment due to lack of efficacy or used rescue medication were considered as non-responders for all time points beyond the time they discontinued or started rescue medication. For patients who discontinued due to reasons other than lack of efficacy, a LOCF procedure was applied to missing data for all 7 ACR components from the point of treatment discontinuation or rescue. Safety was analyzed in all patients who received at least one dose of study drug. Part B Primary efficacy analyses were conducted in the ITT population, which included all randomized patients in cohort 2. Three patients in cohort 2 were randomized (sarilumab 150 mg [n=2] and sarilumab 200 mg [n=1]) but did not receive study medication; these 3 patients are included in the analysis of efficacy. Safety analyses were conducted in all patients in cohorts 1 and 2 who received ≥1 dose of study medication and who were randomized to placebo, sarilumab 150 mg q2w or 200 mg q2w. For categorical endpoints, missing or post rescue responses were imputed by the non-responder or progression imputation.

<table>
<tr><td></td><td>For radiographic progression of structural damage at week 52, missing or post-rescue therapy data were imputed by a linear extrapolation approach for any patient having at least 1 baseline radiograph and ≥1 postbaseline radiograph during the double-blind period. Radiographic data before the rescue therapy period were included as observed. Post-rescue therapy data were imputed using linear extrapolation.</td></tr>
<tr><td>Subgroup analyses</td><td>Not applicable</td></tr>
<tr><td>Baseline characteristics Part A</td><td>For clarity, only baseline characteristics for placebo plus MTX and sarilumab 200 mg q2w plus MTX groups are included.
<table>
<tr><th></th><th>Placebo +MTX n=52</th><th>Sarilumab 200 mg q2w +MTX n=52</th></tr>
<tr><td>Age, mean±SD (years)</td><td>55.2±12.5</td><td>48.7±12.4</td></tr>
<tr><td>Female, %</td><td>73.1</td><td>80.8</td></tr>
<tr><td>Caucasian/White, n (%)</td><td>49 (94.2)</td><td>47 (90.4)</td></tr>
<tr><td>Geographic region, n (%)</td><td></td><td></td></tr>
<tr><td>Western countries</td><td>16 (30.8)</td><td>16 (30.8)</td></tr>
<tr><td>South America</td><td>13 (25.0)</td><td>14 (26.9)</td></tr>
<tr><td>Rest of the world</td><td>23 (44.2)</td><td>22 (42.3)</td></tr>
<tr><td>Duration of RA, mean±SD (years)</td><td>8.07±8.62</td><td>5.95±6.18</td></tr>
<tr><td>MTX dosage, mean±SD (mg/week)</td><td>16.9±4.2</td><td>16.6±3.8</td></tr>
<tr><td>Prior bDMARD exposure, n (%)</td><td>12 (23.1)</td><td>14 (26.9)</td></tr>
<tr><td>Rheumatoid factor (RF) positive, n (%)</td><td>35 (67.3)</td><td>44 (86.3)</td></tr>
<tr><td>Anti-CCP antibody positive, n (%)</td><td>16 (72.7)</td><td>20 (87.0)</td></tr>
<tr><td>Tender joint count (of 68 joints assessed), mean±SD</td><td>27.09±16.12</td><td>25.52±14.21</td></tr>
<tr><td>Swollen joint count (of 66 joints assessed), mean±SD</td><td>17.45±11.68</td><td>16.63±8.94</td></tr>
<tr><td>DAS28-CRP, mean±SD</td><td>6.08±0.86</td><td>6.06±0.90</td></tr>
<tr><td>CRP, median (mg/dL)</td><td>21.8</td><td>19.0</td></tr>
</table></td></tr>
<tr><td>Baseline characteristics Part B</td><td>For clarity, only baseline characteristics for placebo plus MTX and sarilumab 200 mg plus MTX groups are included.
<table>
<tr><th></th><th>Placebo +MTX n=398</th><th>Sarilumab 200 mg +MTX n=399</th></tr>
<tr><td>Female, %</td><td>81</td><td>85</td></tr>
<tr><td>Age, mean±SD (years)</td><td>50.9±11.2</td><td>50.8±11.8</td></tr>
<tr><td>Race</td><td></td><td></td></tr>
<tr><td>White, n (%)</td><td>343 (86.2)</td><td>343 (86.0)</td></tr>
<tr><td>Black, n (%)</td><td>10 (2.5)</td><td>8 (2.0)</td></tr>
<tr><td>Asian, n (%)</td><td>32 (8.0)</td><td>33 (8.3)</td></tr>
<tr><td>Other, n (%)</td><td>13 (3.3)</td><td>15 (3.8)</td></tr>
<tr><td>Geographic region 1, n (%)†</td><td>74 (18.6)</td><td>75 (18.8)</td></tr>
<tr><td>Geographic region 2, n (%)†</td><td>155 (38.9)</td><td>155 (38.8)</td></tr>
<tr><td>Geographic region 3, n (%)†</td><td>169 (42.5)</td><td>169 (42.4)</td></tr>
<tr><td>MTX dosage, mean±SD (mg/week)</td><td>15.6±4.3</td><td>15.3±4.3</td></tr>
<tr><td>Prior bDMARD exposure, n (%)</td><td>82 (20.6)</td><td>78 (19.5)</td></tr>
<tr><td>Concomitant corticosteroids, n (%)</td><td>252 (63.3)</td><td>258 (64.7)</td></tr>
<tr><td>Duration of RA, mean (range) (years)</td><td>9.1 (0.3-44.0)</td><td>8.6 (0.3-34.2)</td></tr>
<tr><td>Seropositive for rheumatoid factor, %</td><td>84</td><td>83</td></tr>
<tr><td>Anti-CCP antibody positive, n (%)</td><td>340 (85.4)</td><td>337 (84.9)</td></tr>
<tr><td>DAS28-CRP, mean±SD</td><td>5.9±0.9</td><td>6.0±0.9</td></tr>
<tr><td>Total SHS, mean±SD</td><td>48.0±65.2</td><td>46.3±57.4</td></tr>
<tr><td>Total SHS, range</td><td>0.0–356.0</td><td>0.0–288.5</td></tr>
</table></td></tr>
</table>

	Swollen joint count (of 66 joints assessed), mean±SD	16.7±9.3	16.8±9.7
	Tender joint count (of 68 joints assessed), mean±SD	26.8±13.7	26.5±14.5
	HAQ DI score, mean±SD	1.6±0.7	1.7±0.6
	CRP, mean±SD (mg/dL)	2.0±2.3	2.2±2.4
	SHS, modified Sharp/van der Heijde score †Region 1: Austria, Australia, Belgium, Canada, Finland, Germany, Greece, Hungary, New Zealand, Norway, Portugal, Spain, and United States. Region 2: Argentina, Brazil, Chile, Colombia, and Mexico. Region 3: Belarus, Estonia, India, Malaysia, Philippines, Poland, Romania, Russia, South Africa, South Korea, Ukraine, Taiwan, and Thailand.		

7.2.2 TARGET study

TABLE 7-5 MAIN STUDY CHARACTERISTICS – TARGET STUDY

Trial name (official title from clinicaltrials.gov)	A randomized, double-blind, parallel, placebo-controlled study assessing the efficacy and safety of sarilumab added to non-biologic DMARD therapy in patients with rheumatoid arthritis who are inadequate responders to or intolerant of TNF-α antagonists (TARGET).
NCT number	NCT01709578
Objective (from clinicaltrials.gov)	Primary objectives To demonstrate that sarilumab added to DMARDs were effective for: • Reduction of signs and symptoms at week 24 and • Improvement of physical function at week 12 in participants with active moderate to severe RA who were inadequate responders or intolerant to TNF-α antagonists. Secondary objectives • Reduction of signs and symptoms at week 12 • Improvement in physical function at week 24 • Improvement in disease activity score as measured by other ACR derived components at weeks 12 and 24 • Improvement in quality of life as measured by PROs at intermediate visits and week 24
Publications – title, author, journal, year	Sarilumab and nonbiologic disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis and inadequate response or intolerance to tumor necrosis factor inhibitors. Fleischmann R et al. Arthritis Rheumatol. 2017 [6]. Sarilumab improves patient-reported outcomes in rheumatoid arthritis patients with inadequate response/intolerance to tumour necrosis factor inhibitors. Strand V et al. RMD open. 2017 (excluded, no additional relevant data).
Study type and design	The TARGET study was a 3-arm, multicenter, randomized, double-blind, parallel, placebo-controlled, phase 3 study. Randomization was performed centrally; patients were allocated 1:1:1 to SC sarilumab 150 mg, 200 mg or placebo q2w in combination with background csDMARD(s) for 24 weeks. Patients were stratified according to the number of previous anti-TNF agents. Investigators and patients were blinded; swollen and tender joints were assessed by an independent assessor with no access to patient data. From week 12, patients with <20% improvement from baseline in swollen or tender joint count were offered rescue treatment. Background csDMARDs had to be stable ≥6 weeks prior to screening.
Follow-up time	Up to 4 weeks of screening, 24-week blinded treatment period and 6 weeks of post-treatment safety follow-up.
Population (inclusion and exclusion criteria) (from clinicaltrials.gov)	Inclusion criteria • Diagnosis of RA ≥6 months duration, according to the ACR/EULAR 2010 RA Classification Criteria • ACR Class I-III functional status, based on 1991 revised criteria

	• Anti-TNF therapy failures, defined by the investigator as participants with an inadequate clinical response, after being treated for ≥3 consecutive months, and/or intolerance to ≥1 anti-TNF blocker(s), resulting in or requiring their discontinuation: o TNF-blockers included, but were not limited to, etanercept, infliximab, adalimumab, golimumab and/or certolizumab • Moderate to severely active RA • Continuous treatment with one or a combination of DMARDs (except for simultaneous combination use of leflunomide and MTX) for ≥12 weeks prior to baseline and on a stable dose(s) for ≥6 weeks prior to screening: o MTX - 6 to 25 mg/week orally or parenterally o Leflunomide - 10 to 20 mg orally daily o Sulfasalazine - 1000 to 3000 mg orally daily o Hydroxychloroquine - 200 to 400 mg orally daily <u>Exclusion criteria</u> • Participants <18 years of age or legal adult age • Past history of, or current, autoimmune or inflammatory systemic or localized joint disease(s) other than RA • History of juvenile idiopathic arthritis or arthritis onset prior to age 16 • Severe active systemic RA, including but not limited to vasculitis, pulmonary fibrosis, and/or Felty's syndrome • Treatment with anti-TNF agents, as follows: o Within 28 days prior to the baseline visit - etanercept o Within 42 days prior to the baseline visit - infliximab, adalimumab, golimumab, certolizumab pegol • Treatment with previous RA-directed biologic agents with other than TNF antagonist mechanisms: o Within 28 days prior to the randomization (baseline) visit - anakinra Within 42 days prior to the randomization (baseline) visit - abatacept o Within 6 months prior to the randomization (baseline) visit - any cell depleting agents including but not limited to rituximab without a normal lymphocyte and cluster of differentiation (CD) 19+ lymphocyte count • Treatment with any DMARD other than those allowed per protocol and limited to the maximum specified dosage within 12 weeks prior to baseline • Treatment with prednisone >10 mg or equivalent per day, or change in dosage within 4 weeks prior to baseline visit • Any parenteral or intra-articular glucocorticoid injection within 4 weeks prior to baseline • Prior treatment with anti- IL-6 or IL-6 receptor antagonist therapies, including tocilizumab or sarilumab, participation in a prior study of sarilumab, irrespective of treatment arm • Prior treatment with a Janus kinase inhibitor (such as tofacitinib) • New treatment or dose-adjustment to ongoing medication for dyslipidemia within 6 weeks prior to randomization, i.e. stable dose for ≥6 weeks prior to randomization • Participation in any clinical research study evaluating another investigational drug or therapy within 5 half-lives or 60 days of first investigational medicinal product (IMP) administration, whichever was longer • History of alcohol or drug abuse within 5 years prior to the screening visit • Participants with a history of malignancy other than adequately-treated carcinoma in-situ of the cervix, non-metastatic squamous cell or basal cell carcinoma of the skin, within 5 years prior to the randomization (baseline) visit. Nonmalignant lymphoproliferative disorders were also excluded

<table>
<tr><td></td><td>• Participants with active tuberculosis or latent tuberculosis infection</td></tr>
<tr><td>Intervention</td><td>Sarilumab SC 150 mg q2w (n=181), 200 mg q2w (n=184) or placebo SC (n=181) q2w in combination with a stable dose of background csDMARD(s).</td></tr>
<tr><td>Primary and secondary endpoints</td><td><u>Primary efficacy endpoints (</u>two co-primary end points were investigated)
• Proportion of patients achieving ACR20 response at week 24
• Change from baseline in physical function as assessed by HAQ-DI at week 12
<u>Secondary efficacy endpoints included</u>
• Change from baseline in DAS28-CRP at week 24
• Proportion of patients achieving ACR50 response at week 24
• Proportion of patients achieving ACR70 response at week 24
• Proportion of patients achieving DAS28-CRP score <2.6 at week 24
• Change from baseline in the HAQ-DI at week 24</td></tr>
<tr><td>Method of analysis</td><td>Primary efficacy and safety analyses were conducted in the ITT population, which consisted of all randomized patients who received ≥1 dose of sarilumab. Patients who received rescue medication or discontinued treatment were considered non-responders in the primary analysis. For the primary analysis of HAQ-DI, data collected after treatment discontinuation or rescue were classified as missing.</td></tr>
<tr><td>Subgroup analyses</td><td>Not applicable</td></tr>
<tr><td>Baseline characteristics</td><td>For clarity, only baseline characteristics for placebo plus DMARD and sarilumab 200 mg plus DMARD groups are included.
<table>
<tr><th></th><th>Placebo + csDMARD n=181</th><th>Sarilumab 200 mg + csDMARD n=184</th></tr>
<tr><td>Female, %</td><td>154 (85.1)</td><td>151 (82.1)</td></tr>
<tr><td>Age, mean±SD (years)</td><td>51.9±12.4</td><td>52.9±12.9</td></tr>
<tr><td>Race, n (%)</td><td></td><td></td></tr>
<tr><td>White, n (%)</td><td>124 (68.5)</td><td>130 (70.7)</td></tr>
<tr><td>Black, n (%)</td><td>7 (3.9)</td><td>5 (2.7)</td></tr>
<tr><td>Asian, n (%)</td><td>1 (0.6)</td><td>1 (0.5)</td></tr>
<tr><td>Other, n (%)</td><td>49 (27.1)</td><td>48 (26.1)</td></tr>
<tr><td>Geographic region 1, %†</td><td>77 (42.5)</td><td>79 (42.9)</td></tr>
<tr><td>Geographic region 2, %†</td><td>74 (40.9)</td><td>74 (40.2)</td></tr>
<tr><td>Geographic region 3, %†</td><td>30 (16.6)</td><td>31 (16.8)</td></tr>
<tr><td>Background csDMARDs</td><td></td><td></td></tr>
<tr><td>MTX, n (%)</td><td>158 (87.3)</td><td>156 (84.8)</td></tr>
<tr><td>Leflunomide, n (%)</td><td>17 (9.4)</td><td>18 (9.8)</td></tr>
<tr><td>Sulfasalazine, n (%)</td><td>5 (2.8)</td><td>15 (8.2)</td></tr>
<tr><td>Hydroxychloroquine, n (%)</td><td>10 (5.5)</td><td>13 (7.1)</td></tr>
<tr><td>Prior exposure to anti-TNF agent</td><td>181 (100)</td><td>184 (100)</td></tr>
<tr><td>1 exposure, n (%)</td><td>135 (74.6)</td><td>140 (76.5)</td></tr>
<tr><td>>1 prior exposure, n (%)</td><td>46 (25.4)</td><td>43 (23.5)</td></tr>
<tr><td>Concomitant corticosteroids, n (%)</td><td>112 (61.9)</td><td>113 (61.4)</td></tr>
<tr><td>Duration of RA, mean±SD (years)</td><td>12.0±10.0</td><td>12.7±9.6</td></tr>
<tr><td>RF positive, n (%)</td><td>142 (78.9)</td><td>132 (72.9)</td></tr>
<tr><td>Anti-CCP antibody positive, n (%)</td><td>150 (83.3)</td><td>137 (76.1)</td></tr>
<tr><td>DAS28-CRP, mean±SD</td><td>6.2±0.9</td><td>6.3±1.0</td></tr>
<tr><td>Tender joint count (of 68 joints assessed), mean±SD</td><td>29.4±14.5</td><td>29.6±15.5</td></tr>
</table></td></tr>
</table>

	Swollen joint count of 66 joints assessed), mean±SD	20.2±11.3	20.0±11.9
	HAQ-DI score, mean±SD	1.8±0.6	1.8±0.6
	CRP, mean±SD (mg/L)	26.0±25.2	30.8±28.4

7.2.3 MONARCH study

TABLE 7-6 MAIN STUDY CHARACTERISTICS – MONARCH STUDY

Trial name (official title from clinicaltrials.gov)	A randomized, double-blind, parallel-group study assessing the efficacy and safety of sarilumab monotherapy versus adalimumab monotherapy in patients with rheumatoid arthritis (MONARCH).
NCT number	NCT02332590
Objective (from clinicaltrials.gov)	Primary objective To demonstrate that sarilumab monotherapy was superior to adalimumab monotherapy with respect to signs and symptoms as assessed by DAS28- ESR in participants with active RA who were either intolerant of or considered inappropriate candidates for continued treatment with MTX, or after at least 12 weeks of continued treatment with MTX, were determined to be inadequate responders. Secondary objectives To demonstrate that sarilumab monotherapy was superior to adalimumab monotherapy in participants with active RA who were either intolerant of, or considered inappropriate candidates for continued treatment with MTX, or after at least 12 weeks of continued treatment with MTX, were determined to be inadequate responders, with respect to: • Reduction of signs and symptoms of RA • Improvement in quality of life assessed by PRO questionnaires Assessment of the safety and tolerability of sarilumab monotherapy (including immunogenicity) throughout the study.
Publications – title, author, journal, year	Efficacy and safety of sarilumab monotherapy versus adalimumab monotherapy for the treatment of patients with active rheumatoid arthritis (MONARCH): a randomised, double-blind, parallel-group phase III trial. Burmester GR et al. Ann Rheum Dis. 2017 [7].
Study type and design	A multicenter, randomized, active-controlled, double-blind, double-dummy, phase 3 superiority trial. Patients were centrally randomized using an interactive voice response system to receive sarilumab plus placebo or adalimumab plus placebo in prefilled matching syringes for SC administration for 24 weeks. Treatment and matching placebo were provided in kits suitable for double-dummy blinding. Investigators did not have access to randomization information except under exceptional medical circumstances. After week 16, dose escalation to weekly administration of adalimumab or matching placebo in the sarilumab group was permitted for patients who did not achieve ≥20% improvement in tender and swollen joint counts. DMARDs and immunosuppressive agents were discontinued prior to the study. Prior use of bDMARDs were not allowed.
Follow-up time	24 weeks of double-blind treatment.
Population (inclusion and exclusion criteria) (from clinicaltrials.gov)	Inclusion criteria • Diagnosis of RA ≥3 months duration • ACR Class I-III functional status • Active RA was defined as:

<table>
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At least 6 of 66 swollen joints and 8 of 68 tender joints, hsCRP ≥8 mg/L or ESR ≥28 mm/H, and DAS28-ESR >5.1

Participants as per Investigator judgment were either intolerant of, or considered inappropriate candidates for continued treatment with MTX, or after at least 12 weeks of continued treatment with MTX, or inadequate responders treated with an adequate MTX dose for at least 12 weeks

<u>Exclusion criteria</u>

Age <18 years or the legal age of consent in the country of the study site, whichever was higher
Current treatment with DMARDs/immunosuppressive agents including MTX, cyclosporine, mycophenolate, tacrolimus, gold, penicillamine, sulfasalazine or hydroxychloroquine within 2 weeks prior to the baseline (randomization visit) or azathioprine, cyclophosphamide within 12 weeks prior to baseline (randomization visit) or leflunomide within 8 weeks prior to the randomization visit, or 4 weeks after cholestyramine washout
Treatment with any prior biologic agent, including anti- IL-6, IL-6 receptor (IL-6R) antagonists, and prior treatment with a Janus kinase inhibitor
Use of parenteral corticosteroids or intra-articular corticosteroids within 4 weeks prior to screening

</td></tr>
<tr><td>Intervention</td><td>Sarilumab SC 200 mg q2w plus placebo q2w (n=184) or adalimumab SC 40 mg q2w plus placebo (n=185).</td></tr>
<tr><td>Primary and secondary endpoints</td><td>
<u>Primary endpoint</u>

Change from baseline in DAS28-ESR score at week 24

<u>Secondary endpoints included</u>

Proportion of patients achieving clinical remission (DAS28-ESR <2.6) at week 24
Proportion of participants achieving ACR50 criteria at week 24
Proportion of participants achieving ACR70 criteria at week 24
Proportion of participants achieving ACR20 criteria at week 24
Change from baseline in HAQ-DI at week 24

</td></tr>
<tr><td>Method of analysis</td><td>Efficacy analyses were conducted in the ITT population, which included all randomized patients, including those who increased the dose frequency of adalimumab or matching placebo. Data collected after permanent treatment discontinuation were excluded.</td></tr>
<tr><td>Subgroup analyses</td><td>Not applicable</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th></th><th>Adalimumab 40mg sc q2w n=185</th><th>Sarilumab 200 mg sc q2w n=184</th></tr>
<tr><td>Age, mean±SD (years)</td><td>53.6±11.9</td><td>50.9±12.6</td></tr>
<tr><td>Female, n (%)</td><td>150 (81.1)</td><td>157 (85.3)</td></tr>
<tr><td>Race White, n (%)</td><td>164 (88.6)</td><td>171 (92.9)</td></tr>
<tr><td>Geographic region 1†</td><td>62 (33.5)</td><td>61 (33.2)</td></tr>
<tr><td>Geographic region 2†</td><td>35 (18.9)</td><td>36 (19.6)</td></tr>
<tr><td>Geographic region 3†</td><td>88 (47.6)</td><td>87 (47.3)</td></tr>
<tr><td>Duration of RA, mean±SD (years)</td><td>6.6±7.8</td><td>8.1±8.1</td></tr>
<tr><td>RF positive, n (%)</td><td>116 (64.8)</td><td>119±66.9</td></tr>
<tr><td>Anti-CCP antibody positive, n (%)</td><td>138 (76.7)</td><td>134 (75.3)</td></tr>
<tr><td>Number of prior csDMARDs, n (%)</td><td></td><td></td></tr>
</table>
</td></tr>
</table>

	1	88 (47.6)	83 (45.1)
	2	58 (31.4)	57 (31.0)
	≥3	39 (21.1)	44 (23.9)
	Prior csDMARDs other than MTX, n (%)		
	Sulfasalazine	44 (23.8)	59 (32.1)
	Leflunomide	45 (24.3)	42 (22.8)
	Hydroxychloroquine	43 (23.2)	41 (22.3)
	Prior csDMARDs in combination with MTX, n (%)	44 (23.8)	35 (19.0)
	Reason for stopping MTX, n (%)		
	Inadequate responder	103 (55.7)	97 (52.7)
	Intolerant	81 (43.8)	87 (47.3)
	Inappropriate for continued treatment	1 (0.5)	0
	Concomitant oral corticosteroids, n (%)	104 (56.2)	98 (53.3)
	DAS28-ESR, mean±SD	6.8±0.8	6.8±0.8
	Swollen joint count (of 66 joints assessed), mean±SD	17.5±10.3	18.6±10.7
	Tender joint count (of 68 joints assessed), mean±SD	26.7±13.6	28.0±13.2
	CRP, mean±SD (mg/L)	24.1±31.0	17.4±21.3
	HAQ-DI score, mean±SD	1.6±0.6	1.6±0.6

7.2.4 CHARISMA study

TABLE 7-7 MAIN STUDY CHARACTERISTICS – CHARISMA STUDY

Trial name	The Chugai humanized anti-human recombinant interleukin-6 monoclonal antibody (CHARISMA) study.
NCT number	Not available
Objective	To establish the safety and efficacy of repeat infusions of tocilizumab, alone and in combination with MTX, in patients with established RA in whom the response to MTX was inadequate and who had continuing disease activity.
Publications – title, author, journal, year	Double-blind randomized controlled clinical trial of the interleukin-6 receptor antagonist, tocilizumab, in European patients with rheumatoid arthritis who had an incomplete response to methotrexate. Maini RN et al. Arthritis Rheum. 2006 [8].
Study type and design	Randomized, double-blind, controlled trial. Randomization was performed centrally and allocation to treatment was done by use of an interactive voice response system, determining inclusion into the group that would minimize any imbalances between MTX dose level at baseline and between patients from a center. All patients and investigators were blinded to the study treatments. MTX had to be stable for ≥4 weeks prior to baseline.
Follow-up time	4 weeks run-in phase, 16 weeks of double-blind treatment and 4 weeks of safety follow-up.
Population (inclusion and exclusion criteria) (as described in article)	Inclusion criteria were a diagnosis of RA according to the ACR revised criteria, disease duration of at least 6 months, active disease (defined as ≥6 tender joints and ≥6 swollen joints, based on a 28-joint count), an ESR ≥28 mm/hour, and/or a CRP level ≥1.0 mg/dL. Patients must also have shown an inadequate response to MTX or a disease flare while receiving MTX (at a dosage of 10-25 mg weekly) during a minimum of 6 months of therapy. An inadequate response was defined as the presence of active disease, as described above, despite MTX therapy. If patients required concomitant treatment with NSAIDs and/or oral steroids, the dose must have been stable for at least 4 weeks prior to study entry and during the course of the study (for steroids, ≤10 mg prednisolone or equivalent). Exclusion criteria included leukopenia (white blood cell count <4.0 x 10^9/liter, absolute neutrophil count <2.0 x 10^9/liter) and/or thrombocytopenia (platelet count <150 x 10^9/liter), any hepatic dysfunction as shown by aspartate transaminase (AST) and alanine transaminase (ALT) levels >1.5-fold the upper limit of normal or significant renal impairment (serum creatinine level >1.5-fold the upper limit of normal). Patients who received DMARDs (excluding MTX) within 4 weeks prior to the start of the study were excluded, as were patients who received anti-TNF agents within 12 weeks or leflunomide within 6 months of infusion of study medication.
Intervention	*Monotherapy*: IV infusions of tocilizumab 2 mg/kg (n=53), 4 mg/kg (n=54) and 8 mg/kg (n=52) q4w in combination with MTX placebo qw. Patients allocated to tocilizumab monotherapy were switched to MTX placebo on day 0. *Combination therapy*: IV infusions of tocilizumab 2 mg/kg (n=52), 4 mg/kg (n=49) and 8 mg/kg (n=50) q4w in combination with a stable dose of MTX (10-25 mg/week) qw. *Control group*: placebo infusions q4w and a stable dose of MTX (10-25 mg/week) qw (n=49).

<table>
<tr><td></td><td>All patients received 5 mg of folic acid weekly for the duration of the study.</td></tr>
<tr><td>Primary and secondary endpoints</td><td><u>Primary endpoint</u>
• Proportion of patients achieving ACR20 response at week 16
<u>Secondary endpoints included</u>
• ACR50 and ACR70 responses, percent and absolute change from baseline in individual disease activity measures (swollen joint count, tender joint count, physician’s global assessment of disease activity, patient’s global assessment of disease activity, patient’s pain score, ESR, CRP level, HAQ score), as well as changes in the duration of early morning stiffness and DAS28.</td></tr>
<tr><td>Method of analysis</td><td>For efficacy endpoints, an ITT full-analysis set was used, comprising all patients who were allocated to receive study medication, had received ≥1 dose, and had post-randomization efficacy data available. All patients who withdrew because of lack of efficacy before the week 16 assessment were included in the analysis as non-responders. For patients who withdrew because of other reasons, the last recorded assessment was carried forward.</td></tr>
<tr><td>Subgroup analyses</td><td>Not applicable</td></tr>
<tr><td>Baseline characteristics</td><td>For clarity, only baseline characteristics for placebo plus MTX and tocilizumab 8 mg/kg plus MTX are included.
<table>
<tr><th></th><th>Placebo + MTX n=49</th><th>Tocilizumab 8 mg/kg + MTX n=50</th></tr>
<tr><td>Age, mean (years)</td><td>50.9</td><td>50.1</td></tr>
<tr><td>Females/males, n</td><td>11/38</td><td>11/39</td></tr>
<tr><td>Duration of RA (months)</td><td>11.2</td><td>10.6</td></tr>
<tr><td>Swollen joint count (28 joints), mean</td><td>16</td><td>15</td></tr>
<tr><td>Tender joint count (28 joints), mean</td><td>12</td><td>11</td></tr>
<tr><td>ESR, mean (mm/hour)</td><td>43</td><td>39†</td></tr>
<tr><td>CRP, mean (mg/L)</td><td>32</td><td>24†</td></tr>
<tr><td>DAS28, mean</td><td>6.75</td><td>6.47†</td></tr>
<tr><td>RF positive, n</td><td>47</td><td>40</td></tr>
<tr><td>MTX dose, n</td><td></td><td></td></tr>
<tr><td>10-12.5 mg/week</td><td>17</td><td>18</td></tr>
<tr><td>15-17.5 mg/week</td><td>24</td><td>24</td></tr>
<tr><td>20-25 mg/week</td><td>8</td><td>8</td></tr>
<tr><td>Patients assessment of pain, mean</td><td>63.8</td><td>57.0†</td></tr>
<tr><td>Duration of MTX therapy, mean±SD (months)</td><td>33.3±27.8</td><td>40.4±32.7</td></tr>
<tr><td>Patient’s global assessment of disease activity, mean</td><td>68.8</td><td>62.1†</td></tr>
<tr><td>Physician’s global assessment of disease activity, mean</td><td>66.0</td><td>61.3†</td></tr>
<tr><td>Duration of early morning stiffness, mean (minutes)</td><td>90.0</td><td>120.0†</td></tr>
</table>
†n=49 patients</td></tr>
</table>

7.2.5 OPTION study

TABLE 7-8 MAIN STUDY CHARACTERISTICS – OPTION STUDY

Trial name (official title from clinicaltrials.gov)	A randomized, double-blind study of safety and reduction in signs and symptoms during treatment with tocilizumab versus placebo, in combination with methotrexate, in patients with moderate to severe rheumatoid arthritis.
NCT number	NCT00106548
Objective	To assess the efficacy of tocilizumab in patients with active rheumatoid arthritis who were receiving background MTX therapy.
Publications – title, author, journal, year	Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. Smolen JS et al. Lancet. 2008 [9].
Study type and design	Randomized, double-blind, placebo-controlled, parallel group, phase 3, three arm, international study. Patients were randomly assigned to receive tocilizumab 4 mg/kg, 8 mg/kg or placebo q4w for 24 weeks in combination with weekly administration of their stable dose of MTX. Randomization was done centrally with an interactive voice response system and stratified by site. Swollen and tender joint counts were performed by trained assessors with no access to patient data, and a physician blinded to patients' treatment made all treatment decisions based on the clinical response and safety data. Patients who did not achieve ≥20% improvement from baseline in both swollen and tender joint counts by week 16 were offered rescue therapy. MTX had to be stable ≥8 weeks before start of the study. All other DMARDs and biological agents were discontinued before the start of the study.
Follow-up time	24-week blinded treatment period followed by 8 weeks of safety follow-up.
Population (inclusion and exclusion criteria) (from clinicaltrials.gov)	Inclusion criteria • Adult patients at least 18 years of age with moderate to severe active RA for at least 6 months • Inadequate response to a stable dose of MTX • Patients of reproductive potential must be using reliable methods of contraception Exclusion criteria • Major surgery (including joint surgery) within 8 weeks before entering study, or planned surgery within 6 months after entering study • Prior treatment failure with an anti-TNF agent • Women who are pregnant or breast-feeding
Intervention	Tocilizumab 8 mg/kg IV (n=205), 4 mg/kg IV (n=214) or placebo (n=204) IV q4w in combination with a stable dose of MTX (10-25 mg/week). Oral corticosteroids (≤10 mg/day of prednisone or equivalent) and NSAIDs were permitted if the dosages had been stable for ≥6 weeks before study entry. All patients received ≥5 mg/week of folic acid.

<table>
<tr><td>Primary and secondary endpoints</td><td><u>Primary endpoint</u>
• Proportion of patients with ACR20 response at week 24
<u>Secondary endpoints included</u>
• Proportion of patients with ACR50 response at week 24
• Proportion of patients with ACR70 response at week 24
• Change from baseline to week 24 in ACR core set components
• DAS28
• EULAR
• HAQ-DI</td></tr>
<tr><td>Method of analysis</td><td>Efficacy analyses were performed on the ITT population, i.e. all patients randomized who received ≥one infusion of study drug. The safety population included all randomized patients who received ≥one infusion of study medication and who had ≥one assessment of safety after randomization. Patients who withdrew before week 24, patients who received rescue therapy and patients whose week 24 categorical endpoints could not be determined due to insufficient data were deemed to be non-responders in the analysis. LOCF imputation was used for tender and swollen joint counts; no imputation was used for missing HAQ, CRP, ESR, and global VAS data.</td></tr>
<tr><td>Subgroup analyses</td><td>Not applicable</td></tr>
<tr><td>Baseline characteristics</td><td>For clarity, only baseline characteristics for placebo plus MTX and tocilizumab 8 mg/kg plus MTX are included.
<table>
<tr><th></th><th>Tocilizumab 8 mg/kg + MTX n=205</th><th>Placebo + MTX n=204</th></tr>
<tr><td>Age, mean±SD (years)</td><td>50.8 (11.8)</td><td>50.6 (12.1)</td></tr>
<tr><td>Males, n (%)</td><td>30 (15)</td><td>45 (22)</td></tr>
<tr><td>Disease duration, mean±SD (years)</td><td>7.5 (7.3)</td><td>7.8 (7.2)</td></tr>
<tr><td>MTX dose, mean±SD (mg/week)</td><td>14.5 (4.4)</td><td>14.8 (4.2)</td></tr>
<tr><td>Number of DMARDs (other than MTX) used before study, mean±SD</td><td>1.5 (1.4)</td><td>1.7 (1.5)</td></tr>
<tr><td>Concomitant steroids, n (%)</td><td>112 (55)</td><td>111 (54)</td></tr>
<tr><td>Previous anti-TNF treatment, n (%)</td><td>11 (5)</td><td>19 (9)</td></tr>
<tr><td>Concomitant NSAIDs, n (%)</td><td>135 (66)</td><td>139 (68)</td></tr>
<tr><td>RF positive (RF ≥15 U/mL), n (%)</td><td>171 (83)</td><td>144 (71)</td></tr>
<tr><td>CRP, mean±SD (mg/L)</td><td>26 (26)</td><td>24 (28)</td></tr>
<tr><td>ESR, mean±SD (mm/hour)</td><td>51.2 (26.6)</td><td>49.7 (26.3)</td></tr>
<tr><td>DAS28 score, mean±SD</td><td>6.8 (0.9)</td><td>6.8 (0.9)</td></tr>
<tr><td>Swollen joint count (28 joints), mean</td><td>19.5 (11.3)</td><td>20.7 (11.7)</td></tr>
<tr><td>Tender joint count (28 joints), mean</td><td>31.9 (15.5)</td><td>32.8 (16.1)</td></tr>
<tr><td>Patient pain VAS, mean±SD (mm)</td><td>59.9 (22.4)</td><td>57.3 (22.2)</td></tr>
<tr><td>Patient global VAS, mean±SD (mm)</td><td>64.8 (22.1)</td><td>63.6 (21.8)</td></tr>
<tr><td>Physician global VAS, mean±SD (mm)</td><td>64.0 (15.3)</td><td>63.7 (14.8)</td></tr>
<tr><td>HAQ-DI score, mean±SD</td><td>1.6 (0.6)</td><td>1.5 (0.6)</td></tr>
</table></td></tr>
</table>

7.2.6 TOWARD study

TABLE 7-9 MAIN STUDY CHARACTERISTICS – TOWARD STUDY

Trial name (official title from clinicaltrials.gov)	A randomized, double-blind study of the effect of tocilizumab on reduction in signs and symptoms in patients with moderate to severe active rheumatoid arthritis and inadequate response to DMARD therapy.
NCT number	NCT00106574
Objective	To examine the efficacy and safety of tocilizumab combined with conventional DMARDs in patients with moderate to severe active RA with an inadequate response to these agents.
Publications – title, author, journal, year	Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: the tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. Genovese MC et al. Arthritis Rheum. 2008 [10].
Study type and design	Randomized, double-blind, placebo-controlled, parallel group, international, multicenter, phase 3 study. Patients were randomly assigned in a 2:1 ratio to receive tocilizumab 8 mg/kg or placebo in combination with their stable DMARD therapy. Patients were assessed using a dual-assessor approach for efficacy and safety evaluations to ensure that blinding was not compromised. Tender and swollen joint counts were performed by trained assessors with no access to patient data. Patients who did not achieve ≥20% improvement from baseline in both swollen and tender joint counts by week 16 were offered rescue therapy. Allowed DMARD therapy (MTX, chloroquine, hydroxychloroquine, parenteral gold, sulfasalazine, azathioprine, and leflunomide) had to be stable ≥8 weeks before start of the study.
Follow-up time	24-week blinded treatment period.
Population (inclusion and exclusion criteria) (from clinicaltrials.gov)	Inclusion criteria • Patients at least 18 years of age with moderate to severe active RA for at least 6 months • Inadequate response to current anti-rheumatic therapies, including 1 or more traditional DMARDs • Stable DMARD therapy for at least 8 weeks before entering study • Patients of reproductive potential must be using reliable methods of contraception Exclusion criteria • Major surgery (including joint surgery) within 8 weeks before entering study, or planned surgery within 6 months after entering study • Patients who have previously failed treatment with an anti-TNF agent • Women who are pregnant or breast-feeding
Intervention	Tocilizumab 8 mg/kg IV (n=805) or placebo (n=415) IV q4w in combination with stable DMARD therapy.

<table>
<tr><td></td><td>Oral corticosteroids (≤10 mg/day of prednisone or equivalent) and NSAIDs/COX2 inhibitors were permitted if the dosages had been stable for ≥6 weeks before study entry. All patients received a stable dose of ≥5 mg/week of folic acid.</td></tr>
<tr><td>Primary and secondary endpoints</td><td><u>Primary endpoint</u>
• Proportion of patients with ACR20 response at week 24
<u>Secondary endpoints included</u>
• Proportion of patients with ACR 50 and ACR 70 responses at week 24
• Mean changes in parameters of ACR core set at week 24
• DAS28-ESR
• EULAR
• HAQ-DI
• FACIT-F
• SF-36</td></tr>
<tr><td>Method of analysis</td><td>Efficacy analyses were performed in the ITT population which included all randomized patients who received ≥1 dose of study treatment. Patients who did not have the required data for a specific time point, who withdrew from the study or who received rescue therapy were classified as non-responders. Safety analyses included all patients who received ≥1 infusion of study treatment and had ≥1 post randomization safety assessment.</td></tr>
<tr><td>Subgroup analyses</td><td>Not applicable</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th></th><th>Tocilizumab 8 mg/kg + DMARDs n=803</th><th>Placebo + DMARDs n=413</th></tr>
<tr><td>Age, mean±SD (years)</td><td>53±13</td><td>54±13</td></tr>
<tr><td>Weight, mean±SD (kg)</td><td>74±18</td><td>73±18</td></tr>
<tr><td>Female, n (%)</td><td>81 (10.1)</td><td>84 (20.3)</td></tr>
<tr><td>Race, %</td><td></td><td></td></tr>
<tr><td>White</td><td>72</td><td>72</td></tr>
<tr><td>Asian Black</td><td>9</td><td>10</td></tr>
<tr><td>American Indian or Native Alaskan</td><td>10</td><td>8</td></tr>
<tr><td>Black</td><td>4</td><td>7</td></tr>
<tr><td>Other</td><td>3</td><td>3</td></tr>
<tr><td>Disease duration</td><td></td><td></td></tr>
<tr><td>mean±SD (years)</td><td>9.8±8.8</td><td>9.8±9.1</td></tr>
<tr><td>Median (minimum-maximum years)</td><td>7.0 (0.4-46.1)</td><td>6.8 (0.5-44.4)</td></tr>
<tr><td>Disease duration <2 years (%)</td><td>19</td><td>20</td></tr>
<tr><td>DAS28, mean±SD</td><td>6.7±1.0</td><td>6.6±1.0</td></tr>
<tr><td>Previous no. of DMARDs/anti-TNF agents taken, mean±SD</td><td>1.6±1.6</td><td>1.6±1.6</td></tr>
<tr><td>No. of background DMARDs</td><td></td><td></td></tr>
<tr><td>1</td><td>77</td><td>75</td></tr>
<tr><td>2 or more</td><td>22</td><td>24</td></tr>
<tr><td>None</td><td>1</td><td>1</td></tr>
<tr><td>Medication at baseline (%)</td><td></td><td></td></tr>
<tr><td>MTX</td><td>75.8</td><td>73.9</td></tr>
<tr><td>Chloroquine/Hydroxychloroquine</td><td>20.6</td><td>19.8</td></tr>
<tr><td>Sulfasalazine</td><td>13.1</td><td>14.3</td></tr>
<tr><td>Leflunomide</td><td>12.1</td><td>15.5</td></tr>
<tr><td>Parenteral gold</td><td>0.2</td><td>0.7</td></tr>
</table>
</td></tr>
</table>

	Azathioprine	2.2	2.2
	Oral steroids	51.2	54.6
	Folic acid	71.8	70.0
	NSAIDs	71.4	77.1
	Other	36.9	34.5
	MTX dosage at baseline, mean (mg/week)	14.7	15.0
	Tender joint count (66 joints assessed), mean±SD	30.1±16.0	29.1±14.8
	Swollen joint count (68 joints assessed), mean±SD	19.7±11.6	18.7±10.8
	C-reactive protein, mean±SD (mg/dL)	2.6±3.2	2.6±4.7
	ESR, mean±SD (mm/hour)	48.2±27.5	49.2±28.3
	HAQ disability index score (0-3 scale), mean±SD	1.5±0.6	1.5±0.6
	Patient's assessment of pain, by VAS (0-100-scale), mean±SD	58±23	59±23
	Patient's assessment of disease activity, by VAS (0-100-mm scale), mean±SD	66±23	66±24
	Physician's assessment of disease activity, by VAS (0-100-mm scale), mean±SD	64±16	63±17

7.2.7 ROSE study

TABLE 7-10 MAIN STUDY CHARACTERISTICS – ROSE STUDY

Trial name (official title from clinicaltrials.gov)	A randomized, double-blind, parallel-group study to evaluate the safety and efficacy of tocilizumab versus placebo in combination with DMARDs in patients with moderate to severe active rheumatoid arthritis.
NCT number	NCT00531817
Objective	To evaluate the efficacy of tocilizumab in US patients with moderate to severe active RA and inadequate clinical response to DMARDs.
Publications – title, author, journal, year	Efficacy of tocilizumab in patients with moderate to severe active rheumatoid arthritis and a previous inadequate response to disease-modifying antirheumatic drugs: the ROSE study. Yazici Y et al. Ann Rheum Dis. 2012 [11].
Study type and design	Randomized, double-blind, placebo-controlled, parallel-group, multicenter, phase 3b clinical trial. Patients were randomly assigned 2:1 to receive tocilizumab 8 mg/kg IV q4w plus stable antirheumatic therapy including DMARD or placebo IV q4w plus DMARD. Doses of permitted DMARD were required to remain stable from ≥7 weeks prior to baseline and throughout the study. Patients were required to discontinue previous biological therapy before randomization. Rescue therapy was permitted from week 16 for patients who did not achieve a ≥20% improvement from baseline in swollen and tender joint counts. The study management team, investigational staff and monitors remained blinded to individual patients' treatment assignments.
Follow-up time	24 weeks blinded treatment period.
Population (inclusion and exclusion criteria) (from clinicaltrials.gov)	Inclusion criteria • Adult patients, ≥18 years of age • Active RA of >6 months duration • Received permitted DMARDs each at a stable dose for ≥7 weeks prior to baseline Exclusion criteria • Rheumatic autoimmune disease or inflammatory joint disease other than RA • Major surgery within 8 weeks prior to screening or planned within 6 months following randomization • Unsuccessful treatment with a biologic agent, including an anti-TNF agent • Previous treatment with tocilizumab
Intervention	Tocilizumab 8 mg/kg IV q4w plus stable antirheumatic therapy including DMARD (n=409) or placebo IV q4w plus DMARD (n=205). Corticosteroids and NSAIDs were allowed in stable dose.
Primary and secondary endpoints	Primary endpoint • Proportion of patients with ACR50 response at week 24 Secondary endpoints included At weeks 4, 8, 12, 16, 20, 24: • Proportion of patients with ACR20, ACR50 or ACR70 response

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

EULAR
DAS-28
ESR level
CRP level
FACIT-F

</td></tr>
<tr><td>Method of analysis</td><td>The intent-to-treat (ITT) population consisted of all randomly assigned patients who received at least one administration of study medication. The safety population included all patients who received at least one administration of study medication and who had at least one safety assessment after receiving study medication. Patients who received rescue therapy and patients who did not have data required to assess efficacy outcomes at week 24 were classified as non-responders. LOCF methodology was used for missing joint count data. Groups were not stratified by history of TNF inhibitor use.</td></tr>
<tr><td>Subgroup analyses</td><td>Not applicable</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th></th><th>Tocilizumab 8 mg/kg + DMARD n=409</th><th>Placebo + DMARD n=205</th></tr>
<tr><td>Women, n (%)</td><td>325 (79.5)</td><td>172 (83.9)</td></tr>
<tr><td>Age, mean±SD (years)</td><td>55.2±12.06</td><td>55.8±12.42</td></tr>
<tr><td>Race, n (%)</td><td></td><td></td></tr>
<tr><td>White</td><td>328 (80.2)</td><td>170 (82.9)</td></tr>
<tr><td>Black</td><td>53 (13.0)</td><td>17 (8.3)</td></tr>
<tr><td>Hispanic</td><td>12 (2.9)</td><td>9 (4.4)</td></tr>
<tr><td>Asian</td><td>7 (1.7)</td><td>4 (2.0)</td></tr>
<tr><td>American Indian/Alaska native</td><td>4 (1.0)</td><td>3 (1.5)</td></tr>
<tr><td>Other</td><td>5 (1.2)</td><td>2 (1.0)</td></tr>
<tr><td>Duration of RA, mean±SD (years)</td><td>8.62±8.93</td><td>8.52±9.05</td></tr>
<tr><td>DAS28, mean±SD</td><td>6.53±1.03</td><td>6.55±1.01</td></tr>
<tr><td>Number of previous DMARD/anti-TNF, mean±SD</td><td>1.35±1.41</td><td>1.31±1.23</td></tr>
<tr><td>Past use of anti-TNF, n (%)</td><td>155 (37.9)</td><td>78 (38.0)</td></tr>
<tr><td>Number of past anti-TNF, n (%)</td><td></td><td></td></tr>
<tr><td>1</td><td>110 (26.9)</td><td>55 (26.8)</td></tr>
<tr><td>2</td><td>35 (8.6)</td><td>21 (10.2)</td></tr>
<tr><td>3</td><td>10 (2.4)</td><td>2 (1.0)</td></tr>
<tr><td>Reasons for anti-TNF continuation, n (%)</td><td>n = 155</td><td>n = 78</td></tr>
<tr><td>Discomfort</td><td>19 (12.3)</td><td>9 (11.5)</td></tr>
<tr><td>Lack of efficacy</td><td>19 (12.3)</td><td>9 (11.5)</td></tr>
<tr><td>Safety</td><td>7 (4.5)</td><td>3 (3.8)</td></tr>
<tr><td>Other</td><td>127 (81.9)</td><td>65 (83.3)</td></tr>
<tr><td>Unknown</td><td>2 (1.3)</td><td>2 (2.6)</td></tr>
<tr><td>Past use of DMARD, n (%)</td><td>278 (68.0)</td><td>144 (70.2)</td></tr>
<tr><td>Number of past DMARDs, n (%)</td><td>n = 134</td><td>n = 62</td></tr>
<tr><td>1</td><td>130 (31.8)</td><td>69 (33.7)</td></tr>
<tr><td>2</td><td>75 (18.3)</td><td>44 (21.5)</td></tr>
<tr><td>3</td><td>42 (10.3)</td><td>18 (8.8)</td></tr>
<tr><td>4</td><td>18 (4.4)</td><td>8 (3.9)</td></tr>
<tr><td>5</td><td>7 (1.7)</td><td>5 (2.4)</td></tr>
<tr><td>>5</td><td>6 (1.5)</td><td>0</td></tr>
<tr><td>Reasons for DMARD discontinuation (antimetabolite)*, n (%)</td><td>134</td><td>62</td></tr>
<tr><td>Discomfort</td><td>16 (11.9)</td><td>5 (8.1)</td></tr>
</table>
</td></tr>
</table>

Lack of efficacy	40 (29.9)	14 (22.6)
Safety	6 (4.5)	5 (8.1)
Other	38 (28.4)	11 (17.7)
Unknown	45 (33.6)	30 (48.4)
Number of background DMARD, n (%)		
1	354 (86.6)	175 (85.4)
2	48 (11.7)	27 (13.2)
3 or more	6 (1.5)	2 (1.0)
None	1 (0.2)	1 (0.5)
MTX dose, n	n = 353	n = 178
Mean±SD (mg/week)	17.0±4.68	17.2±10.71
Oral steroid use, n (%)	176 (43)	80 (39)
Swollen joint count, mean±SD	19.7±12.4	19.9±12.1
Tender joint count, mean±SD	29.7±16.5	30.4±16.9
ESR, mean±SD (mm/h)†	46.0±23.64	47.3±22.42
CRP, mean±SD (nmol/h)‡	174.3±218.4	171.4±212.0
Patient's global assessment of pain, mean±SD (VAS 0-100 mm)†	56.5±22.6	55.9±22.8
Patient's global assessment of disease activity, mean±SD (VAS 0-100 mm)†	62.3±22.5	61.7±21.9
Physician's global assessment of disease activity, mean±SD (VAS 0-100 mm)†	62.2±18.25	62.8±18.33

*Lack of efficacy was also the most common reason for discontinuation of antimalarial agents and gold.

†Sample size differed from the ITT population for the following parameters: ESR (tocilizumab, n = 408); patient's global assessment of pain (tocilizumab, n=405; placebo, n=203), patient's global assessment of disease (tocilizumab n=405, placebo n=203); physician's global assessment of disease (tocilizumab, n=408; placebo, n=203).

7.2.8 LITHE study

TABLE 7-11 MAIN STUDY CHARACTERISTICS – LITHE STUDY

Trial name (official title from clinicaltrials.gov)	A randomized, double-blind study of safety and prevention of structural joint damage during treatment with tocilizumab versus placebo, in combination with methotrexate, in patients with moderate to severe rheumatoid arthritis.
NCT number	NCT00106535
Objective	To assess the efficacy and safety of tocilizumab plus MTX versus MTX alone in preventing structural joint damage and improving physical function and disease activity in patients with moderate to severe RA and inadequate responses to MTX.
Publications – title, author, journal, year	Tocilizumab inhibits structural joint damage in rheumatoid arthritis patients with inadequate responses to methotrexate: results from the double-blind treatment phase of a randomized placebo-controlled trial of tocilizumab safety and prevention of structural joint damage at one year. Kremer JM et al. Arthritis Rheum. 2011 [12]. Tocilizumab inhibits structural joint damage and improves physical function in patients with rheumatoid arthritis and inadequate responses to methotrexate: LITHE study 2-year results. Fleischmann et al. J Rheumatol. 2013 (excluded). Clinical efficacy and safety maintained up to 5 years in patients with rheumatoid arthritis treated with tocilizumab in a randomised trial. Kremer JM et al. Clin Exp Rheumatol. 2016 (excluded).
Study type and design	Randomized, placebo-controlled, parallel-group, multicenter, phase 3 trial. Patients were randomized to IV tocilizumab 8 mg/kg, 4 mg/kg or placebo (1:1:1 ratio) q4w in combination with a stable dose of MTX. Randomization was stratified by site. Patients who did not achieve ≥20% improvement from baseline in swollen and tender joint counts by week 16 were offered rescue therapy in 2 steps. Patients who did not respond to second-step rescue therapy discontinued treatment. Each investigator used his or her own clinical judgment to determine whether a patient should discontinue the study because of insufficient clinical response. MTX had to be stable ≥8 weeks before baseline. All other DMARDs and biological agents were discontinued before study entry.
Follow-up time	1 year double-blind, placebo-controlled treatment phase followed by a second year of open-label therapy and an optional 3-year open-label extension phase (second year and extension study not reported here).
Population (inclusion and exclusion criteria) (from clinicaltrials.gov)	<u>Inclusion criteria</u> • Adult patients at least 18 years of age with moderate to severe active RA for at least 6 months • Inadequate response to a stable dose of MTX • Patients of reproductive potential must be using reliable methods of contraception <u>Exclusion criteria</u> • Major surgery (including joint surgery) within 8 weeks before entering study, or planned surgery within 6 months after entering study • Prior treatment failure with an anti-TNF agent

	• Women who are pregnant or breast-feeding
Intervention	Tocilizumab 8 mg/kg IV (n=398), 4 mg/kg IV (n=399) or placebo (n=393) IV q4w in combination with a stable dose of MTX (10-25 mg/week). Oral corticosteroids (≤10 mg/day of prednisone or equivalent) and NSAIDs were permitted if the dosages had been stable for ≥6 weeks before study entry. All patients received ≥5 mg/week of folic acid.
Primary and secondary endpoints	<u>Co-primary endpoints at week 52</u> • Change from baseline in the total Genant-modified Sharp score and • Change in physical function as measured by the area under the curve AUC for change from baseline in HAQ-DI <u>Secondary endpoints included</u> • Change from baseline in erosion and joint space narrowing scores (weeks 24 and 52) • Total Genant-modified Sharp score at week 24 • Proportions of patients with no progression of the total, erosion, or joint space narrowing scores (no progression of the total score was an exploratory analysis) • ACR20, ACR50 and ACR70 • Change in DAS28-ESR • Proportions of patients with low levels of disease activity (DAS28 ≤3.2) • DAS remission (DAS28 <2.6)
Method of analysis	Efficacy analyses were conducted using the ITT population, which included all randomly assigned patients who received ≥1 dose of study medication. Safety analyses were conducted in all patients who received ≥1 dose of study medication and who had ≥1 post-randomization assessment of safety. For efficacy analyses, only data obtained until the switch to rescue therapy were included. Missing or post-rescue radiographic data at week 52 were imputed by linear extrapolation for any patient with 1 baseline assessment and ≥1 postbaseline assessment before rescue therapy. The AUC of the change in the HAQ DI was calculated using the latest non-missing values before rescue/missing data and then standardized to 52 weeks. For analyses of continuous variables, data obtained after the switch to rescue therapy were excluded. ACR20, ACR50, and ACR70 response rates were analyzed with non-responder imputation (any missing or post-rescue data).
Subgroup analyses	Not applicable

Baseline characteristics

	Tocilizumab 8 mg/kg + MTX n=398	**Placebo + MTX n=393**
Female/male (%)	82/18	83/17
Age, mean±SD (years)	53.4±11.7	51.3±12.4
MTX dose, mean±SD (mg/week)	15.4±10.6	15.0±4.2
No. of previous DMARDs/anti-TNF agents, mean±SD†	1.6±1.4	1.6±1.5
Past use of DMARDs, %†	75.4	71.2
Past use of anti-TNF agents, %	10.8	11.5
Taking concomitant steroids, %	62	70
Duration of RA, mean (range) (years)	9.3 (0.6-48.8)	9.0 (0.5-44.3)
Rheumatoid factor positive, %	83	82
DAS28, mean±SD	6.6±1.0	6.5±1.0
Total Genant-modified Sharp score, mean (range)‡	28.8 (0-178.7)	28.5 (0-190.5)
Swollen joint count (n = 66), mean±SD	17.3±9.5	16.6±9.2
Total joint count (n = 68), mean±SD	29.3±15.2	27.9±14.8
HAQ score, mean±SD	1.5±0.6	1.5±0.6
CRP, mean±SD (mg/dl)	2.3±2.6	2.2±2.5
ESR, mean±SD (mm/hour)	46.4±24.8	46.5±24.7
Estimated yearly rate of progression in the total Genant-modified Sharp score§	3.1	3.2

For clarity, only baseline characteristics for tocilizumab 8 mg/kg plus MTX and placebo plus MTX are included.

†Not counting MTX, to which patients had shown an inadequate response at the time of screening.

‡ Because erosions were not restricted to the joints that were assessed by the total Genant-modified Sharp score, some patients had an erosion score of 0 at baseline despite the presence of at least 1 erosion.

§ Calculated as the baseline total Genant-modified Sharp score divided by the mean duration of disease at baseline.

7.2.9 RADIATE study

TABLE 7-12 MAIN STUDY CHARACTERISTICS – RADIATE STUDY

Trial name	A randomized, double-blind study of safety and reduction in signs and symptoms during treatment with tocilizumab versus placebo, in combination with methotrexate, in patients with moderate to severe active rheumatoid arthritis and inadequate response to anti-TNF therapy.
NCT number	NCT00106522
Objective	To compare the safety and efficacy, with regard to reduction of signs and symptoms, of tocilizumab versus placebo in combination with MTX in patients with moderate to severe active RA currently on MTX therapy, and who have had an inadequate response to prior therapy with an anti-TNF agent.
Publications – title, author, journal, year	IL 6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. Emery P et al. Ann Rheum Dis. 2008 [13]. Improvements in health-related quality of life after treatment with tocilizumab in patients with rheumatoid arthritis refractory to tumour necrosis factor inhibitors: results from the 24-week randomized controlled RADIATE study. Strand V et al. Rheumatology (Oxford). 2012 (excluded, no usable data).
Study type and design	A randomized, double-blind, placebo controlled, parallel group, phase 3 study. Participants were randomly assigned to tocilizumab IV 8 mg/kg, 4 mg/kg or placebo IV q4w. Joint assessors were blinded to other data. Rescue therapy was offered at week 16 in all cases of treatment failure (<20% improvement in both swollen and tender joint count).
Follow-up time	24 weeks double-blind treatment period.
Population (inclusion and exclusion criteria) (from Clinicaltrials.gov)	<u>Inclusion criteria</u> • Adult patients at least 18 years of age with moderate to severe active RA for at least 6 months • Inadequate response to current anti-rheumatic therapies, including MTX • Inadequate response or intolerance to treatment with 1 or more anti-TNF therapies within 1 year of entering study • On stable MTX for at least 8 weeks before entering study • Patients of reproductive potential must be using reliable methods of contraception <u>Exclusion criteria</u> • Major surgery (including joint surgery) within 8 weeks before screening, or planned major surgery within 6 months after entering study • Women who are pregnant or breast-feeding
Intervention	Tocilizumab 8 mg/kg IV (n=175), 4 mg/kg IV (n=163) or placebo (n=160) IV q4w in combination with a stable dose of MTX (10-25 mg/week). No other DMARDs were allowed. Oral corticosteroids (≤10 mg/day of prednisone or equivalent) and NSAIDs were permitted. All patients received folic acid.

<table>
<tr><td>Primary and secondary endpoints
(from clinicaltrials.gov)</td><td><u>Primary endpoint</u>
• Proportion of patients with ACR 20 response at week 24
• Safety: AEs, laboratory parameters, vital signs, ECGs
<u>Secondary endpoints</u>
• Proportion of patients with ACR 50 and ACR 70 responses at week 24
• Mean changes in parameters of ACR core set at week 24</td></tr>
<tr><td>Method of analysis</td><td>Primary endpoint analysis was performed on the ITT population including all patients receiving ≥1 administration of study treatment. Safety data were presented using the safety population, comprising all ITT patients with ≥1 post-randomization assessments of safety.

Patients on rescue therapy or with insufficient data to calculate the change from baseline ACR score at a specific time point were classified as non-responders at that time point. In the case of missing data, swollen and tender joint count scores were calculated as the LOCF. There was no imputation for missing data for the remaining ACR components.</td></tr>
<tr><td>Subgroup analyses</td><td>Not applicable</td></tr>
<tr><td>Baseline characteristics</td><td>For clarity, only baseline characteristics for tocilizumab 8 mg/kg plus MTX and placebo plus MTX are included.
<table>
<tr><th></th><th>Tocilizumab 8 mg/kg
+ MTX
n=170</th><th>Placebo
+ MTX
n=158</th></tr>
<tr><td>Age, mean±SD (years)</td><td>53.9±12.7</td><td>53.4±13.3</td></tr>
<tr><td>Female, %</td><td>84</td><td>79</td></tr>
<tr><td>Disease duration, mean±SD (years)</td><td>12.6±9.3</td><td>11.4±9.2</td></tr>
<tr><td>No of previous anti-TNF, %</td><td></td><td></td></tr>
<tr><td>1</td><td>50</td><td>42</td></tr>
<tr><td>2</td><td>32</td><td>44</td></tr>
<tr><td>>3</td><td>18</td><td>14</td></tr>
<tr><td>Previous anti-TNF therapy, %</td><td></td><td></td></tr>
<tr><td>Etanercept</td><td>38.3</td><td>30.6</td></tr>
<tr><td>Adalimumab</td><td>30.3</td><td>39.4</td></tr>
<tr><td>Infliximab</td><td>31.4</td><td>29.4</td></tr>
<tr><td>No of previous DMARD, mean±SD</td><td>1.9±1.7</td><td>2.1±1.6</td></tr>
<tr><td>Baseline MTX dose, mean±SD (mg/week)</td><td>15.7±4.4</td><td>16.5±4.8</td></tr>
<tr><td>Receiving oral steroids, %</td><td>52</td><td>58</td></tr>
<tr><td>DAS28 score, mean±SD</td><td>6.79±0.93</td><td>6.80±1.06</td></tr>
<tr><td>Rheumatoid factor, %</td><td>79</td><td>75</td></tr>
<tr><td><lower limit of normal hemoglobin, n (%)</td><td>60 (35.3)</td><td>57 (36.1)</td></tr>
<tr><td>Tender joint count, mean±SD</td><td>31.7±15.4</td><td>30.4±16.8</td></tr>
<tr><td>Swollen joint count, mean±SD</td><td>18.9±10.9</td><td>18.9±11.1</td></tr>
<tr><td>Erythrocyte sedimentation rate, mean±SD (mm/h)</td><td>49.1±27.9</td><td>54.6±32.7</td></tr>
<tr><td>C-reactive protein, mean±SD (mg/dl)</td><td>2.80±3.37</td><td>3.71±4.12</td></tr>
<tr><td>HAQ-DI, mean±SD</td><td>1.7±0.6</td><td>1.7±0.6</td></tr>
<tr><td>Pain VAS, mean±SD (100 mm)</td><td>64.7±20.6</td><td>64.1±21.8</td></tr>
<tr><td>Patient VAS, mean±SD (100 mm)</td><td>70.2±20.0</td><td>70.9±21.1</td></tr>
<tr><td>Physician VAS, mean±SD (100mm)</td><td>66.4±18.0</td><td>67.5±16.1</td></tr>
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7.2.10 Olokizumab study

TABLE 7-13 MAIN STUDY CHARACTERISTICS – OLOKIZUMAB STUDY (TOCILIZUMAB INCLUDED AS COMPARATOR)

Trial name (official title from clinicaltrials.gov)	Randomized, double-blind, placebo-controlled, dose ranging study with an active comparator to evaluate the efficacy and safety of CDP6038 administered subcutaneously for 12 weeks to subjects with rheumatoid arthritis having previously failed TNF-blocker therapy.
NCT number	NCT01242488
Objective	To evaluate the safety, efficacy, pharmacokinetics, and immunogenicity of CDP6038 treatment in adult subjects with active rheumatoid arthritis who have had an inadequate response to anti-TNF therapy.
Publications – title, author, journal, year	Efficacy and safety of olokizumab in patients with rheumatoid arthritis with an inadequate response to TNF inhibitor therapy: outcomes of a randomised Phase IIb study. Genovese MC et al. Ann Rheum Dis. 2014 [14].
Study type and design	Phase 2b, dose-ranging, double-blind, placebo and active-controlled, multicenter, randomized study. Patients were randomized to 1 of 9 treatment arms; placebo or olokizumab (60, 120 or 240 mg) q4w or q2w, or 8 mg/kg tocilizumab q4w. Randomization was performed centrally using an interactive voice-response system and was stratified according to the number of prior failed TNF inhibitors (1 vs 2 or more). Patients were not permitted to use DMARDs other than MTX within 12 weeks prior to screening.
Follow-up time	12 weeks double-blind treatment period followed by 12 weeks of safety follow-up.
Population (inclusion and exclusion criteria) (from clinicaltrials.gov)	<u>Inclusion criteria</u> • Diagnosis of RA (according to the 1987 ACR classification criteria OR a score of ≥6 as defined by the ACR/European League Against Rheumatism Classification and Diagnostic Criteria for rheumatoid arthritis) for at least 6 months prior to screening • Must have been treated with MTX 12.5-25 mg/week, for at least 6 weeks prior to screening. Doses of 10 to < 12.5mg/week are allowed if there is documented intolerance • Have moderately to severely active RA with at least 6 tender and 6 swollen joints • CRP ≥1.2 times the upper limit of normal (central laboratory) or erythrocyte sedimentation rate of more than 28mm/hour • Intolerant or inadequate response to treatment (i.e. TNF blocker failure) ≥1 licensed TNF-blocker therapies within 2 years of screening <u>Exclusion criteria</u> • Diagnosis of any other inflammatory arthritis or secondary, noninflammatory type of arthritis, such as psoriatic arthritis, lupus, gout, or ankylosing spondylitis • Wheelchair bound or bedridden • Use of DMARDs other than MTX • Treatment with tocilizumab or any other anti-IL-6 investigational therapies at any time • Treatment with other biologics within 4-24 weeks (depending on the biologic)

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History of ongoing, chronic or recurrent infections or recent serious or life-threatening infection
Known concurrent acute or chronic viral hepatitis B or C infection or HIV infection
Vaccinations (other than injectable influenza or pneumococcal) within 8 weeks prior to screening or plan to receive vaccines during the study
Concurrent or history of malignancy with the exception of nonmelanoma skin cancer successfully treated more than 2 years prior to screening or cervical cancer successfully treated more than 5 years prior to screening.
History of chronic alcohol abuse or drug addiction within the last 1 year or current drug addiction or use of illicit drugs

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<tr><td>Intervention</td><td>Placebo q2w (n=22) or q4w (n=23), olokizumab 60 mg q2w (n=20), 120 mg q2w (n=22) or 240 mg q2w (n=23), olokizumab 60 mg q4w (n=23), 120 mg q4w (n=23) or 240 mg q4w (n=22), or 8 mg/kg tocilizumab q4w (n=43) plus stable dose of MTX.

Use of stable dose of steroids and NSAIDs were allowed.</td></tr>
<tr><td>Primary and secondary endpoints</td><td><u>Primary endpoint</u>

• Change from baseline in the DAS28-CRP for CDP6038 and placebo at week 12

<u>Secondary endpoints</u>

• ACR20 response rates for the CDP6038 and placebo arms at week 12
• ACR50 response rates for the CDP6038 and placebo arms at week 12
• ACR70 response rates for the CDP6038 and placebo arms at week 12</td></tr>
<tr><td>Method of analysis</td><td>Efficacy outcomes were assessed in the full analysis set (FAS), consisting of all randomized patients who received ≥1 dose of study medication and had ≥1 post-baseline efficacy measurement. Safety variables were analyzed using the safety set comprising all patients who received ≥1 dose, or partial dose, of study medication. Missing data for swollen and tender joint count, HAQ-DI and CDAI change from baseline were imputed using LOCF.</td></tr>
<tr><td>Subgroup analyses</td><td>Not applicable</td></tr>
<tr><td>Baseline characteristics</td><td>For clarity, only baseline characteristics for placebo plus MTX q4w and tocilizumab 8 mg/kg plus MTX q4w are included.
<table>
<tr><th></th><th>TCZ 8 mg/kg + MTX n=43</th><th>PBO q4w + MTX n=22</th></tr>
<tr><td>Age, mean (years)</td><td>56.58</td><td>58.18</td></tr>
<tr><td>Female, %</td><td>86.0</td><td>77.3</td></tr>
<tr><td>Prior failed TNF-inhibitor, n (%)</td><td></td><td></td></tr>
<tr><td>1</td><td>25 (58.1)</td><td>12 (54.5)</td></tr>
<tr><td>≥2</td><td>18 (41.9)</td><td>10 (45.5)</td></tr>
<tr><td>Concomitant MTX, n (%)</td><td>42 (97.7)</td><td>21 (95.5)</td></tr>
<tr><td>Disease duration, median (years)</td><td>10.55</td><td>7.45</td></tr>
<tr><td>CRP >15 mg/l, n (%)</td><td>16 (37.2)</td><td>7 (31.8)</td></tr>
<tr><td>DAS28(CRP), mean</td><td>5.72</td><td>5.69</td></tr>
<tr><td>DAS28(CRP) >5.1, n (%)</td><td>33 (76.7)</td><td>16 (72.7)</td></tr>
<tr><td>Tender joint count, median (min-max)</td><td>25.00 (4.0-66.0)</td><td>22.00 (8.0-58-0)</td></tr>
<tr><td>Swollen joint count, median (min-max)</td><td>12.38 (6.0-32.0)</td><td>13.17 (4.0-44.7)</td></tr>
<tr><td>Clinical disease activity index (CDAI), median (min-max)</td><td>35.65 (17.7-62.5)</td><td>36.25 (19.0-60.0)</td></tr>
<tr><td>HAQ-DI, median (min-max)</td><td>1.63 (0.0-2.9)</td><td>1.38 (0.0-2.4)</td></tr>
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7.2.11 ADACTA study

TABLE 7-14 MAIN STUDY CHARACTERISTICS – ADACTA STUDY

Trial name (official title from clinicaltrials.gov)	A multi-center, randomized, blinded, parallel-group study of the reduction of signs and symptoms during monotherapy treatment with tocilizumab 8 mg/kg intravenously versus adalimumab 40 mg subcutaneously in patients with rheumatoid arthritis.
NCT number	NCT01119859
Objective	To evaluate the efficacy and safety of tocilizumab versus adalimumab as monotherapy in patients with rheumatoid arthritis who are intolerant of methotrexate or where continued treatment with methotrexate was considered inappropriate.
Publications – title, author, journal, year	Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial. Gabay C et al. Lancet. 2013 [15]. Impact of tocilizumab monotherapy on patient-reported outcomes in patients with rheumatoid arthritis from two randomised controlled trials. Strand V et al. RMD open. 2017 (excluded, no additional relevant data).
Study type and design	Randomized, parallel-group, double-blind, phase 4 study. Eligible patients were randomly assigned (1:1, block size of four) by an interactive voice response system to receive tocilizumab 8 mg/kg q4w plus placebo or adalimumab 40 mg q2w plus placebo. Site investigators enrolled patients, the random allocation sequence was generated by the study sponsor and sponsor personnel assigned patients to adalimumab or tocilizumab. Patients were stratified by region (North America vs non-North America) and duration of RA (<2 years vs ≥2 years). Investigators, patients and sponsor personnel were masked to assignment. Patients with≤20% improvement in swollen joint count and tender joint count from baseline to week 16, or any time after, were eligible for escape treatment. Patients had to stop taking all csDMARDs except leflunomide ≥2 weeks before baseline; leflunomide had to be withdrawn ≥12 weeks before baseline or after standard washout.
Follow-up time	24-week double-blind treatment period followed by 8 weeks of safety follow-up.
Population (inclusion and exclusion criteria) (from clinicaltrials.gov)	Inclusion criteria • Adult patients, ≥ 18 years of age • RA of > 6 months duration • Intolerant of MTX or continued treatment with MTX is considered inappropriate • All DMARD are to be withdrawn prior to receiving study drug • Weight ≤150 kg Exclusion criteria • Major surgery (including joint surgery) within 12 weeks prior to baseline or planned major surgery within 6 months after baseline • History of or current inflammatory joint disease other than RA • Treatment with a biologic agent at any time prior to baseline • Intra-articular or parenteral corticosteroids ≤ 4 weeks prior to baseline

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

- Active current infection or history of recurrent bacterial, viral, fungal or mycobacterial infection

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<tr><td>Intervention</td><td>Tocilizumab 8 mg/ kg IV q4w plus placebo SC q2w (n=163) or adalimumab 40 mg SC q2w plus placebo IV q4w (n=162) for 24 weeks.</td></tr>
<tr><td>Primary and secondary endpoints</td><td>

<u>Primary endpoint</u>

- Change from baseline to week 24 in DAS28

<u>Secondary endpoints included</u>

- Proportion of patients with a remission response (DAS28 <2.6) at week 24
- Proportion of patients with low disease activity (DAS28 ≤3.2) at week 24
- Proportion of patients with ACR20/50/70 response at week 24

</td></tr>
<tr><td>Method of analysis</td><td>The safety population included all patients who received ≥1 dose of tocilizumab or adalimumab and had ≥1 post-dose safety assessment. The ITT population included patients who received ≥1 dose of tocilizumab or adalimumab and had ≥1 efficacy measurement.

Missing data were imputed by LOCF; data at the time of escape were carried forward for patients who received escape treatment at week 16 or later.</td></tr>
<tr><td>Subgroup analyses</td><td>Not applicable</td></tr>
<tr><td>Baseline characteristics</td><td>

	Tocilizumab 8 mg/kg n=163	**Adalimumab 40 mg n=162**
Women, n (%)	129 (79)	133 (82)
Age, mean±SD (years)	54.4±13.0	53.3±12.4
White, n (%)	145 (89)	133 (82)
Duration of rheumatoid arthritis, mean±SD (years)	7.3 (8.1)	6.3±6.9
Previous disease-modifying antirheumatic drugs, mean±SD (n)	2.0±1.1	2.0±1.1
Stopped taking MTX <2 months before baseline, n (%)	99 (61)	102 (63)
Disease activity, mean±SD		
Disease activity score (28 joints)	6.7±0.9	6.8±0.9
Swollen joint count (28 joints)	11.3±5.3	12.4±5.4
Tender joint count (28 joints)	15.9±6.7	16.5±7.0
Clinical Disease Activity Index	40.8±12.3	43.1±12.6
Simplified Disease Activity Index	43.4±13.2	45.6±13.9
C-reactive protein concentration, ($x10^{-2}$ g/l)	2.6±3.1	2.5±3.9
Erythrocyte sedimentation rate, (mm/h)	50.5±29.0	45.5±25.4
Patient visual analogue scale (mm)	71.2±20.8	73.4±17.0
Physician visual analogue scale (mm)	65.5±16.4	67.7±17.0
Health Assessment Questionnaire score	1.6±0.6	1.7±0.6
Use oral corticosteroid, n (%)	89 (55)	92 (57)
Rheumatoid factor positive, n (%)	122 (75)	119 (73)
Anticyclic citrullinated peptide positive, n (%)	127 (78)	117 (72)

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</table>

7.3 Statistical considerations

The statistical methodology followed the specifications in the assessment protocol for Kevzara.

All the outcomes requested by the Danish Medicines Council were binary by nature leading to binomial outcomes. Hence the methodology used was identical for all outcomes and clinical questions. Thus, the method is summarized here instead of in appendix 7.4 (results per study) and appendix 7.5 (results per PICO, comparative analyses).

No studies found during the literature search included both sarilumab and tocilizumab, so direct comparisons were not possible. Furthermore, among the included studies the duration varied from 12 weeks to 52 weeks. Since incidence of the outcomes is expected to vary during a study, it was not considered appropriate to try to standardize to a common duration across studies and therefore comparisons have only been performed between studies and outcomes with the same duration.

For some of the studies found, it was not possible to establish whether the responder rates presented in the literature were original data or model-based estimates and/or it was not possible to determine the total number of patients used as the denominator. Since at least one example indicated that the responder rates were model-based, and since the assessment protocol and the approach described below request original data, these publications and/or outcomes were not included in the analyses. Within each of the populations (3.1, 3.2 and 3.3 as described in the assessment protocol), where studies with both sarilumab and tocilizumab were found, only 1 study was available for each drug that reported the same outcomes for the same treatment duration. There was therefore no basis for meta-analytic approaches, and the indirect comparisons reduced to simple comparisons via either placebo (sections 5.2 and 5.3) or adalimumab (section 5.4). For clinical question 3.4, only 1 study was found, thus no comparative analysis could be performed.

For efficacy outcomes, the ITT population was used as denominator, while the safety population was used as denominator for safety outcomes. Discontinuation due to lack of effect was in general handled as a safety outcome, using the safety population as denominator, except for MOBILITY Part B, where the ITT population was used since it was not possible to relate the outcome to the safety population.

For the within-study analyses the study arm incidences and 95% confidence intervals (CIs) were found as exact Clopper-Pearson intervals which give exact results also when the incidence is 0. The within study comparative analyses were performed with generalized linear models using Proc Genmod SAS v. 9.4 with a log-link leading to estimates of the risk ratio (or effect ratio for the efficacy outcomes). The assessment protocol from the Danish Medicines Council specifies the absolute difference to be calculated as difference from a normal comparator level in a Danish setting using the estimated risk or effect ratio. More formally, this means finding the absolute difference as $(RR - 1)*P_0$ where RR is the risk or effect ratio and P_0 is the normal comparator level in a Danish setting for the given outcome. Since no published data exist for a Danish population, it has not been possible for the applicant to establish valid estimates for the P_0 values. During a telephone meeting, the statistical representative from the Danish Medicines Council proposed that the comparator levels from each study included could be used to establish P_0, and this approach was therefore implemented. When this approach is used for the within study comparisons, the expression $(RR - 1)*P_0 = (P_1/P_0 - 1)*P_0$ reduces to $P_1 - P_0$ and the results are presented from the generalized linear model as above but with the identity link. Thus, the statistical analyses are based on a relative approach, and the absolute differences are only presented with estimates and CIs.

For some outcomes and studies no cases were observed, i.e. the binomial outcome was zero, with the associated added complications of the comparative analysis. We have in these cases used the so-called 2+2 approach[1]. For the derivation of absolute CIs using the approach described above for outcomes and studies with zero incidences in both arms, in combination with the 2+2 approach, the limits may seem counterintuitive and it is advised that interpretation is based mainly on the relative intervals.

The between-study comparisons of sarilumab and tocilizumab were performed using Bucher's method. The calculations were based on the log-transformed scale, retrieved from the above generalized models for the individual studies, and then back-transformed to present estimates and CIs as ratios. For the absolute differences, the tocilizumab rates from each study were used as P_0 and the RR and CI from the relative analyses were inserted into $(RR - 1)*P_0$.

For clinical question 3.1, TSS was assessed using the modified Sharp/van der Heijde scoring in the sarilumab study while the Genant-modified Sharp score was used in the tocilizumab study. The indirect comparison adjusts for background differences between studies, including minor differences in scoring algorithms, and therefore the comparison based on Bucher's method was also applied for this outcome.

[1] Agresti and Caffo. Simple and effective confidence intervals for proportions and differences of proportions result from adding two successes and two failures. Amer Statist. 2000;54(4):280-288.

7.4 Results per study

7.4.1 MOBILITY study – part A

TABLE 7-15 RESULTS PER STUDY – MOBILITY STUDY PART A

Trial name:	**A randomized, double-blind, placebo-controlled, multicenter, two-part, dose ranging and confirmatory study with an operationally seamless design, evaluating efficacy and safety of SAR153191 on top of methotrexate (MTX) in patients with active rheumatoid arthritis who are inadequate responders to MTX therapy (MOBILITY) [4].**									
NCT number:	**NCT01061736**									
				Estimated absolute difference in effect			**Estimated relative difference in effect (risk ratio or effect ratio)**			**Description of methods used for estimation**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Ratio**	**95% CI**	***P* value**	
Mortality	Sarilumab	51	0.00 (0.00, 0.07)	0.00	(-0.05, 0.05)		1.00	(0.06, 15.57)	1.000	See appendix 7.3
	Placebo	51	0.00 (0.00, 0.07)							
ACR50	Sarilumab	52	0.40 (0.27, 0.55)	0.25	(0.08, 0.42)		2.63	(1.28, 5.38)	0.008	See appendix 7.3
	Placebo	52	0.15 (0.07, 0.28)							
Withdrawal due to AE	Sarilumab	51	0.08(0.02, 0.19)	0.04	(-0.05, 0.13)		2.00	(0.38, 10.44)	0.411	See appendix 7.3
	Placebo	51	0.04(0.00, 0.13)							
Withdrawal due to lack of effect	Sarilumab	51	0.02(0.00, 0.10)	-0.02	(-0.09, 0.05)		0.50	(0.05, 5.34)	0.566	See appendix 7.3
	Placebo	51	0.04 (0.00, 0.13)							
Serious infections	Sarilumab	51	0.00 (0.00, 0.07)	0.00	(-0.05, 0.05)		1.00	(0.06, 15.57)	1.000	See appendix 7.3
	Placebo	51	0.00 (0.00, 0.07)							

7.4.2 MOBILITY study – part B

TABLE 7-16 RESULTS PER STUDY – MOBILITY STUDY PART B

Trial name:	**A randomized, double-blind, placebo-controlled, multicenter, two-part, dose ranging and confirmatory study with an operationally seamless design, evaluating efficacy and safety of SAR153191 on top of methotrexate (MTX) in patients with active rheumatoid arthritis who are inadequate responders to MTX therapy (MOBILITY) [5].**									
NCT number:	**NCT01061736**									
				Estimated absolute difference in effect			**Estimated relative difference in effect (risk ratio or effect ratio)**			**Description of methods used for estimation**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Ratio**	**95% CI**	***P* value**	
Mortality	Sarilumab	424	0.00 (0.00, 0.01)	-0.00	(-0.01, 0.01)		0.50	(0.05, 5.53)	0.575	See appendix 7.3
	Placebo	427	0.00 (0.00, 0.02)							
ACR50; 24 weeks	Sarilumab	399	0.46 (0.41, 0.51)	0.29	(0.23, 0.35)		2.75	(2.15, 3.51)	<.001	See appendix 7.3
	Placebo	398	0.17 (0.13, 0.21)							
ACR50; 52 weeks	Sarilumab	399	0.43 (0.38, 0.48)	0.25	(0.19, 0.31)		2.37	(1.87, 3.00)	<.001	See appendix 7.3
	Placebo	398	0.18 (0.14, 0.22)							
Withdrawal due to AE	Sarilumab	424	0.14 (0.11, 0.18)	0.09	(0.05, 0.13)		2.97	(1.82, 4.84)	<.001	See appendix 7.3
	Placebo	427	0.05 (0.03, 0.07)							
Withdrawal due to lack of effect	Sarilumab	399	0.02 (0.01, 0.03)	0.01	(-0.01, 0.02)		1.99	(0.50, 7.92)	0.326	See appendix 7.3 Note that the denominator was the ITT population since this was the data available
	Placebo	398	0.01 (0.00, 0.02)							
Serious infections	Sarilumab	424	0.04 (0.02, 0.06)	0.02	(-0.01, 0.04)		1.71	(0.79, 3.70)	0.171	See appendix 7.3
	Placebo	427	0.02 (0.01, 0.04)							
TSS no progression	Sarilumab	399	0.56 (0.51, 0.61)	0.17	(0.10, 0.24)		1.44	(1.24, 1.67)	<.001	See appendix 7.3
	Placebo	398	0.39 (0.34, 0.44)							
HAQ-DI, change ≥0.22; 24 weeks	Sarilumab	399	0.58 (0.53, 0.63)	0.19	(0.12, 0.26)		1.48	(1.27, 1.71)	<.001	See appendix 7.3
	Placebo	398	0.39 (0.34, 0.44)							

Trial name:	**A randomized, double-blind, placebo-controlled, multicenter, two-part, dose ranging and confirmatory study with an operationally seamless design, evaluating efficacy and safety of SAR153191 on top of methotrexate (MTX) in patients with active rheumatoid arthritis who are inadequate responders to MTX therapy (MOBILITY) [5].**									
NCT number:	**NCT01061736**									
				Estimated absolute difference in effect			**Estimated relative difference in effect (risk ratio or effect ratio)**			**Description of methods used for estimation**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Ratio**	**95% CI**	***P* value**	
HAQ-DI, change ≥0.22; 52 weeks	Sarilumab	399	0.53 (0.48, 0.58)	0.20	(0.13, 0.27)		1.61	(1.36, 1.91)	<.001	See appendix 7.3
	Placebo	398	0.33 (0.28, 0.38)							
HAQ-DI, change ≥0.30; 24 weeks	Sarilumab	399	0.51 (0.46, 0.56)	0.18	(0.11, 0.25)		1.54	(1.30, 1.82)	<.001	See appendix 7.3
	Placebo	398	0.33 (0.29, 0.38)							
HAQ-DI, change ≥0.30; 52 weeks	Sarilumab	399	0.48 (0.43, 0.53)	0.21	(0.15, 0.28)		1.82	(1.50, 2.21)	<.001	See appendix 7.3
	Placebo	398	0.26 (0.22, 0.31)							

7.4.3 TARGET study

TABLE 7-17 RESULTS PER STUDY – TARGET STUDY

Trial name:	**A randomized, double-blind, parallel, placebo-controlled study assessing the efficacy and safety of sarilumab added to non-biologic DMARD therapy in patients with rheumatoid arthritis who are inadequate responders to or intolerant of TNF-α antagonists (TARGET) [6].**									
NCT number:	**NCT01709578**									
				Estimated absolute difference in effect			**Estimated relative difference in effect (risk ratio or effect ratio)**			**Description of methods used for estimation**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Ratio**	**95% CI**	***P* value**	
Mortality	Sarilumab	184	0.00 (0.00, 0.02)	-0.01	(-0.02, 0.01)		0.49	(0.04, 5.38)	0.561	See appendix 7.3
	Placebo	181	0.01 (0.00, 0.03)							
ACR50	Sarilumab	184	0.41 (0.34, 0.48)	0.23	(0.13, 0.32)		2.24	(1.57, 3.19)	<.001	See appendix 7.3
	Placebo	181	0.18 (0.13, 0.25)							
Withdrawal due to AE	Sarilumab	184	0.09 (0.05, 0.14)	0.05	(-0.00, 0.10)		2.09	(0.93, 4.72)	0.076	See appendix 7.3
	Placebo	181	0.04 (0.02, 0.09)							
Withdrawal due to lack of effect	Sarilumab	184	0.01 (0.00, 0.04)	-0.02	(-0.04, 0.01)		0.39	(0.08, 2.00)	0.261	See appendix 7.3
	Placebo	181	0.03 (0.01, 0.06)							
Serious infections	Sarilumab	184	0.01 (0.00, 0.04)	-0.00	(-0.02, 0.02)		0.98	(0.14, 6.91)	0.987	See appendix 7.3
	Placebo	181	0.01 (0.00, 0.04)							
HAQ-DI, change ≥0.22	Sarilumab	184	0.56 (0.48, 0.63)	0.21	(0.11, 0.31)		1.58	(1.25, 2.00)	<.001	See appendix 7.3
	Placebo	181	0.35 (0.28, 0.43)							
HAQ-DI, change ≥0.30	Sarilumab	184	0.47 (0.40, 0.55)	0.16	(0.06, 0.26)		1.50	(1.15, 1.95)	0.003	See appendix 7.3
	Placebo	181	0.31 (0.25, 0.39)							

7.4.4 MONARCH study

TABLE 7-18 RESULTS PER STUDY – MONARCH

Trial name:	**A randomized, double-blind, parallel-group study assessing the efficacy and safety of sarilumab monotherapy versus adalimumab monotherapy in patients with rheumatoid arthritis (MONARCH) [7].**									
NCT number:	**NCT02332590**									
				Estimated absolute difference in effect			**Estimated relative difference in effect (risk ratio or effect ratio)**			**Description of methods used for estimation**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Ratio**	**95% CI**	***P* value**	
Mortality	Sarilumab	184	0.01 (0.00, 0.03)	0.01	(-0.01, 0.02)		2.00	(0.18,21.87)	0.570	See appendix 7.3
	Placebo	184	0.00 (0.00, 0.02)							
ACR50	Sarilumab	184	0.46 (0.38, 0.53)	0.16	(0.06, 0.26)		1.54	(1.17, 2.02)	0.002	See appendix 7.3
	Placebo	185	0.30 (0.23, 0.37)							
Withdrawal due to AE	Sarilumab	184	0.06 (0.03, 0.10)	-0.01	(-0.06, 0.04)		0.85	(0.39, 1.84)	0.673	See appendix 7.3
	Placebo	184	0.07 (0.04, 0.12)							
Withdrawal due to lack of effect	Sarilumab	184	0.01 (0.00, 0.04)	-0.01	(-0.04, 0.01)		0.50	(0.09, 2.70)	0.420	See appendix 7.3
	Placebo	184	0.02 (0.01, 0.05)							
Serious infections	Sarilumab	184	0.01 (0.00, 0.04)	0.00	(-0.02, 0.02)		1.00	(0.14, 7.02)	1.000	See appendix 7.3
	Placebo	184	0.01 (0.00, 0.04)							
HAQ-DI, change ≥0.22	Sarilumab	184	0.67 (0.60, 0.74)	0.13	(0.03, 0.23)		1.25	(1.06, 1.47)	0.009	See appendix 7.3
	Placebo	185	0.54 (0.47, 0.61)							
HAQ-DI, change ≥0.30	Sarilumab	184	0.62 (0.55, 0.69)	0.14	(0.04, 0.24)		1.30	(1.08, 1.57)	0.006	See appendix 7.3
	Placebo	185	0.48 (0.40, 0.55)							

7.4.5 CHARISMA study

TABLE 7-19 RESULTS PER STUDY – CHARISMA STUDY

Trial name:	**The Chugai humanized anti-human recombinant interleukin-6 monoclonal antibody (CHARISMA) study [8].**									
NCT number:	**Not available**									
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Risk ratio**	**95% CI**	***P* value**	
Mortality	Tocilizumab	50	0.00 (0.00, 0.07)	-0.00	(-0.05, 0.05)		0.98	(0.06,15.26)	0.989	See appendix 7.3 Note that since no deaths were mentioned in the article, it was assumed that there was none in either group
	Placebo	49	0.00 (0.00, 0.07)							
Withdrawal due to AE	Tocilizumab	50	0.12 (0.05, 0.24)	0.04	(-0.08, 0.16)		1.47	(0.44, 4.89)	0.530	See appendix 7.3
	Placebo	49	0.08 (0.02, 0.20)							
Withdrawal due to lack of effect	Tocilizumab	50	0.02 (0.00, 0.11)	-0.10	(-0.20, -0.00)		0.16	(0.02, 1.31)	0.088	See appendix 7.3
	Placebo	49	0.12 (0.05, 0.25)							
Serious infections	Tocilizumab	50	0.06 (0.01, 0.17)	0.06	(-0.02, 0.14)		3.92	(0.45,33.92)	0.214	See appendix 7.3
	Placebo	49	0.00 (0.00, 0.07)							

7.4.6 OPTION study

TABLE 7-20 RESULTS PER STUDY – OPTION STUDY

Trial name:	**A randomized, double-blind study of safety and reduction in signs and symptoms during treatment with tocilizumab versus placebo, in combination with methotrexate, in patients with moderate to severe rheumatoid arthritis [9].**									
NCT number:	**NCT00106548**									
				Estimated absolute difference in effect			**Estimated relative difference in effect (risk ratio or effect ratio)**			**Description of methods used for estimation**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Ratio**	**95% CI**	***P* value**	
Mortality	Tocilizumab	206	0.00 (0.00, 0.02)	-0.00	(-0.01, 0.01)		0.99	(0.06,15.73)	0.995	See appendix 7.3 Note that since no deaths were mentioned in the article, it was assumed that there was none in either group
	Placebo	204	0.00 (0.00, 0.02)							
ACR50	Tocilizumab	205	0.44 (0.37, 0.51)	0.33	(0.25, 0.41)		4.07	(2.66, 6.22)	<.001	See appendix 7.3
	Placebo	204	0.11 (0.07, 0.16)							
Withdrawal due to AE	Tocilizumab	206	0.06 (0.03, 0.10)	0.03	(-0.01, 0.07)		1.98	(0.76, 5.18)	0.163	See appendix 7.3
	Placebo	204	0.03 (0.01, 0.06)							
Withdrawal due to lack of effect	Tocilizumab	206	0.00 (0.00, 0.02)	-0.01	(-0.04, 0.01)		0.25	(0.03, 2.20)	0.210	See appendix 7.3
	Placebo	204	0.01 (0.00, 0.04)							
Serious infections	Tocilizumab	206	0.03 (0.01, 0.06)	0.02	(-0.01, 0.05)		2.97	(0.61,14.55)	0.179	See appendix 7.3
	Placebo	204	0.01 (0.00, 0.03)							
HAQ-DI, change ≥0.30	Tocilizumab	205	0.40 (0.34, 0.48)	0.17	(0.09, 0.26)		1.76	(1.30, 2.37)	<.001	See appendix 7.3
	Placebo	204	0.23 (0.17, 0.29)							

7.4.7 TOWARD study

TABLE 7-21 RESULTS PER STUDY – TOWARD STUDY

Trial name:	**A randomized, double-blind study of the effect of tocilizumab on reduction in signs and symptoms in patients with moderate to severe active rheumatoid arthritis and inadequate response to DMARD therapy [10].**									
NCT number:	**NCT00106574**									
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Risk ratio**	**95% CI**	***P* value**	
Mortality	Tocilizumab	802	0.00 (0.00, 0.01)	-0.00	(-0.01, 0.01)		0.52	(0.07, 3.65)	0.508	See appendix 7.3
	Placebo	414	0.00 (0.00, 0.02)							
Withdrawal due to AE	Tocilizumab	802	0.04 (0.03, 0.05)	0.02	(0.00, 0.04)		2.00	(0.93, 4.31)	0.077	See appendix 7.3
	Placebo	414	0.02 (0.01, 0.04)							
Serious infections	Tocilizumab	802	0.03 (0.02, 0.04)	0.01	(-0.01, 0.03)		1.42	(0.64, 3.16)	0.391	See appendix 7.3
	Placebo	414	0.02 (0.01, 0.04)							

7.4.8 ROSE study

TABLE 7-22 RESULTS PER STUDY – ROSE STUDY

Trial name:	**A randomized, double-blind, parallel-group study to evaluate the safety and efficacy of tocilizumab versus placebo in combination with DMARDs in patients with moderate to severe active rheumatoid arthritis [11].**									
NCT number:	**NCT00531817**									
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Risk ratio**	**95% CI**	***P* value**	
Mortality	Tocilizumab	409	0.01 (0.00, 0.02)	0.00	(-0.01, 0.02)		2.01	(0.23,17.91)	0.530	See appendix 7.3
	Placebo	205	0.00 (0.00, 0.02)							
Withdrawal due to AE	Tocilizumab	409	0.07 (0.04, 0.09)	0.03	(-0.01, 0.06)		1.69	(0.78, 3.66)	0.181	See appendix 7.3
	Placebo	205	0.04 (0.02, 0.08)							
Withdrawal due to lack of effect	Tocilizumab	409	0.02 (0.01, 0.04)	-0.00	(-0.03, 0.02)		0.80	(0.27, 2.42)	0.695	See appendix 7.3
	Placebo	205	0.02 (0.01, 0.06)							
Serious infections	Tocilizumab	409	0.03 (0.02, 0.05)	0.02	(0.01, 0.04)		6.01	(0.79,45.94)	0.084	See appendix 7.3
	Placebo	205	0.00 (0.00, 0.03)							

7.4.9 LITHE study

TABLE 7-23 RESULTS PER STUDY – LITHE STUDY

Trial name:	**A randomized, double-blind study of safety and prevention of structural joint damage during treatment with tocilizumab versus placebo, in combination with methotrexate, in patients with moderate to severe rheumatoid arthritis [12].**									
NCT number:	**NCT00106535**									
				Estimated absolute difference in effect			**Estimated relative difference in effect (risk ratio or effect ratio)**			**Description of methods used for estimation**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Ratio**	**95% CI**	***P* value**	
Mortality	Tocilizumab	399	0.01 (0.00, 0.03)	0.00	(-0.01, 0.02)		1.96	(0.36,10.67)	0.434	See appendix 7.3
	Placebo	392	0.01 (0.00, 0.02)							
Withdrawal due to AE	Tocilizumab	399	0.08 (0.06, 0.11)	0.05	(0.02, 0.09)		2.95	(1.51, 5.75)	0.002	See appendix 7.3
	Placebo	392	0.03 (0.01, 0.05)							
Withdrawal due to lack of effect	Tocilizumab	399	0.01 (0.00, 0.02)	-0.03	(-0.04, -0.01)		0.16	(0.04, 0.73)	0.017	See appendix 7.3
	Placebo	392	0.03 (0.02, 0.05)							
TSS no progression	Tocilizumab	398	0.87 (0.84, 0.91)	0.14	(0.08, 0.19)		1.18	(1.11, 1.27)	<.001	See appendix 7.3
	Placebo	393	0.74 (0.69, 0.78)							
HAQ-DI, change ≥0.30	Tocilizumab	263	0.63 (0.57, 0.69)	0.10	(0.00, 0.20)		1.19	(0.99, 1.42)	0.058	See appendix 7.3
	Placebo	146	0.53 (0.44, 0.61)							

7.4.10 RADIATE study

TABLE 7-24 RESULTS PER STUDY – RADIATE STUDY

Trial name:	**A randomized, double-blind study of safety and reduction in signs and symptoms during treatment with tocilizumab versus placebo, in combination with methotrexate, in patients with moderate to severe active rheumatoid arthritis and inadequate response to anti-TNF therapy [13].**									
NCT number:	**NCT00106522**									
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Risk ratio**	**95% CI**	***P* value**	
Mortality	Tocilizumab	175	0.00 (0.00, 0.02)	-0.00	(-0.02, 0.02)		0.92	(0.06,14.51)	0.950	See appendix 7.3
	Placebo	160	0.00 (0.00, 0.02)							
Withdrawal due to AE	Tocilizumab	175	0.06 (0.03, 0.10)	0.01	(-0.04, 0.06)		1.14	(0.46, 2.82)	0.772	See appendix 7.3
	Placebo	160	0.05 (0.02, 0.10)							
Withdrawal due to lack of effect	Tocilizumab	175	0.02 (0.01, 0.06)	-0.10	(-0.15, -0.04)		0.19	(0.07, 0.55)	0.002	See appendix 7.3
	Placebo	160	0.12 (0.07, 0.18)							
Serious infections	Tocilizumab	175	0.05 (0.02, 0.09)	0.01	(-0.03, 0.06)		1.46	(0.49, 4.38)	0.497	See appendix 7.3
	Placebo	160	0.03 (0.01, 0.07)							

7.4.11 Olokizumab study

TABLE 7-25 RESULTS PER STUDY – OLOKIZUMAB STUDY

Trial name:	**Randomized, double-blind, placebo-controlled, dose ranging study with an active comparator to evaluate the efficacy and safety of CDP6038 administered subcutaneously for 12 weeks to subjects with rheumatoid arthritis having previously failed TNF-blocker therapy [14].**									
NCT number:	**NCT01242488**									
				Estimated absolute difference in effect			**Estimated relative difference in effect (risk ratio or effect ratio)**			**Description of methods used for estimation**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Ratio**	**95% CI**	***P* value**	
Mortality	Tocilizumab	43	0.00 (0.00, 0.08)	-0.02	(-0.11, 0.07)		0.53	(0.03, 8.15)	0.651	See appendix 7.3
	Placebo	22	0.00 (0.00, 0.15)							
ACR50	Tocilizumab	43	0.23 (0.12, 0.39)	0.20	(0.05, 0.35)		5.87	(0.80,42.76)	0.081	See appendix 7.3
	Placebo	22	0.00 (0.00, 0.15)							
Serious infections	Tocilizumab	43	0.05 (0.01, 0.16)	0.03	(-0.08, 0.13)		1.60	(0.18,14.56)	0.677	See appendix 7.3
	Placebo	22	0.00 (0.00, 0.15)							

7.4.12 ADACTA study

TABLE 7-26 RESULTS PER STUDY – ADACTA STUDY

Trial name:	**A multi-center, randomized, blinded, parallel-group study of the reduction of signs and symptoms during monotherapy treatment with tocilizumab 8 mg/kg intravenously versus adalimumab 40 mg subcutaneously in patients with rheumatoid arthritis [15].**									
NCT number:	**NCT01119859**									
				Estimated absolute difference in effect			**Estimated relative difference in effect (risk ratio or effect ratio)**			**Description of methods used for estimation**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Ratio**	**95% CI**	***P* value**	
Mortality	Tocilizumab	162	0.01 (0.00, 0.04)	0.01	(-0.01, 0.04)		3.00	(0.32,28.54)	0.339	See appendix 7.3
	Placebo	162	0.00 (0.00, 0.02)							
ACR50	Tocilizumab	163	0.47 (0.39, 0.55)	0.19	(0.09, 0.30)		1.70	(1.26, 2.29)	<.001	See appendix 7.3
	Placebo	162	0.28 (0.21, 0.35)							
Withdrawal due to AE	Tocilizumab	162	0.06 (0.03, 0.10)	-0.01	(-0.06, 0.04)		0.90	(0.38, 2.16)	0.813	See appendix 7.3
	Placebo	162	0.06 (0.03, 0.11)							
Withdrawal due to lack of effect	Tocilizumab	162	0.04 (0.02, 0.09)	-0.04	(-0.10, 0.01)		0.50	(0.21, 1.21)	0.123	See appendix 7.3
	Placebo	162	0.09 (0.05, 0.14)							
Serious infections	Tocilizumab	162	0.04 (0.01, 0.08)	-0.01	(-0.05, 0.04)		0.86	(0.29, 2.50)	0.777	See appendix 7.3
	Placebo	162	0.04 (0.02, 0.09)							
HAQ-DI, change ≥0.22	Tocilizumab	163	0.56 (0.48, 0.64)	0.05	(-0.06, 0.16)		1.10	(0.90, 1.35)	0.347	See appendix 7.3
	Placebo	162	0.51 (0.43, 0.59)							

7.5 Results per PICO (clinical question)

7.5.1 Clinical question 3.1: Added clinical value of sarilumab compared to tocilizumab in combination with csDMARD for bio-naïve patients with moderate to severe RA

TABLE 7-27 RESULTS REFERRING TO TREATMENT WITH SARILUMAB IN COMBINATION WITH DMARDS IN BIO-NAÏVE PATIENTS

Results per outcome	Studies included in the analysis	Absolute difference in effect			Relative difference in effect (risk ratio or effect ratio)			Methods used for quantitative synthesis
		Difference	CI	*P* value	Ratio	CI	*P* value	
Mortality	Genovese et al 2015 (MOBILITY Part B) / Kremer et al 2011 (LITHE)	-0.01	(-0.01, 0.04)		0.26	(0.01, 4.82)	0.363	See appendix 7.3
ACR50	Genovese et al 2015 (MOBILITY Part B) / Smolen et al 2008 (OPTION)	-0.14	(-0.26, 0.05)		0.68	(0.41, 1.10)	0.117	See appendix 7.3
Withdrawal due to AE	Genovese et al 2015 (MOBILITY Part B) / Kremer et al 2011 (LITHE)	0.00	(-0.05, 0.11)		1.01	(0.44, 2.31)	0.985	See appendix 7.3
Withdrawal due to lack of effect	Genovese et al 2015 (MOBILITY Part B) / Kremer et al 2011 (LITHE)	0.06	(0.00, 0.46)		12.18	(1.60,92.82)	0.016	See appendix 7.3
TSS, no progression	Genovese et al 2015 (MOBILITY Part B) / Kremer et al 2011 (LITHE)	0.19	(0.02, 0.38)		1.21	(1.03, 1.43)	0.023	See appendix 7.3
HAQ-DI, change ≥0.30, 24 weeks	Genovese et al 2015 (MOBILITY Part B) / Smolen et al 2008 (OPTION)	-0.05	(-0.15, 0.10)		0.87	(0.62, 1.23)	0.447	See appendix 7.3
HAQ-DI, change ≥0.30, 52 weeks	Genovese et al 2015 (MOBILITY Part B) / Kremer et al 2011 (LITHE)	0.33	(0.11, 0.63)		1.53	(1.18, 2.00)	0.002	See appendix 7.3

7.5.2 Clinical question 3.2: Added clinical value of sarilumab compared to tocilizumab in combination with csDMARD for patients with moderate to severe RA who have to change biological or tsDMARD treatment

TABLE 7-28 RESULTS REFERRING TO TREATMENT WITH SARILUMAB IN COMBINATION WITH DMARDS IN BIO-EXPERIENCED PATIENTS

Results per outcome		Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	Difference	CI	*P* value	Risk ratio	CI	*P* value	
Mortality	Fleischmann et al 2017 (TARGET) / Emery et al 2008 (RADIATE)	-0.00	(-0.01, 0.11)		0.54	(0.01,20.78)	0.739	See appendix 7.3
Withdrawal due to AE	Fleischmann et al 2017 (TARGET) / Emery et al 2008 (RADIATE)	0.05	(-0.03, 0.30)		1.83	(0.54, 6.18)	0.331	See appendix 7.3
Withdrawal due to lack of effect	Fleischmann et al 2017 (TARGET) / Emery et al 2008 (RADIATE)	0.02	(-0.02, 0.30)		2.04	(0.29,14.23)	0.470	See appendix 7.3
Serious infections	Fleischmann et al 2017 (TARGET) / Emery et al 2008 (RADIATE)	-0.01	(-0.04, 0.24)		0.67	(0.07, 6.29)	0.728	See appendix 7.3

7.5.3 Clinical question 3.3: Added clinical value of sarilumab compared to tocilizumab to bio-naïve patients with moderate to severe RA where treatment with csDMARDs is not an option

TABLE 7-29 RESULTS REFERRING TO SARILUMAB MONOTHERAPY IN BIO-NAÏVE PATIENTS

Results per outcome	Studies included in the analysis	Absolute difference in effect			Relative difference in effect (risk ratio or effect ratio)			Methods used for quantitative synthesis
		Difference	CI	*P* value	Ratio	CI	*P* value	
Mortality	Burmester et al 2017 (MONARCH) / Gabay et al 2013 (ADACTA)	-0.01	(-0.02, 0.31)		0.67	(0.02,17.82)	0.809	See appendix 7.3
ACR50	Burmester et al 2017 (MONARCH) / Gabay et al 2013 (ADACTA)	-0.05	(-0.19, 0.17)		0.90	(0.60, 1.35)	0.619	See appendix 7.3
Withdrawal due to AE	Burmester et al 2017 (MONARCH) / Gabay et al 2013 (ADACTA)	-0.00	(-0.04, 0.11)		0.94	(0.29, 3.03)	0.918	See appendix 7.3
Withdrawal due to lack of effect	Burmester et al 2017 (MONARCH) / Gabay et al 2013 (ADACTA)	0.00	(-0.04, 0.25)		1.00	(0.15, 6.70)	1.000	See appendix 7.3
Serious infections	Burmester et al 2017 (MONARCH) / Gabay et al 2013 (ADACTA)	0.01	(-0.03, 0.36)		1.17	(0.13,10.77)	0.892	See appendix 7.3
HAQ-DI, change ≥0.22	Burmester et al 2017 (MONARCH) / Gabay et al 2013 (ADACTA)	0.07	(-0.07, 0.27)		1.13	(0.87, 1.47)	0.354	See appendix 7.3

Protokol for vurdering af den kliniske merværdi af sarilumab til reumatoid artrit

Handelsnavn	Kevzara
Generisk navn	Sarilumab
Firma	Sanofi-Aventis Denmark A/S
ATC-kode	L04AC14
Virkningsmekanisme	Sarilumab er et humant monoklonalt antistof (IgG1-subtype), der binder sig specifikt til både opløselige og membranbundne IL-6 receptorer (IL-6Rα) og hæmmer IL-6-medieret signalering
Administration/dosis	Subkutant, 200 mg hver anden uge
Forventet EMA-indikation	Sarilumab er i kombination med methotrexat (MTX) indiceret til behandling af moderat til svær, aktiv reumatoid artritis (RA) hos voksne patienter, som enten har haft utilstrækkelig respons på, eller som ikke tolererer en eller flere sygdomsmodificerende antireumatiske lægemidler (DMARDs). Sarilumab kan gives som monoterapi i tilfælde af intolerans over for MTX, eller når behandling med MTX er uhensigtsmæssig
Godkendelsesdato Offentliggørelsesdato Dokumentnummer Versionsnummer	15/3-2018 15/3-2018 16287 1.0

Indhold

Forkortelser

ACR50:	*American College of Rheumatology 50 % response*
AE:	*Adverse Event* (bivirkning)
bDMARD:	Biologisk *Disease Modifying Anti Rheumatic Drug*
CI:	Konfidensinterval
CRP:	C-reaktivt protein
csDMARD:	Konventionelt syntetisk *Disease Modifiying Anti Rheumatic Drug*
DANBIO:	Dansk reumatologisk kvalitets- og forskningsdatabase
DMARD:	*Disease Modifying Anti Rheumatic Drug*
EMA:	*European Medicines Agency*
EPAR:	*European Public Assessment Report*
EULAR:	*European League Against Rheumatism*
GRADE:	System til vurdering af evidens (Grading of Recommendations Assessment, Development and Evaluation System)
HAQ-DI	*Health Assessment Questionnaire Disability Index*
i.v.:	Intravenøst
MTX:	Methotrexat
OR:	Odds Ratio
RA:	Reumatoid Artrit
RADS:	Rådet for Anvendelse af Dyr Sygehusmedicin
RCT:	*Randomised Controlled Trial*
RR:	Relativ Risiko
SAE:	*Serious Adverse Event* (alvorlig bivirkning)
s.c.:	Subkutant
tsDMARD:	Targeteret syntetisk *Disease Modifying Anti Rheumatic Drug*
TNF:	*Tumor Necrosis Factor*
TSS:	*Total Sharp Score*
VAS:	Visuel Analog Skala

1 Formål

Protokollen har til formål at definere de kliniske spørgsmål, der ønskes belyst i vurderingen af sarilumab som mulig standardbehandling af patienter med reumatoid artrit. I protokollen angives en definition af populationer, komparator og effektmål, der skal præsenteres i den endelige ansøgning, samt de metoder der ønskes anvendt til den komparative analyse. Arbejdet med protokollen er igangsat på baggrund af den foreløbige ansøgning vedrørende sarilumab, modtaget den 12. februar 2018.

Protokollen danner grundlaget for den endelige ansøgning for vurderingen af den kliniske merværdi af sarilumab sammenlignet med dansk standardbehandling. Sanofi-Aventis har tilkendegivet, at sarilumab efter deres vurdering ikke har klinisk merværdi sammenlignet med tocilizumab. Medicinrådet har accepteret, at sarilumab på den baggrund kan vurderes i Medicinrådets hurtigere proces på syv uger (www.medicinraadet.dk). Sanofi-Aventis påtager sig ansvaret for, at lægemidlet under processen kan kategoriseres anderledes og i så fald skal indgå i et sædvanligt procesforløb på 12 uger.

Alle effektmål, der er opgivet i denne protokol, skal besvares med en sammenlignende analyse mellem sarilumab og komparator, tocilizumab, af både absolutte og relative værdier for de udspecificerede populationer i de angivne måleenheder (se tabel 1). Litteratursøgning og databehandling udføres som beskrevet i protokollen (jf. afsnit 5).

2 Baggrund

Reumatoid artrit (RA) er en systemisk og progredierende sygdom [1], der er karakteriseret ved inflammation i led og lednære strukturer og kan medføre leddestruktion. Sygdommen medfører ledsmerter, nedsat funktionsevne og en betydelig del af patienterne bliver helt eller delvist uarbejdsdygtige. Udover leddestruktion kan sygdommen medføre systemiske manifestationer og er forbundet med øget mortalitet, især pga. arteriosklerose og lungeinvolvering. Ætiologien er multifaktoriel, med miljøpåvirkninger (eksempelvis tobaksrygning) som risikofaktor samt en genetisk komponent.

Sygdommen klassificeres efter 2010 ACR/EULAR, kriterier defineret af American College of Rheumatology (ACR) og European League Against Rheumatism (EULAR) [2]. Klassifikationen er baseret på antal involverede led, autoimmun serologi, akutfaserespons og symptomvarighed.

RA forekommer globalt, men med geografisk og etnisk variation. I en nyere populationsbaseret dansk undersøgelse er incidensen mellem 32 og 35 pr. 100.000 og størst hos kvinder [3]. Sygdommen kan debutere i alle aldre, men typisk mellem 50 og 70 år [4]. I Dansk reumatologisk kvalitets- og forskningsdatabase (DANBIO) var der ved udgangen af 2016 registreret 21.488 patienter i behandling for RA, hvoraf ca. 5.000 var i biologisk behandling [5].

Antallet af RA patienter i biologisk behandling er stigende, således er antallet vokset med ca. 1.500 patienter siden 2010 [5–8], hvilket svarer til en gennemsnitlig stigning på ca. 250 bionaive patienter pr. år siden 2010. Der er før 2010 beskrevet en stigning på ca. 500 bionaive patienter pr. år [9], og det skønnes, at det egentlige tal ligger et sted imellem 250 og 500. Det anslås, at mindst 20 % af patienter i biologisk behandling vil skifte præparat i løbet af et år [10], hvilket hovedsageligt skyldes mangel på effekt eller uacceptable bivirkninger. Det vil sige, at ca. 1.000 (20 % af 5.000) af patienterne i biologisk behandling i 2016 vil have skiftet lægemiddel i løbet af et år.

2.1 Nuværende behandling

Der findes ingen kurativ behandling, men tidlig behandling kan bremse sygdommen og bedre prognosen. Behandlingen er principielt livslang og består af immunhæmmende medicin, der er delt op i symptomlindrende behandling (smertestillende behandling (NSAID)) og sygdomsmodificerende behandling (Disease Modifying Anti Rheumatic Drugs, DMARDs). Vigtige principper er tidlig og målrettet behandling for at forebygge leddestruktion. Behandlingen er en specialistopgave, der bør varetages af reumatologer.

Ved behandlingsopstart med DMARDs anvendes methotrexat (MTX) som førstevalg. Ved inadækvat respons kombineres dette præparat med andre konventionelle syntetiske DMARDs (csDMARDs), typisk salazopyrin og hydroxychloroquin (triple behandling). Hvis lav sygdomsaktivitet/remission ikke opnås, er næste behandlingsmulighed biologisk behandling/targeteret syntetisk behandling (bDMARDs/tsDMARDs) i kombination med MTX. De biologiske DMARDs kan opdeles i TNF-inhibitorer (adalimumab, certolizumab, etanercept, golimumab og infliximab) og biologiske lægemidler med andre virkningsmekanismer (rituximab, tocilizumab, sarilumab og abatacept). Dertil kommer de targeterede syntetiske DMARDS (tsDMARDs, baricitinib og tofacitinib). I den nuværende behandlingsvejledning fra RADS indgår 8 bDMARDs [10].

De fleste patienter vil blive behandlet med csDMARDs alene eller i kombination med bDMARDs eller tsDMARD. For nogle patienter vil biologisk monoterapi være eneste mulige behandling. Et nyligt studie baseret på data fra DANBIO [11] viste, at 19 % af RA-patienter var i biologisk monoterapi. Af disse var 70 % initieret på monoterapi med bDMARDs, og 30 % havde tidligere været i kombinationsterapi med MTX.

2.2 Sarilumab

Sarilumab er et humant monoklonalt antistof (IgG1-subtype), der binder sig specifikt til både opløselige og membranbundne IL-6 receptorer (IL-6Rα) og hæmmer IL-6-medieret signalering. Sarilumab gives subkutant i en dosis af 200 mg hver anden uge. Sarilumab kan enten gives i kombination med MTX eller som monoterapi.

3 Kliniske spørgsmål

Protokollen indeholder fire kliniske spørgsmål, da patientpopulationen defineret i EMAs indikation i dansk klinisk praksis opdeles i fire subpopulationer. Der skelnes mellem bionaive (patienter der ikke tidligere er behandlet med bDMARDs eller tsDMARDs og skal startes på en af disse) og bioerfarne (patienter der tidligere er behandlet med bDMARDs eller tsDMARDs og skal skiftes til en anden), samt mellem kombinationsterapi og monoterapi.

Tocilizumab er valgt som komparator, og lægemidlet er ét af flere anbefalede alternativer i det gældende RADS-baggrundsnotat vedrørende behandling af reumatoid artritis [10]. Ydermere har tocilizumab samme virkningsmekanisme som sarilumab, hvilket ligger til grund for Medicinrådets accept af ansøgers ønske om at blive behandlet i den hurtige proces.

3.1 Hvilken klinisk merværdi tilbyder sarilumab sammenlignet med tocilizumab i kombination med csDMARD til bionaive patienter med moderat til svær RA?

Population

Patienter i csDMARD-behandling med fortsat moderat til svær sygdomsaktivitet.

Intervention

Sarilumab, s.c. 200 mg hver anden uge i kombination med csDMARD.

Komparator

Tocilizumab, s.c. 162 mg én gang ugentligt eller i.v. 8 mg/kg (dog højst 800 mg) hver 4. uge i kombination med csDMARD.

Effektmål

Se tabel 1.

3.2 Hvilken klinisk merværdi tilbyder sarilumab sammenlignet med tocilizumab i kombination med csDMARD til patienter med moderat til svær RA, der skal skifte biologisk eller targeteret syntetisk behandling?

Population

Patienter i csDMARD-behandling med fortsat moderat til svær sygdomsaktivitet trods behandling med bDMARDs eller tsDMARDs.

Intervention

Sarilumab, s.c. 200 mg hver anden uge i kombination med csDMARD.

Komparator

Tocilizumab, s.c. 162 mg én gang ugentligt eller i.v. 8 mg/kg (dog højst 800 mg) hver 4. uge i kombination med csDMARD.

Effektmål

Se tabel 1.

3.3 Hvilken klinisk merværdi tilbyder sarilumab sammenlignet med tocilizumab til bionaive patienter med moderat til svær RA, hvor behandling med csDMARDs ikke er en mulighed?

Population

Patienter med RA med fortsat moderat til svær sygdomsaktivitet, som endnu ikke har modtaget biologisk eller targeteret syntetisk behandling, og hvor behandling med csDMARDs ikke er en mulighed.

Intervention

Sarilumab, s.c. 200 mg hver anden uge.

Komparator

Tocilizumab, s.c. 162 mg én gang ugentligt eller i.v. 8 mg/kg (dog højst 800 mg) hver 4. uge.

Effektmål

Se tabel 1.

3.4 Hvilken klinisk merværdi tilbyder sarilumab sammenlignet med tocilizumab til patienter med moderat til svær RA, som skal skifte biologisk eller targeteret syntetisk behandling, og hvor behandling med csDMARDs ikke er en mulighed?

Population

Patienter med RA med fortsat moderat til svær sygdomsaktivitet trods behandling med bDMARDs eller tsDMARDs, hvor behandling med csDMARDs ikke er en mulighed.

Intervention

Sarilumab, s.c. 200 mg hver anden uge.

Komparator

Tocilizumab, s.c. 162 mg én gang ugentligt eller i.v. 8 mg/kg (dog højst 800 mg) hver 4. uge.

Effektmål

Se tabel 1.

3.5 Valg af effektmål

Tabel 1 summerer de valgte effektmål, deres vigtighed, mindste klinisk relevante forskel og kategori.
For alle effektmål ønskes både absolutte og relative værdier, jævnfør ansøgningsskemaet. For de relative værdier vurderes den kliniske relevans (merværdi), jævnfør væsentlighedskriterierne beskrevet i Medicinrådets metodehåndbog for vurdering af nye lægemidler. De relative effektestimater kan angives i relativ risiko (RR), odds ratio (OR) eller hazard ratio (HR). Det skal begrundes i ansøgningen, hvis der afviges fra de ønskede effektmål.

Effektmål*	**Vigtighed**	**Kategori**	**Måleenhed**	**Mindste klinisk relevante forskel**
Mortalitet	Kritisk	Dødelighed	Andel patenter	-
American College of Rheumatology 50 % response, ACR50	Kritisk	Alvorlige symptomer og bivirkninger	Andel patienter	Forskel på 15 procentpoint mellem grupperne
Behandlingsophør grundet uønskede hændelser	Kritisk	Alvorlige symptomer og bivirkninger	Andel patienter	Forskel på 5 procentpoint mellem grupperne
Behandlingsophør grundet manglende effekt	Vigtigt	Alvorlige symptomer og bivirkninger	Andel patienter	Forskel på 10 procentpoint mellem grupperne
Alvorlige infektioner	Vigtigt	Alvorlige symptomer og bivirkninger	Andel patienter	Forskel på 5 procentpoint mellem grupperne
Total Sharp Score, TSS	Vigtigt	Ikke-alvorlige symptomer og bivirkninger	Andel patienter	Forskel på 10 procentpoint mellem grupperne
Health Assessment Questionnaire Disability Index, HAQ-DI	Vigtigt	Helbredsrelateret livskvalitet	Andel patienter	Forskel på 15 procentpoint mellem grupperne

Tabel 1: Liste over valgte effektmål. For hvert effektmål er angivet deres vigtighed. For kritiske og vigtige effektmål er desuden angivet den mindste klinisk relevante forskel.
* For alle effektmål ønskes data med længst mulig opfølgningstid.

Kritiske effektmål

Mortalitet: Det er i udgangspunktet altid relevant at belyse, om lægemidler forlænger patienternes overlevelse. Studier har vist, at RA-patienter har øget risiko for udvikling af hjertekarsygdomme og øget overordnet dødelighed [12,13]. Eftersom RA i sig selv ikke er forbundet med akut død, er mortalitet ikke umiddelbart et relevant effektmål i det forventede tidsinterval. Data vedrørende mortalitet vil blive inkluderet, analyseret og rapporteret i et format, der tilsvarer datakvaliteten. Hvis der findes lægemidler, der påvirker dødeligheden indenfor studiernes tidsramme, vil dette fremgå af vurderingen.

ACR50: Det primære mål for effekt er ACR50. Dette er defineret som 50 % forbedring i både ømme og hævede led samt 50 % forbedring inden for mindst tre ud af følgende fem kategorier: patientens overordnede vurdering, lægens overordnede vurdering, patientens vurdering af smerter, HAQ-DI-score og

C-Reaktivt Protein (CRP). Fagudvalget vurderer, at en 50 %'s forbedring er et patientrelevant effektmål og betragtes her som tilstrækkeligt for at definere respons. En absolut værdi for den mindste klinisk relevante forskel for ACR50 er defineret som en forskel i opnået respons mellem de to patientgrupper (intervention vs. komparator) på 15 procentpoint.

Behandlingsophør grundet uønskede hændelser (*withdrawals due to AE* eller d*iscontinuation of study drug due to AE*): Dette effektmål indgik i den nuværende behandlingsvejledning fra RADS som overordnet mål for bivirkninger [10]. Det er fagudvalgets vurdering, at uønskede hændelser, der fører til ophør af behandlingen, er et brugbart surrogatmål for bivirkninger. Den mindste klinisk relevante forskel defineres som en forskel på 5 procentpoint mellem grupperne, hvilket rummer den nuværende ligestilling mellem bDMARDs i den eksisterende RADS-vejledning [10].

Vigtige effektmål

Behandlingsophør grundet manglende effekt: Dette effektmål indgik ikke i den nuværende behandlingsvejledning fra RADS. Fagudvalget mener, dette er et vigtigt effektmål, da forskelle i manglende effekt af lægemidler med potentielle bivirkninger skal afdækkes. Fagudvalget mener, at en belysning af dette effektmål vil bidrage til at muliggøre valg af den bedste behandling først og dermed reducere unødvendig behandling.

Total Sharp Score (TSS) er et relevant radiologisk effektmål, der kan tolkes som et udtryk for sygdomsprogression [14]. Den mindste klinisk relevante forskel i TSS er defineret ved antal patienter uden progression [15]. Her fastsættes en forskel på 10 procentpoint mellem grupperne som den mindste klinisk relevante forskel. På standardbehandling forventes ca. 80 % af patienterne at være uden progression i løbet af et år [16], og en ændring på 10 % vil være detekterbar i klinisk praksis.

Alvorlige infektioner: Udover behandlingsophør grundet bivirkninger ønskes antallet af alvorlige infektioner (som defineret i de kliniske studier) opgjort selvstændigt, da disse særligt frygtes af patienter og klinikere, siden de kan forårsage pauser i behandlingen. For at rumme variansen i antallet af infektioner mellem ligestillede lægemidler i RADS-behandlingsvejledningen [10] defineres den mindste, betydende kliniske forskel som 5 procentpoint.

HAQ-DI er inkluderet som et mål for patienternes invaliditet/funktionstab og afspejler i denne sammenhæng livskvalitet. Det er et domænespecifikt instrument, der er pålideligt, velundersøgt og valideret [17]. HAQ-DI er valgt fremfor et generisk instrument, idet fagudvalget vurderer, at det er af større relevans for RA-patienter, og fordi det anvendes i dansk klinisk praksis og bl.a. registreres ved ambulante besøg.

Fagudvalget vurderer, at den mindste klinisk relevante forskel er 15 procentpoint i antal patienter, der oplever positiv respons. Respons er defineret som en ændring på 0,22 i HAQ-DI-score fra baseline [18].

4 Litteratursøgning

Databaser for søgningen

Relevant litteratur søges i databaserne MEDLINE (via PubMed eller Ovid) og CENTRAL (via Cochrane Library).

Derudover skal EMAs European public assessment reports (EPAR) konsulteres for både det aktuelle lægemiddel og dets komparator(er).

Søgetermer

Søgningen skal inkludere det generiske navn og handelsnavnet for både det aktuelle lægemiddel og dets komparator(er), som kombineres med termer for indikationen.

Søgningen skal som minimum indeholde termer, som er beskrivende for de områder, der angivet i tabellen herunder. Både indekseret (f.eks. Medical Subject Headings, MeSH) og fritekstsøgning skal anvendes.

Sarilumab (Kevzara) *Termer for det generiske navn, handelsnavn og alternative stavemåder og eventuelle MeSH/Supplementary Concepts kombineres med **OR**. AND kan bruges, hvor flere termer skal forekomme samtidigt for at beskrive lægemidlet korrekt, f.eks. ved coformuleringer.*	*Blokkene til venstre og højre kombineres med **AND***	**Rheumatoid arthritis** *Termer for indikationen, alternative stavemåder og eventuelle MeSH kombineres med **OR**. AND kan bruges, hvor flere termer skal forekomme samtidigt for at beskrive indikationen korrekt.*
*Ovenstående og nedenstående blokke kombineres med **OR***		
Tocilizumab (RoActemra) *Termer for det generiske navn, handelsnavn, alternative stavemåder og eventuelle MeSH/Supplementary Concepts kombineres med **OR**. AND kan bruges, hvor flere termer skal forekomme samtidigt for at beskrive lægemidlet korrekt, f.eks. ved coformuleringer.*		

De anvendte søgetermer, og hvordan de er blevet kombineret, dokumenteres separat for hver af de to databaser.

Kriterier for udvælgelse af litteratur

Der ekskluderes først på titel- og abstractniveau, dernæst ved gennemlæsning af fuldtekstartikler. Artikler, der ekskluderes ved fuldtekstlæsning, skal fremgå med forfatter, årstal og titel i en eksklusionsliste, hvor eksklusionen begrundes kort. Den samlede udvælgelsesproces skal afrapporteres ved brug af et PRISMA-flowdiagram (http://prisma-statement.org/PRISMAStatement/FlowDiagram.aspx).

Ved usikkerheder om, hvorvidt en artikel på titel- og abstractniveau lever op til inklusions- og eksklusionskriterierne, skal der anvendes et forsigtighedsprincip til fordel for artiklen, hvorved fuldtekstartiklen vurderes.

Inklusions- og eksklusionskriterier: Andre studiedesign end randomiserede kontrollerede forsøg (RCT) ekskluderes, fase I og IIa ekskluderes, studier med andre populationer end de valgte ekskluderes, og studier, som ikke rapporterer mindst et af de kritiske eller vigtige effektmål, ekskluderes.

Vurderingen af klinisk merværdi baseres på data fra publicerede fuldtekstartikler og data fra EMAs EPAR – Public assessment report. Data skal derudover stemme overens med protokollens beskrivelser. Upublicerede data og data fra f.eks. abstracts kan fremsendes og vil indgå i vurderingen, såfremt Medicinrådet finder, at de er nødvendige for at sikre en fair sammenligning. Data skal i så fald stamme fra de forsøg, hovedpublikationerne rapporterer fra, og ansøger skal acceptere, at Medicinrådet offentliggør dem i ansøgningsskemaet og i rapporten vedr. klinisk merværdi.

5 Databehandling/analyse

De inkluderede studier og baselinekarakteristikken af studiepopulationerne beskrives i Medicinrådets ansøgningsskema. Det skal angives, hvilke studier der benyttes til at besvare hvilke kliniske spørgsmål.

Al relevant data skal som udgangspunkt ekstraheres ved brug af Medicinrådets ansøgningsskema. Der skal udføres en komparativ analyse for hvert enkelt effektmål på baggrund af relevant data fra inkluderede studier. For hvert effektmål og studie angives analysepopulation (f.eks. intention-to-treat (ITT), per-protocol) samt metode. Resultater for ITT-populationen skal angives, hvis muligt, hvis komparative analyser ikke i udgangspunktet er baseret på denne population. Alle ekstraherede data skal krydstjekkes med de resultater, der beskrives i EPAR'en. Findes uoverensstemmelser, gives en mulig grund herfor.

Hvis ekstraherede data afviger fra de forhåndsdefinerede PICO-beskrivelser specielt ift. præspecificeret population og effektmål, begrundes dette.

Hvis data for et effektmål ikke er tilgængelig for alle deltagere i et studie, vil der ikke blive gjort forsøg på at erstatte manglende data med en meningsfuld værdi. Det vil sige, at alle analyser udelukkende baseres på tilgængelige data på individniveau.

For effektmål (ORR, SAE, behandlingsstop pga. bivirkninger og ikkealvorlige bivirkninger) hvor det er naturligt at beregne både absolut og relativ forskel, vil den relative forskel være basis for statistiske analyser. Den absolutte forskel vil derefter blive beregnet, baseret på den estimerede relative forskel for et antaget niveau på hændelsesraten i komparatorgruppen. Det antagne niveau vil afspejle det forventede niveau i Danmark ved behandling med komparator (hvis relativ risiko (RR) = 0,5 og antaget andel med hændelse i komparatorgruppen er 30 %, da er den absolutte risiko reduktion (ARR) = 30 – 30 x 0,5 = 15 %-point).

Hvis der er mere end et sammenlignende studie, foretages en metaanalyse for de effektmål, hvor det er metodemæssigt forsvarligt. Hvis der ikke foreligger sammenlignende studier, kan data eventuelt syntetiseres indirekte (evt. i form af formelle netværksmetaanalyser eller ved brug af Buchers metode), hvis intervention og komparator er sammenlignet med samme alternative komparator i separate studier.

Medicinrådet forbeholder sig retten til at foretage sensitivitets- og subgruppeanalyser på baggrund af studiernes validitet og relevans.

For effektmål, hvor forskellige måleinstrumenter er brugt på tværs af de inkluderede studier, vil eventuelle metaanalyser blive baseret på standardized mean difference (SMD). Den estimerede SMD vil blive omregnet til den foretrukne skala for effektmålet. Til dette formål anvendes medianen af de observerede standardafvigelser i de inkluderede studier.

Hvis det ikke er en mulighed at udarbejde metaanalyser (herunder netværksmetaanalyser), syntetiseres data narrativt. Studie- og patientkarakteristika samt resultater fra de inkluderede studier beskrives narrativt og i tabelform med angivelse af resultater pr. effektmål for både intervention og komparator(er). Forskelle i patientkarakteristika og studiekontekst (f.eks. geografi og årstal) mellem studier skal beskrives og vurderes for at afgøre, hvorvidt resultaterne er sammenlignelige.

Valget af syntesemetode (metaanalyse eller narrativ beskrivelse) begrundes, og specifikke analysevalg truffet i forhold til metoden skal fremgå tydeligt.

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7 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende gigtsygdomme

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