Medicinrådet

Baggrund for Medicinrådets anbefaling vedrørende tofacitinib som mulig standardbehandling til psoriasisartrit

Versionsnr.: 1.0

Medicinrådet

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 mulig 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.

Om anbefalingen

Anbefalingen er Medicinrådets vurdering af, om omkostningerne ved behandling med lægemidlet er rimelige i forhold til lægemidlets kliniske værdi.

Lægemidlet vurderes efter Metodehåndbog for Medicinrådets arbejde med at udarbejde fælles regionale vurderinger af nye lægemidlers og nye indikationers kliniske merværdi – version 1. Se Medicinrådets metodehåndbog for yderligere information.

Dokumentoplysninger	
Godkendelsesdato	25. september 2019
Ikrafttrædelsesdato	25. september 2019
Dokumentnummer	57732
Versionsnummer	1.0

Medicinrådet, Dampfærgevej 27-29, 3. th., 2100 København Ø
www.medicinraadet.dk
Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 25. september 2019

Indhold

1 Lægemiddelinformationer

Lægemidlets oplysninger	
Handelsnavn	Xeljanz
Generisk navn	Tofacitinib
Firma	Pfizer
ATC-kode	L04AA29
Virkningsmekanisme	Janus kinase inhibitor
Administration/dosis	Tabletter 5 mg 2 gange dagligt
EMA-indikation	Tofacitinib i kombination med MTX er indiceret til behandling af aktiv psoriasisartrit (PsA) hos voksne patienter, som har haft utilstrækkeligt respons på, eller som ikke har tolereret behandling med et tidligere sygdomsmodificerende antireumatisk lægemiddel (DMARD).

2 Medicinrådets anbefaling

Medicinrådet **anbefaler** tofacitinib som mulig standardbehandling af psoriasisartrit (PsA) til behandlingsnaive og -erfarne patienter **uden** samtidig moderat til svær plaque psoriasis, da der er et rimeligt forhold mellem lægemidlets værdi og omkostningerne for denne patientgruppe. Patienterne skal have haft utilstrækkelig respons på eller ikke tåle et eller flere konventionelle sygdomsmodificerende antireumatiske lægemidler. Medicinrådet **anbefaler ikke** tofacitinib til PsA-patienter **med** samtidig moderat til svær plaque psoriasis, da der ikke er evidens for effekten af tofacitinib i denne patientpopulation.

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

1. Hvilken klinisk merværdi tilbyder tofacitinib til bionaive patienter med PsA uden samtidig moderat til svær plaque psoriasis, sammenlignet med adalimumab?
2. Hvilken klinisk merværdi tilbyder tofacitinib til bioerfarne patienter med PsA uden samtidig moderat til svær plaque psoriasis, sammenlignet med secukinumab?
3. Hvilken klinisk merværdi tilbyder tofacitinib til bionaive patienter med PsA og samtidig moderat til svær plaque psoriasis, sammenlignet med adalimumab?
4. Hvilken klinisk merværdi tilbyder tofacitinib til bioerfarne patienter med PsA og samtidig moderat til svær plaque psoriasis, sammenlignet med secukinumab?

3 Formål

Formålet med Baggrund for Medicinrådets anbefaling vedrørende tofacitinib som mulig standardbehandling til psoriasisartrit er at skabe gennemsigtighed om det materiale, der ligger til grund for Medicinrådets anbefaling.

4 Baggrund

Psoriasisartrit (PsA) er en kronisk inflammatorisk ledsygdom, der ofte (men ikke nødvendigvis) optræder sammen med den kroniske hudsygdom psoriasis. Diagnosen stilles på baggrund af objektiv undersøgelse af bevægeapparat og hud sammen med serologi og biokemi. Prævalensen er svær at estimere grundet manglen på klare diagnostiske kriterier, men den estimeres at være på 0,1 %. Ca. 2-3 % af den danske befolkning får psoriasis i løbet af livet, og det skønnes, at op til ca. 15 % af patienter med psoriasis udvikler PsA. Sygdommen debuterer oftest i alderen 40-50 år, og prævalensen er ens for mænd og kvinder.

4.1 Sagsbehandlingstid og proces for Medicinrådets vurdering

Medicinrådet modtog den foreløbige ansøgning den 18. april 2018, og protokollen blev sendt til ansøger den 29. maj 2018. Den endelige ansøgning blev modtaget den 3. maj 2019. Medicinrådet har derfor gennemført vurderingen af tildrakizumab på 20 uger og 5 dage.

5 Medicinrådets vurdering af samlet klinisk merværdi

Medicinrådet vurderer, at tofacitinib til psoriasisartrit giver ingen klinisk merværdi til patienter uden samtidig moderat til svær plaque psoriasis, dvs.:

- **Ingen klinisk merværdi** for bionaive patienter med psoriasisartrit uden samtidig moderat til svær plaque psoriasis sammenlignet med adalimumab (lav evidenskvalitet).
- **Ingen klinisk merværdi** for bioerfarne patienter med psoriasisartrit uden samtidig moderat til svær plaque psoriasis sammenlignet med secukinumab (lav evidenskvalitet).

Til patienter med samtidig moderat til svær plaque psoriasis kan tofacitinibs merværdi ikke dokumenteres, da størstedelen af patienterne i studierne ikke har samtidig moderat til svær plaque psoriasis, dvs:

- **Ikkedokumenterbar merværdi** for bionaive patienter med psoriasisartrit med samtidig moderat til svær plaque psoriasis (evidensens kvalitet kan ikke vurderes).
- **Ikkedokumenterbar merværdi** for bioerfarne patienter med psoriasisartrit med samtidig moderat til svær plaque psoriasis (evidensens kvalitet kan ikke vurderes).

6 Høring

Ansøger havde ikke kommentarer til kategoriseringen (se bilag 3).

7 Resumé af økonomisk beslutningsgrundlag

Amgros har vurderet de gennemsnitlige meromkostninger pr. patient ved brug af tofacitinib sammenlignet med adalimumab og secukinumab.

I scenariet, Amgros mener, er mest sandsynligt, er de gennemsnitlige meromkostninger for tofacitinib lidt højere end for adalimumab og lavere end for secukinumab.

Medicinrådet vurderer på den baggrund, at der er et rimeligt forhold mellem lægemidlets værdi og omkostningerne for patienter uden samtidig moderat til svær plaque psoriasis. Omvendt vurderer Medicinrådet, at forholdet ikke er rimeligt for patienter med samtidig moderat til svær plaque psoriasis.

8 Overvejelser omkring alvorlighed/forsigtighed

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

9 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende gigtsygdomme

Formand	**Indstillet af**
Ulrik Tarp Overlæge, dr.med.	Lægevidenskabelige Selskaber og Dansk Reumatologisk Selskab
Medlemmer	**Udpeget af**
Salome Kristensen Overlæge	Region Nordjylland
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Connie Ziegler Patient/patientrepræsentant	Danske Patienter
En patient/patientrepræsentant	Danske Patienter
Tidligere medlemmer, der har bidraget til arbejdet	**Udpeget af**
Claus Rasmussen Overlæge og klinisk lektor	Region Nordjylland
Mikala Vasehus Holck Klinisk farmaceut	Dansk Selskab for Sygehusapoteksledelse
Anett Brøgger Patient/patientrepræsentant	Danske Patienter

Medicinrådets sekretariat

Medicinrådet Dampfærgevej 27-29, 3. th. 2100 København Ø + 45 70 10 36 00 medicinraadet@medicinraadet.dk
Sekretariatets arbejdsgruppe: Jeppe Schultz Christensen (projekt- og metodeansvarlig) Nicoline Kerzel Duel (projektdeltagere) Charlotte Wulff Johansen (koordinator) Jan Odgaard-Jensen (biostatistiker) Bettina Fabricius Christensen (informationsspecialist) Tenna Bekker (teamleder)

10 Versionslog

Version	Dato	Ændring
1.0	25. september 2019	Godkendt af Medicinrådet.

11 Bilag

Bilagsliste:

- Amgros' beslutningsgrundlag
- Amgros' sundhedsøkonomiske analyse
- Høringssvar fra ansøger
- Vurdering af den kliniske merværdi af tofacitinib til psoriasisartrit
- Ansøgers endelige ansøgning
- Protokol for vurdering af den kliniske merværdi af tofacitinib til psoriasisartrit

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Beslutningsgrundlag til Medicinrådet

Dette dokument er Amgros' vurdering af tofacitinib (Xeljanz), alene eller i kombination med methrotrexat (MTX), indiceret til behandling af voksne patienter med psoriasisatrit (PsA), som enten har haft utilstrækkelig respons på, eller som ikke tolererer en eller fleresygdomsmodificerede antireumatiske lægemidler (DMARDs). Vurderingen er baseret på lægemidlets gennemsnitlige inkrementelle omkostninger, baseret på SAIP (sygehusapotekets indkøbspris) sammenholdt med Medicinrådets vurdering af den kliniske merværdi.

Dato for Medicinrådsbeslutning	25-09-2019
Firma	Pfizer ApS (ansøger)
Lægemiddel	Tofacitinib (Xeljanz)
Indikation	Behandling af voksne patienter med psoriasisatrit (PsA), som enten har haft utilstrækkelig respons på, eller som ikke tolererer en eller flere sygdomsmodificerende antireumatiske lægemidler (DMARDs)

Amgros' vurdering

- Amgros vurderer, at der **er** et rimeligt forhold mellem meromkostningerne og den kliniske merværdi for tofacitinib (Xeljanz) sammenlignet med adalimumab som mulig standardbehandling til bionaive patienter med PsA uden samtidig moderat til svær plaque psoriasis

- Amgros kan **ikke vurdere** om der er et rimeligt forhold mellem meromkostningerne og den kliniske merværdi for tofacitinib (Xeljanz) sammenlignet med adalimumab som mulig standardbehandling til bionaive patienter med PsA med samtidig moderat til svær plaque psoriasis.

- Amgros vurderer, at der **er** et rimeligt forhold mellem meromkostningerne og den kliniske merværdi for tofacitinib (Xeljanz) sammenlignet med secukinumab som mulig standardbehandling til bioerfarne patienter med PsA uden samtidig moderat til svær plaque psoriasis

- Amgros kan **ikke vurdere** om der er et rimeligt forhold mellem meromkostningerne og den kliniske merværdi for tofacitinib (Xeljanz) sammenlignet med secukinumab som mulig standardbehandling til bioerfarne patienter med PsA med samtidig moderat til svær plaque psoriasis.

Overordnet konklusion

Medicinrådet har vurderet, at tofacitinib (Xeljanz) til bionaive patienter uden samtidig moderat til svær plaque psorisasis giver **ingen klinisk merværdi** sammenlignet med adalimumab.

Medicinrådet har vurderet, at tofacitinib (Xeljanz) til bionaive patienter med samtidig moderat til svær plaque psoriasis giver **ikkedokumenterbar merværdi** sammenlignet med adalimumab.

Medicinrådet har vurderet, at tofacitinib (Xeljanz) til bioerfarne patienter uden samtidig moderat til svær plaque psorisasis giver **ingen klinisk merværdi** sammenlignet med secukinumab.

Medicinrådet har vurderet, at tofacitinib (Xeljanz) til bioerfarne patienter med samtidig moderat til svær plaque psoriasis giver **ikkedokumenterbar merværdi** sammenlignet med secukinumab.

Behandling med tofacitinib (Xeljanz) til bionaive patienter uden samtidig moderat til svær plaque psoriasis er forbundet med meromkostninger sammenlignet med adalimumab. Amgros vurderer at forholdet mellem klinisk merværdi og omkostning er rimeligt.

Behandling med tofacitinib (Xeljanz) til bioerfarne patienter uden samtidig moderat til svær plaque psoriasis er forbundet med besparelser sammenlignet med secukinumab. Amgros vurderer at forholdet mellem klinisk merværdi og omkostning er rimeligt.

Andre overvejelser

Amgros har indgået en aftale med Pfizer ApS om indkøb af tofacitinib (Xeljanz) til en SAIP, som er lavere end AIP. Konklusionen er baseret på SAIP for tofacitinib (Xeljanz).

I forhold til nuværende behandlingsvejledning er det Amgros' vurdering, at det vil være hensigtsmæssigt, at tofacitinib (Xeljanz) anbefales, så den i fremtiden kan konkurrenceudsættes på lige fod med øvrige 1. linjebehandlinger.

Konklusion for populationen

Tabel 1 Merværdi, meromkostninger og Amgros' vurdering (baseret på SAIP)

Population	Komparator	Merværdi	Usikkerhed for klinisk merværdi	Amgros' konklusion om forholdet mellem meromkostninger og merværdi
Bionaive patienter med psoriasisatrit uden samtidig moderat til svær plaque psoriasis	Adalimumab	Ingen klinisk merværdi	Lav evidenskvalitet	Rimeligt
Bionaive patienter med psoriasisatrit med samtidig moderat til svær plaque psoriasis	Adalimumab	Ikkedokumenterbar merværdi	Evidensens kvalitet kan ikke vurderes	Kan ikke vurderes
Bioerfarne patienter med psoriasisatrit uden samtidig moderat til svær plaque psoriasis	Secukinumab	Ingen klinisk merværdi	Meget lav evidenskvalitet	Rimeligt
Bioerfarne patienter med psoriasisatrit med samtidig moderat til svær plaque psoriasis	Secukinumab	Ikkedokumenterbar merværdi	Evidensens kvalitet kan ikke vurderes	Kan ikke vurderes

Supplerende informationer (resumé af resultaterne fra afrapporteringen)

Konklusion på omkostnings- og budgetkonsekvensanalyserne

Resultatet fra Amgros' afrapportering på omkostningsanalyserne er gengivet i det følgende. For uddybende gennemgang af analyse og resultater henvises til afrapporteringen på http://www.amgros.dk.

Amgros' afrapportering - Inkrementelle omkostninger per patient

Behandling med tofacitinib (Xeljanz) er forbundet med meromkostninger sammenlignet med behandling med adalimumab til bionaive patienter og besparelser sammenlignet med secukinumab til bioerfarne patienter.

I tabel 2 og 3 ses de inkrementelle omkostninger for tofacitinib (Xeljanz)og komparatorerne.

Amgros' hovedanalyse resulterer i inkrementelle omkostninger per patient for tofacitinib (Xeljanz) på ca. [redacted] sammenlignet med adalimumab og ca. [redacted] sammenlignet med secukinumab.

Tabel 2: Resultatet af hovedanalyse ved sammenligning med adalimumab til bioerfarne patienter, SAIP, diskonteret, DKK.

	Tofacitinib (Xeljanz)	Adalimumab	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Administrations- og patientomkostninger	7.758	7.877	-119
Totale omkostninger	[redacted]	[redacted]	[redacted]

Tabel 3: Resultatet af hovedanalyse ved sammenligning med secukinumab til bioerfarne patienter, SAIP, diskonteret, DKK.

	Tofacitinib (Xeljanz)	Secukinumab	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Administrations- og transportomkostninger	7.758	7.877	-119
Totale omkostninger	[redacted]	[redacted]	[redacted]

Hvis analysen udføres med AIP bliver de inkrementelle omkostninger til ca. 16.400 DKK per patient sammenlignet med adalimumab og -70.000 DKK sammenlignet med secukinumab.

Amgros' afrapportering – Budgetkonsekvenser

Amgros vurderer, at anbefaling af tofacitinib (Xeljanz) som mulig standardbehandling vil resultere i budgetkonsekvenser på ca [redacted] for bionaive patienter og [redacted] for bioerfarne patienter. Hvis analysen udføres med AIP, er budgetkonsekvenserne hhv. ca. 5 mio. DKK i år 5 og -ca. -29,1 mio. DKK i år 5.

XELJANZ (TOFACITINIB)

PSORIASISARTRIT

AMGROS 30. juli 2019

AMGROS

OPSUMMERING

Baggrund

Tofacitinib (Xeljanz), alene eller i kombination med methotrexat (MTX), er indiceret til behandling af psoriasisartrit (PsA) hos voksne patienter, som enten har haft utilstrækkelig respons på, eller som ikke tolererer en eller flere sygdomsmodificerende antireumatiske lægemidler (DMARDs). Amgros' vurdering tager udgangspunkt i dokumentation indsendt af Pfizer.

Analyse

I analysen estimeres de inkrementelle omkostninger og budgetkonsekvenserne for regionerne, forbundet med behandling med tofacitinib (Xeljanz) sammenlignet med adalimumab og secukinumab.

Inkrementelle omkostninger og budgetkonsekvenser

Amgros har vurderet de gennemsnitlige meromkostninger per patient ved brug af tofacitinib (Xeljanz) sammenlignet med komparatorerne. De inkrementelle omkostninger er angivet i SAIP.

I scenariet Amgros mener er mest sandsynligt, er de gennemsnitlige meromkostninger for tofacitinib (Xeljanz) ca. [redacted] sammenlignet med adalimab til bionaive patienter (P1) og ca. [redacted] sammenlignet med secukinumab til bioerfarne patienter (P2). Hvis analysen udføres med AIP bliver de inkrementelle omkostninger til sammenligning ca. 16.400 DKK per patient sammenlignet med adalimumab og -70.000 DKK sammenlignet med secukinumab.

Amgros vurderer, at budgetkonsekvenserne for regionerne per år ved anbefaling af tofacitinib (Xeljanz) som standardbehandling vil være ca. [redacted] i år 5 for P1 og ca. [redacted] i år 5 for P2. Hvis analysen udføres med AIP, er budgetkonsekvenserne hhv. ca. 4,9 mio. DKK i år 5 sammenlignet med adalimumab og -29,1 mio. DKK i år 5 sammenlignet med secukinumab.

Konklusion

Behandling med tofacitinib (Xeljanz) er forbundet med meromkostninger sammenlignet med behandling med adalimumab og besparelser sammenlignet med secukinumab. Meromkostningerne og besparelserne for anbefaling af tofacitinib (Xeljanz) er drevet af lægemiddelomkostningerne.

Liste over forkortelser

AIP	Apotekernes indkøbspris
DKK	Danske kroner
DMARDs	Disease modifying antirheumatic drugs
DRG	Diagnose Relaterede Grupper
mAb	Monoklonalt antistof
MTX	Methotrexat
PsA	Psoriasisartrit
RA	Reumatoid artritis
SAIP	Sygehusapotekernes indkøbspriser
SPC	Summary of Product Characteristics
RADS	Rådet for anvendelse af dyr sygehusmedicin

INDHOLD

LOG

Ansøgning	
Lægemiddelfirma:	Pfizer ApS
Handelsnavn:	Xeljanz
Generisk navn:	Tofacitinib
Indikation:	Tofacitinib (Xeljanz), alene eller i kombination med methotrexat (MTX), er indiceret til behandling af psoriasisartrit (PsA) hos voksne patienter, som enten har haft utilstrækkelig respons på, eller som ikke tolererer en eller flere sygdomsmodificerede antireumatiske lægemidler (DMARDs)
ATC-kode:	L04AA29

Proces	
Ansøgning modtaget hos Amgros:	03-05-2019
Endelig rapport færdig:	30-07-2019
Sagsbehandlingstid fra endelig ansøgning:	88 dage
Arbejdsgruppe:	**Louise Greve Dal** Lianna Geertsen Pernille Winther Johansen Line Brøns Jensen Mark Friborg

Priser
Denne rapport bygger på analyser udført på baggrund sygehusapotekernes indkøbspriser (SAIP). Enkelte steder er analysens resultat yderligere angivet på baggrund af listepriser (AIP).

1 BAGGRUND

Tofacitinib (Xeljanz) er, alene eller i kombination med methotrexat (MTX), indiceret til behandling af psoriasisartrit (PsA) hos voksne patienter, som enten har haft utilstrækkelig respons på, eller som ikke tolererer en eller flere sygdomsmodificerende antireumatiske lægemidler (DMARDs). Pfizer (herefter omtalt som ansøger) er markedsføringstilladelsesindehaver af tofacitinib (Xeljanz) og har den 03.05.2018 indsendt en ansøgning til Medicinrådet om anbefaling af tofacitinib (Xeljanz) som standardbehandling på danske hospitaler af den nævnte indikation. Som et led i denne ansøgning vurderer Amgros, på vegne af Medicinrådet de økonomiske analyser, ansøger har sendt som en del af den samlede ansøgning til Medicinrådet. Denne rapport er Amgros' vurdering af de fremsendte økonomiske analyser (herefter omtalt som analysen).

1.1 Problemstilling

Formålet med analysen er at estimere de inkrementelle omkostninger forbundet med behandling til psoriasisartrit (PsA) hos voksne patienter, i form af de gennemsnitlige inkrementelle omkostninger per patient og de samlede budgetkonsekvenser for regionerne ved anbefaling af tofacitinib (Xeljanz), som standardbehandling på danske hospitaler af den nævnte indikation. I analyserne sammenlignes behandling med tofacitinib (Xeljanz) med behandling med adalimumab og secukinumab, der er defineret i Medicinrådets protokol.(1)

1.2 Patientpopulation

PsA er en kronisk inflammatorisk ledsygdom, der ofte (men ikke nødvendigvis) optræder sammen med den kroniske hudsygdom psoriasis. Det skønnes at op til ca. 15% af patienter med psoriasis udvikler PsA.(1) Prævalensen er svær at estimere grundet manglen på klare diagnostiske kriterier, men den estimeres at være på 0,1%. Sygdommen debuterer oftest i alderen 40-50 år, og prævalensen er ens for mænd og kvinder.(1)

1.3 Nuværende behandling

Den nuværende behandling af patienter med artrit anvendes smertelindrende og DMARDs (disease modifying antirheumatic drugs). Til patienter med lav sygdomsaktivitet og lav risiko for progressiv ledsygdom (under 5 led) anvendes monoterapi med lægemidler af typen konventionelle DMARDs (csDMARDs), hvor methotrexat (MTX) sædvanligvis er førstevalg i dansk klinisk praksis. Ved patienter med betydelig ledaffektion (mere end fire led) eller ved utilstrækkelig effekt af DMARDs, kan biologisk behandling indledes.(1)

Af biologisk behandling benyttes på nuværende tidspunkt TNF-alfa hæmmere infliximab, adalimumab, etanercept, certolizumab pegol og golimumab. Desuden benyttes ustekinumab, som et monokonalt antistof mod interleukin 12 og interleukin 23, samt secukinumab, der er et monoklonalt antistof mod interleukin 17A.(1)

1.4 Behandling med tofacitinib (Xeljanz)

Indikation

Tofacitinib (Xeljanz) er, alene eller i kombination med methotrexat (MTX), indiceret til behandling af psoriasisartrit (PsA) hos voksne patienter, som enten har haft utilstrækkelig respons på, eller som ikke tolererer en eller flere sygdomsmodificerende antireumatiske lægemidler (DMARDs).(1)

Virkningsmekanisme

Tofacitinib (Xeljanz) virker ved at binde sig til og blokere Janus kinase-familiens enzymer. Disse enzymer spiller en vigtig rolle i inflammationsprocessen ved UC og ved at blokere enzymerne, reduceres inflammationen og andre sygdomssymptomer.(1)

Dosering

Den anbefalede dosis er 5 mg to gange dagligt i otte uger efterfulgt af 5 mg to gange dagligt. Tofacitinib (Xeljanz) gives som en tablet, og patienten kan dermed selv administrere behandlingen.(1)

1.4.1 Komparator

Medicinrådet har defineret komparator som de lægemidler, der aktuelt anbefales som 1. linjebehandling, til bionaive og bioerfarne patienter med PsA, *med* og *uden* samtidig moderat til svær plaque psoriasis. De nævnte komparatorer er(1):

- Adalimumab i den anbefalede dosis (subkutan injektion á 40 mg hver 14. dag)
- Secukinumab i den anbefalede dosis til bioerfarne patienter (subkutan injektion á 300 mg uge 0,1,2,3,4 og herefter månedligt)

Se tabel 1.

Tabel 1: Definerede populationer og komparatorer.

Population	Komparator
P1: Bionaive patienter (patienter der ikke har modtaget biologisk behandling tidligere) med PsA *uden* og *med* moderat til svær plaque psoriasis.	Adalimumab
P2: Bioerfarne patienter (patienter der tidligere har modtaget biologisk behandling) med PsA *uden* og *med* moderat til svær plaque psoriasis.	Secukinumab

1.5 Medicinrådets kliniske spørgsmål

Medicinrådet har vurderet den kliniske merværdi af behandling med tofacitinib (Xeljanz) sammenlignet med adalimumab for følgende populationer(1):

- Hvad er den kliniske merværdi af tofacitinib (Xeljanz) til bionaive patienter med PsA **uden** samtidig moderat til svær plaque psoriasis sammenlignet med adalimuab?(1)
- Hvad er den kliniske merværdi af tofacitinib (Xeljanz) til bionaive patienter med PsA **med** samtidig moderat til svær plaque psoriasis sammenlignet med adalimuab?(1)

Medicinrådet har vurderet den kliniske merværdi af behandling med tofacitinib (Xeljanz) sammenlignet med secukinumab for følgende populationer(1):

- Hvad er den kliniske merværdi af tofacitinib (Xeljanz) til bioerfarne patienter med PsA **uden** samtidig moderat til svær plaque psoriasis sammenlignet med sekukinumab?(1)
- Hvad er den kliniske merværdi af tofacitinib (Xeljanz) til bioerfarne patienter med PsA **med** samtidig moderat til svær plaque psoriasis sammenlignet med sekukinumab?(1)

2 VURDERING AF INDSENDT ØKONOMISK ANALYSE

I analysen af gennemsnitlige behandlingsomkostninger per patient sammenlignes behandling med tofacitinib (Xeljanz) med behandling med adalimumab til bionaive patienter med PsA *uden* og *med* moderat til svær plaque psoriasis og med behandling med secukinumab til bioerfarne patienter med PsA *uden* og *med* moderat til svær plaque psoriasis.

2.1 Model, metode og forudsætninger

2.1.1 Modelbeskrivelse

Ansøger har indsendt en omkostningsanalyse, der estimerer de gennemsnitlige omkostninger for behandling med tofacitinib (Xeljanz) og komparatorerne. Analysen anvender et begrænset samfundsperspektiv, hvor lægemiddelomkostninger, administrationsomkostninger og transportomkostninger inkluderes. Analysen inkluderer ikke monitorerings eller bivirkningsrelaterede omkostninger, da disse antages at være ens på tværs af lægemidlerne.

Da overlevelse ikke er en faktor, der varierer på tværs af behandlingerne, er analysen en simpel opgørelse af omkostningerne forbundet med behandlingen. De gennemsnitlige omkostninger estimeres på baggrund af en række estimerede ressourceforbrug og værdisætning af dette ressourceforbrug.

Amgros' vurdering

Amgros vurderer, at modeltilgangen er acceptabelt.

2.1.2 Analyseperspektiv

Ansøger har indsendt en omkostningsanalyse med et begrænset samfundsperspektiv. Analysen har en tidshorisont på 18 måneder. Dette valg har ansøger argumenteret ud fra at samme tidshorisont gør sig gældende i en RADS behandlingsvejledning for rheumatoid artritis (RA).(2) Desuden finder ansøger at alle forskelle i relevante omkostninger ligger inden for en tidshorisont på 18 måneder. Omkostninger der ligger efter det første år, er diskonteret med en rate på 4 %.

Amgros' vurdering

Analysens begrænsede samfundsperspektiv og diskonteringsrate er i tråd med Amgros' retningslinjer og accepteres.

2.1.3 Omkostninger

Det følgende afsnit om omkostninger redegør for hvordan og hvilke omkostninger ansøger har inkluderet i analysen.

Lægemiddelomkostninger

Ansøger har inkluderet omkostninger til lægemidler. Priserne for de lægemidler ansøger anvender i analysen, er angivet i tabel 2. Alle priser er i SAIP.

Beregning af den samlede dosering af lægemidlerne og de heraf følgende omkostninger over 18 uger, er illustreret i tabellen nedenfor.(3–5) Ansøger antager at der ikke er noget spild forbundet med brugen af lægemidlerne.

Tabel 2: Anvendte lægemiddelpriser, DKK, SAIP.

	Tofacitinib (Xeljanz)	Adalimumab	Secukinumab
Styrke	5 mg	40 mg	150 mg
Pakningsstørrelse	56 tabletter	2 hætteglas	2 hætteglas
Dosis per administration	1	1	2
Pris	[redacted]	[redacted]	[redacted]
Antal doser (18 måneder)	1106	39,5	23,5
Lægemiddelomkostninger, gns. patient (18 måneder)	[redacted]	[redacted]	[redacted]

Amgros' vurdering

Doseringen er i tråd med lægemidlernes SmPC og seneste behandlingsvejledning fra RADS.
Amgros vurderer derfor at doseringen og beregningen af lægemiddelomkostningerne er acceptabelt.

Administrationsomkostninger

Ansøger har anvendt Amgros' udvidet sammenligningsgrundlag på reumatoid artritis (RA) som kilde for administrationsomkostningerne for de tre lægemidler.(6) Secukinumab er ikke en del af det udvidede sammenligningsgrundlag for RA. Ansøger argumenterer for at secukinumab er sammenlignelig med adalimumab angående subkutan administration og derfor anvendes samme administrationsomkostninger for adalimumab til secukinumab behandlingen.(6)

Tabel 3: Administrationsomkostninger, 18 måneder, DKK.

	Tofacitinib (Xeljanz)	Adalimumab	Secukinumab
Læge (tid)	2.753	2.550	2.550
Sygeplejerske (tid)	1.852	2.114	2.114
Transport	1.651	1.642	1.642
Blodprøver	1.437	1.421	1.421
Lokale	65	72	72
Utensilier	0	78	78
Total	**7.758**	**7.877**	**7.877**

Amgros' vurdering

Ansøger har anvendt Amgros' udvidede sammenligningsgrundlag på området reumatoid artritis som et estimat for administrationsomkostningerne på RA. Da sygdomsområderne er forskellige, vil der kunne forekomme forskel i omkostningerne. Amgros mener ligeledes der er stor usikkerhed omkring estimeringen af administrationsomkostningerne for secukinumab.
Amgros' vurderer dog at det ikke vil have den store betydning for de samlede omkostninger i denne sammenhæng. Ansøgers tilgang accepteres.

Patientomkostninger

Ansøger har valgt at patientomkostningerne ekskluderes, da lægemidlerne administreres hjemme, og antager at patienttid benyttet på at hente lægemidlerne er ens. Ansøger inkluderer dog transportomkostninger, jf. tabel 3.

Amgros' vurdering

Ansøger har anvendt Amgros' udvidede sammenligningsgrundlag på området reumatoid artritis som et estimat for administrationsomkostningerne på PsA. Da sygdomsområderne er forskellige, vil der kunne forekomme forskel i omkostningerne.
Amgros' vurderer dog at det ikke vil have den store betydning for de samlede omkostninger i denne sammenhæng. Ansøgers tilgang accepteres.

2.2 Følsomhedsanalyser

Ansøger har ikke udarbejdet følsomhedsanalyser, da de argumenterer for at den primære forskel i de inkrementelle omkostninger ligger i lægemiddelomkostninger, og at andre parametre har meget lille eller ingen betydning for analysens resultat.

Amgros' vurdering

Amgros vurderer at ansøgers antagelse er rimelig.

3 RESULTATER

3.1 Ansøgers hovedanalyse

Resultaterne fra ansøgers hovedanalyse præsenteres i tabel 4 og 5.

Ansøger estimerer i analysen de inkrementelle omkostninger per patient for tofacitinib (Xeljanz) sammenlignet med adalimumab til ca. [redacted] for P1. Sammenlignes tofacitinib (Xeljanz) med secukinumab estimeres en inkrementelomkostning på ca. [redacted]

Hvis analysen udføres på baggrund af AIP, bliver lægemiddelomkostningerne for tofacitinib (Xeljanz) ca. 111.800 DKK, mens de totale inkrementelle omkostninger bliver ca. 16.400 DKK sammenlignet med adalimumab og ca. -70.000 DKK sammenlignet med secukinumab.

Tabel 4: Resultatet af ansøgers hovedanalyse ved sammenligning med adalimumab (P1), SAIP, diskonteret, DKK.

	Tofacitinib (Xeljanz)	Adalimumab	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Administrations- og patientom-kostninger	7.758	7.877	-119
Totale omkostninger	[redacted]	[redacted]	[redacted]

Tabel 5: Resultatet af ansøgers hovedanalyse ved sammenligning med secukinumab (P2), SAIP, diskonteret, DKK.

	Tofacitinib (Xeljanz)	Secukinumab	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Administrations- og transport-omkostninger	7.758	7.877	-119
Totale omkostninger	[redacted]	[redacted]	[redacted]

Amgros' vurdering

Amgros vurderer ansøgers resultater som rimelige.

4 BUDGETKONSEKVENSER

Budgetkonsekvenserne per år er baseret på antagelsen om, at **tofacitinib (Xeljanz)** vil blive anbefalet som standardbehandling. Man ser derfor på to scenarier:

- **Tofacitinib (Xeljanz)** bliver anbefalet som standardbehandling af Medicinrådet til indikationen, som denne analyse omhandler
- **Tofacitinib (Xeljanz)** bliver ikke anbefalet som standardbehandling

Budgetkonsekvenserne bliver differencen mellem budgetkonsekvenserne i de to scenarier.

4.1 Ansøgers estimater

4.1.1 Patientpopulation og markedsandel

Medicinrådet har i protokollen ikke angivet deres vurdering over antallet af patienter. Ansøger har derfor selv udarbejdet et estimat. Ansøger antager på baggrund af behandlingsvejledningen af RADS for PsA, at der er 120 bionaive patienter per år og 220 bioerfarne patienter per år i Danmark.(2)

Ansøger antager på baggrund af studier at 50% af patienter på TNF-hæmmere vil have udgået fra behandling efter 4-5 år. Ansøger antager en ens rate per år for udgåede patienter, svarende til at 15 patienter af bionaive udgår behandlingen per år, i år 2 til år 5 og 27,5 patienter udgår behandling i de bioerfarne per år i år 2 til år 5.(7–9)

Ansøger antager at tofacitinib (Xeljanz) ersatter alle nye patienter, og dermed et markedsoptag på 100%.

Tabel 6 og 7 viser ansøgers estimat af antal patienter årligt.

Tabel 61: Ansøgers estimat af antal nye patienter per år, P1.

	Anbefales som standardbehandling						Anbefales ikke som standardbehandling				
	År 1	År 2	År 3	År 4	År 5		År 1	År 2	År 3	År 4	År 5
Tofacitinib (Xeljanz)	120	105	90	75	60		0	0	0	0	0
Adalimumab	0	0	0	0	0		120	105	90	75	60

Tabel 72: Ansøgers estimat af antal nye patienter per år, P2.

	Anbefales som standardbehandling						Anbefales ikke som standardbehandling				
	År 1	År 2	År 3	År 4	År 5		År 1	År 2	År 3	År 4	År 5
Tofacitinib (Xeljanz)	220	193	165	138	110		0	0	0	0	0
Secukinumab	0	0	0	0	0		220	193	165	138	110

Amgros' vurdering af estimeret antal patienter

Amgros vurderer at antallet af estimerede patienter på baggrund af RADS behandlingsvejledning virker rimeligt.
Amgros accepterer ansøgers estimat af antal patienter.

4.1.2 Estimat af budgetkonsekvenser

Ansøger har inkluderet de samme omkostninger i budgetkonsekvensanalysen, som der er inkluderet i omkostningsanalysen. Med de indlagte antagelser estimerer ansøger, at anvendelse af tofacitinib (Xeljanz) vil resultere i budgetkonsekvenser på ca. [redacted] per år for bionaive patienter og [redacted] per år for bioerfarne patienter.
Ansøgers estimat af budgetkonsekvenserne fremgår af tabel 8 og 9.

Tabel 8: Ansøgers hovedanalyse for totale budgetkonsekvenser (bionaive patienter), mio. DKK, ikke-diskonterede tal.

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Tabel 9: Ansøgers hovedanalyse for totale budgetkonsekvenser (bioerfarne patienter), mio. DKK, ikke-diskonterede tal.

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Amgros' vurdering
Ansøger har inkluderet patientomkostninger til transport. Dette er ikke i overensstemmelse med Amgros' metodevejledning.
Amgros ekskluderer dette i egen budgetkonsekvensanalyse

4.1.3 Følsomhed af budgetkonsekvenserne

Ansøger har udarbejdet følsomhedsanalyser, der belyser ændringen i antallet af patienter med +/- 10 % Resultatet viser henholdsvis stigende og faldende budgetkonsekvenser.

4.2 Amgros' estimater af budgetkonsekvenser

Amgros anvender ansøgers estimat for hovedanalysen men ekskluderer omkostninger til patienttransport. Amgros' estimat af budgetkonsekvenser for henholdsvis bionaive (P1) og bioerfarne (P2) ses i tabel 10 og 11.

Tabel 10: Amgros' hovedanalyse for totale budgetkonsekvenser P1, mio. DKK, ikke-diskonterede tal.

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Tabel 11: Amgros' hovedanalyse for totale budgetkonsekvenser P2, mio. DKK, ikke-diskonterede tal.

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Budgetkonsekvenserne for regionerne når tofacitinib (Xeljanz) sammenlignes med adalimumab til bionaive (P1) patienter for nævnte indikation resulterer i ca. [redacted] DKK til [redacted] DKK i år 5.

Budgetkonsekvenserne for regionerne når tofacitinib (Xeljanz) sammenlignes med secukinumab til bioerfarne (P2) patienter for nævnte indikation resulterer i ca. [redacted]. DKK til [redacted] DKK i år 5.

Laves analysen i AIP resulterer budgetkonsekvenserne i henholdsvis 4,9 mio. DKK i år 5 for P1, og ca. -29,1 mio. DKK i år 5 for P2.

5 DISKUSSION

Behandling med tofacitinib (Xeljanz) er forbundet med meromkostninger sammenlignet med behandling med adalimumab (P1) og besparelser sammenlignet med secukinumab (P2). De inkrementelle omkostninger for tofacitinib (Xeljanz) er drevet af lægemiddelomkostningerne.

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AMGROS

REGIONERNES
LÆGEMIDDELORGANISATION

AMGROS I/S
DAMPFÆRGEVEJ 27-29
2100 KØBENHAVN Ø

TLF: 8871 3000
WWW.AMGROS.DK

Kære Jeppe

Vi har nu læst Jeres høringssvar igennem.

Vi finder det meget gennemarbejdet og velargumenterende og vi har ingen kommentarer.

Med venlig hilsen/Kind regards
Trine Pilgaard

Den 21. aug. 2019 kl. 10.42 skrev Pilgaard, Trine <Trine.Pilgaard@pfizer.com>:

Kære Jeppe

Mange tak for jeres udkast.

Vi skal nok kigge høringssvaret igennem og sende eventuelle kommentarer allersenest d 4/9.

Bedste hilsner,
Trine

From: Jeppe Schultz Christensen <JCC@medicinraadet.dk>
Sent: 21. august 2019 09:30
To: Pilgaard, Trine <Trine.Pilgaard@pfizer.com>; Dahl, Palle <Palle.Dahl@pfizer.com>
Cc: Nicoline Kerzel Duel <NKD@medicinraadet.dk>
Subject: [EXTERNAL] Høring over udkast til vurdering af klinisk merværdi for tofacitinib til psoriasisartrit

Kære Trine og Palle

Sekretariatet fremsender hermed udkast til Medicinrådets vurdering af klinisk merværdi for tofacitinib til psoriasisartrit.
Medicinrådet drøfter vurderingen af klinisk merværdi den 28/8-19. I får besked fra sekretariat, hvis Rådet har ændringer til vurderingen.

I har i alt 14 dage til at sende eventuelle bemærkninger til kategoriseringen af den kliniske merværdi. **Jeres frist for at indgive høringssvar er derfor den 4/9-19.** I er selvfølgelig velkomne til at sende eventuelle bemærkninger inden denne dato. I må også gerne meddele, hvis I ikke har kommentarer til kategoriseringen.

Vurderer sekretariatet og fagudvalget, at jeres høringssvar giver anledning til at revurdere kategoriseringen af den kliniske merværdi, skal Rådet drøfte vurderingen igen. Det vil med overvejende sandsynlighed udskyde tidspunktet for Rådets drøftelse af anbefalingen.

Jeres eventuelle høringssvar indgår i det materiale, som bliver fremlagt for Medicinrådet i forbindelse med behandlingen af anbefalingen. Jeres eventuelle høringssvar bliver offentliggjort sammen med anbefalingen.

Mvh
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Medicinrådets behandling af personoplysninger

Når du har kontakt med Medicinrådet (f.eks. når du sender en e-mail til os), indsamler og behandler vi dine personoplysninger (f.eks. kontaktoplysninger i form af navn, e-mailadresse, titel/stilling mv.) I Medicinrådets persondatapolitik finder du mere information om Medicinrådets behandling af personoplysninger, dine rettigheder og oplysninger om, hvordan du kan kontakte os.

Medicinrådet

Medicinrådets vurdering af klinisk merværdi for tofacitinib til behandling af psoriasisartrit

Versionsnr.: 1.0

Medicinrådet

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 mulig 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.

Om vurderingen af klinisk merværdi

Vurderingen af klinisk merværdi er Medicinrådets vurdering af, hvor effektiv og sikkert lægemidlet er i forhold til andre lægemidler til den samme gruppe patienter.

Vurderingen af klinisk merværdi indgår, når Medicinrådet skal beslutte, om lægemidlet anbefales som mulig standardbehandling.

Lægemidlet vurderes efter Metodehåndbog for Medicinrådets arbejde med at udarbejde fælles regionale vurderinger af nye lægemidlers og nye indikationers kliniske merværdi – version 1. Se Medicinrådets metodehåndbog for yderligere information.

Dokumentoplysninger	
Godkendelsesdato	28. august 2019
Ikrafttrædelsesdato	28. august 2019
Dokumentnummer	48572
Versionsnummer	1.0

Medicinrådet, Dampfærgevej 27-29, 3. th., 2100 København Ø
www.medicinraadet.dk
Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 28. august 2019

Indhold

1 Lægemiddelinformationer

Lægemidlets oplysninger	
Handelsnavn	Xeljanz
Generisk navn	Tofacitinib
Firma	Pfizer
ATC-kode	L04AA29
Virkningsmekanisme	Janus kinase inhibitor
Administration/dosis	Tabletter 5 mg 2 gange dagligt
EMA-indikation	Tofacitinib i kombination med MTX er indiceret til behandling af aktiv psoriasisartrit (PsA) hos voksne patienter, som har haft utilstrækkeligt respons på, eller som ikke har tolereret behandling med et tidligere sygdomsmodificerende antireumatisk lægemiddel (DMARD).

2 Medicinrådets konklusion vedrørende klinisk merværdi

Medicinrådet vurderer, at tofacitinib til psoriasisartrit giver ingen klinisk merværdi til patienter uden samtidig moderat til svær plaque psoriasis dvs.:

- **Ingen klinisk merværdi** for bionaive patienter med psoriasisartrit uden samtidig moderat til svær plaque psoriasis sammenlignet med adalimumab (lav evidenskvalitet).
- **Ingen klinisk merværdi** for bioerfarne patienter med psoriasisartrit uden samtidig moderat til svær plaque psoriasis sammenlignet med secukinumab (lav evidenskvalitet).

Til patienter med samtidig moderat til svær plaque psoriasis kan tofacitinibs merværdi ikke dokumenteres:

- **Ikkedokumenterbar merværdi** for bionaive patienter med psoriasisartrit med samtidig moderat til svær plaque psoriasis (evidensens kvalitet kan ikke vurderes).
- **Ikkedokumenterbar merværdi** for bioerfarne patienter med psoriasisartrit med samtidig moderat til svær plaque psoriasis (evidensens kvalitet kan ikke vurderes).

Medicinrådet kategoriserer lægemidlers 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.

3 Forkortelser

ACR	*American College of Rheumatology*
BSA	Kropsoverflade berørt af psoriasis (*Psoriasis-affected body surface area)*
CI	*Confidence Interval* (konfidensinterval)
CRP	C-reaktivt protein
csDMARD	*Conventional Synthetic Disease Modifying Antirheumatic Drug*
DMARD	*Disease Modifying Antirheumatic Drug*
EMA	*European Medicines Agency*
EPAR	*European Public Assessment Report*
GRADE	System til vurdering af evidens (*Grading of Recommendations Assessment, Development and Education System)*
HAQ-DI	*Health Assessment Questionnaire Disability Index*
mTSS	*modified Total Sharp Score*
MTX	Methotrexat
PASI	*Psoriasis Area Severity Index*
PASI75:	Psoriasis Area Severity Index score på 75 procent
PsA	Psoriasisartrit
RR	Relativ risiko
s.c.	Subkutan injektion
TNF	*Tumor Necrosis Factor*
VAS	*Visual Analogue Scale*

4 Formål

Formålet med Medicinrådets vurdering af klinisk merværdi af tofacitinib til psoriasisartrit er at vurdere den kliniske merværdi i forhold til et eller flere lægemidler til samme patientgruppe (komparator(-er)).

Med udgangspunkt i den kliniske merværdi og en omkostningsanalyse udarbejdet af Amgros vurderer Medicinrådet, om tofacitinib anbefales som mulig standardbehandling.

5 Baggrund

Psoriasisartrit

Psoriasisartrit (PsA) er en kronisk inflammatorisk ledsygdom, der ofte (men ikke nødvendigvis) optræder sammen med den kroniske hudsygdom psoriasis [1]. Patogenesen er en T-celle medieret inflammation af leddenes synovialmembraner, som også kan være rettet mod rygsøjlen og senernes vedhæftning til knoglerne. Sygdommen betragtes som multifaktoriel og er betinget af både genetiske og miljømæssige faktorer [2].

PsA kan således både manifestere sig ved inflammation i perifere led og i rygsøjlen, og der kan desuden optræde ekstra-artikulære symptomer som inflammation i senetilhæftninger (entesit), hævede fingre eller tæer (daktylit) og negledystrofi [3]. Patienterne kan også have betændelse i øjets regnbue- og årehinde (uveitis) eller kronisk inflammatorisk tarmsygdom. Det kan være vanskeligt at skelne diagnostisk mellem PsA og spondylartrit af anden art.

I den nationale behandlingsvejledning for PsA fra Dansk Reumatologisk Selskab beskrives, at der mangler validerede kliniske diagnosekriterier for PsA, men at der er udviklet klassifikationskriterier, som kan benyttes som støtte. Diagnosen stilles på baggrund af objektiv undersøgelse af bevægeapparat og hud, sammen med serologi og biokemi [3].

Prævalensen er svær at estimere grundet manglen på klare diagnostiske kriterier, men den estimeres at være på 0,1 %. Det skønnes, at op til ca. 15 % af patienter med psoriasis udvikler PsA [3]. Sygdommen debuterer oftest i alderen 40-50 år, og prævalensen er ens for mænd og kvinder.

Nuværende behandling

Den nuværende behandling af patienter med psoriasisartrit er dels smertelindrende, dels sygdomsmodificerende. Sygdomsmodificerende behandling (*disease modifying antirheumatic drugs* (DMARDs)) gives ved betydelig affektion af led. Til patienter med lav sygdomsaktivitet og lav risiko for progressiv ledsygdom (under 5 led) anvendes monoterapi med lægemidler af typen konventionelle DMARDs (csDMARDs), hvor methotrexat (MTX) sædvanligvis er førstevalg i dansk klinisk praksis [3].

Ved patienter med betydelig ledaffektion (mere end fire led) eller ved utilstrækkelig effekt af csDMARDs, eventuelt i kombination med lokale steroidinjektioner [1], kan biologisk behandling indledes. Kriterierne for at indlede biologisk behandling omfatter sygdomsaktivitet, fravær af kontraindikationer, og at beslutningen træffes på konference med speciallæger i reumatologi [3].

Af biologisk behandling benyttes på nuværende tidspunkt TNF-alfa hæmmerne infliximab, adalimumab, etanercept, certolizumab og golimumab. Desuden benyttes ustekinumab, som er et monoklonalt antistof mod interleukin 12 og interleukin 23, samt secukinumab og ixekizumab, der er monoklonale antistoffer mod interleukin 17.

Den nuværende lægemiddelrekommandation for biologisk behandling af PsA er delt op i behandling til flere forskellige patientgrupper, afhængig af om patienten har samtidig moderat til svær psoriasis, uveitis eller inflammatorisk tarmsygdom. Flere af ovenstående lægemidler er godkendt til både PsA og en eller flere af de nævnte indikationer, hvilket har betydning for, hvilke lægemidler der anvendes til de relevante patientgrupper. F.eks. anvendes adalimumab, infliximab, golimumab og ustekinumab til patienter med PsA og samtidig inflammatorisk tarmsygdom (Crohn's sygdom eller colitis ulcerosa), da disse lægemidler har begge indikationer.

Anvendelse af det nye lægemiddel

Tofacitinib virker ved at binde sig til og hæmme Janus kinase-familiens enzymer. Den anbefalede dosis er 5 mg 2 gange dagligt. Psoriasisartrit er en kronisk sygdom, og behandles typisk indtil patienten ikke længere har effekt af behandlingen. Tofacitinib gives som tablet.

Tofacitinib har desuden EMA-indikationerne kronisk leddegigt og colitis ulcerosa.

6 Metode

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

Ansøgers ansøgning opfylder ikke den præspecificerede protokol, der blev godkendt i Medicinrådet den 29. maj 2018. Ansøgningen afviger på følgende områder:

- Ansøger adresserer klinisk spørgsmål 1 og 3 som ét klinisk spørgsmål, da data ikke muliggør en opdeling af patienterne. Størstedelen af patienterne i studierne har ikke moderat til svær plaque psoriasis.
- Tilsvarende adresserer ansøger klinisk spørgsmål 2 og 4 som ét klinisk spørgsmål, da data ikke muliggør en opdeling af patienterne. Størstedelen af patienterne i studierne har ikke moderat til svær plaque psoriasis.

Jf. protokollen har fagudvalget opstillet følgende kliniske spørgsmål:

1. *Hvilken klinisk merværdi tilbyder tofacitinib til bionaive patienter med PsA uden samtidig moderat til svær plaque psoriasis, sammenlignet med adalimumab?*
2. *Hvilken klinisk merværdi tilbyder tofacitinib til bioerfarne patienter med PsA uden samtidig moderat til svær plaque psoriasis, sammenlignet med secukinumab?*
3. *Hvilken klinisk merværdi tilbyder tofacitinib til bionaive patienter med PsA og samtidig moderat til svær plaque psoriasis, sammenlignet med adalimumab?*
4. *Hvilken klinisk merværdi tilbyder tofacitinib til bioerfarne patienter med PsA og samtidig moderat til svær plaque psoriasis, sammenlignet med secukinumab?*

Fagudvalget vurderer på baggrund af ovenstående, at ansøgningen kan anvendes til at besvare klinisk spørgsmål 1 og 2 (patienter uden samtidig moderat til svær plaque psoriasis), men ikke spørgsmål 3 og 4 (patienter med samtidig moderat til svær plaque psoriasis).

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.

7 Litteratursøgning

Ansøger har den 25. april 2019 gennemført en systematisk litteratursøgning som efterspurgt i protokollen for tofacitinib. Søgningen resulterede i inklusionen af ét studie vedr. bionaive patienter og fire studier vedr. bioerfarne patienter. De fem studier er beskrevet i tabel 1.

Tabel 1. Publikationer inkluderet i analyserne af den kliniske merværdi af tofacitinib

Publikationer	Klinisk forsøg	NCT-nummer	Population
Tofacitinib or Adalimumab versus placebo for Psoriatic Arthritis. **Mease et al. 2017. NEJM.** [4]	OPAL BROADEN	NCT01877668	Bionaive
Tofacitinib or adalimumab versus placebo: patient-reported outcomes from OPAL Broaden-a phase III study of active psoriatic arthritis in patients with an inadequate response to conventional synthetic disease-modifying antirheumatic drugs. **Strand et al. 2019. RMD Open** [5]**.**	OPAL BROADEN	NCT01877668	Bionaive
Tofacitinib for Psoriatic Arthritis in Patients with an Inadequate Response to TNF Inhibitors. **Gladman et al. 2017. NEJM.** [6]	OPAL BEYOND	NCT01882439	Bioerfarne
Effect of tofacitinib on patient-reported outcomes in patients with active psoriatic arthritis and an inadequate response to tumour necrosis factor inhibitors in the phase III, randomised controlled trial: OPAL Beyond. **Strand et al. 2019. RMD Open** [7]**.**	OPAL BEYOND	NCT01882439	Bioerfarne
Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomized, double-blind, placebo-controlled, phase 3 trial. **McInnes et al. 2015. Lancet** [8]**.**	FUTURE 2	NCT01752634	Bioerfarne
Efficacy of subcutaneous Secukinumab in patients with active psoriatic arthritis stratified by prior TNF inhibitor use: results from the randomized placebo-controlled FUTURE 2 study. **Kavanaugh et al. 2016, J Rheum** [9]**.**	FUTURE 2	NCT01752634	Bioerfarne
Efficacy and safety of secukinumab administration by autoinjector in patients with psoriatic arthritis: results from a randomized, placebo-controlled trial (FUTURE 3). **Nash et al. 2018. Arthritis Research & Therapy** [10]	FUTURE 3	NCT01989468	Bioerfarne
Secukinumab improves active psoriatic arthritis symptoms and inhibits radiographic progression: primary results from the randomized, double-blind, phase III FUTURE 5 study. **Mease et al. 2018. BMJ** [11]**.**	FUTURE 5	NCT02404350	Bioerfarne

Ansøger har udover ovenstående indsendt data fra tofacitinibs, adalimumabs og secukinumabs European Public Assessment Report (EPAR) [12–14].

8 Databehandling

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. Medicinrådet har suppleret med følgende yderligere beregninger:

- For effektmålene *behandlingsophør grundet uønskede hændelser*, *behandlingsophør grundet manglende effekt* og *alvorlige infektioner* i klinisk spørgsmål 1 har Medicinrådet udregnet de absolutte og relative effektforskelle.
- Til at besvare klinisk spørgsmål 1 har Medicinrådet udregnet absolutte og relative forskelle efter 12 måneders opfølgning for effektmålene: ACR50, behandlingsophør grundet uønskede hændelser, behandlingsophør grundet manglende effekt, PASI75 og alvorlige infektioner.

Fagudvalget vurderer, at det indleverede datagrundlag er tilstrækkeligt til at vurdere den kliniske merværdi af tofacitinib. Fagudvalget har følgende bemærkninger til datagrundlaget:

- Ansøger anvender data fra OPAL BROADEN til at besvare klinisk spørgsmål 1 og 3 samlet, hvilket dermed vedrører patienter både med og uden samtidig moderat til svær plaque psoriasis. Studiet inkluderer begge patientpopulationer, men andelen af patienter med moderat til svær plaque psoriasis er lav (henholdsvis 12,8 % for patienter der får tofacitinib og 12,7 % for patienter der får adalimumab). Fagudvalget vurderer derfor, at studierne kan anvendes til besvarelsen af klinisk spørgsmål 1 men ikke af klinisk spørgsmål 3, da langt størstedelen af patienterne ikke har samtidig moderat til svær plaque psoriasis.
- Ansøger anvender data fra OPAL BEYOND til at besvare klinisk spørgsmål 2 og 4 samlet, hvilket dermed vedrører patienter både med og uden samtidig moderat til svær plaque psoriasis. Studiet inkluderer begge patientpopulationer, men andelen af patienter med moderat til svær plaque psoriasis er lav (henholdsvis 23,6 % for patienter der får tofacitinib og 23,6 % for patienter der får placebo). Fagudvalget vurderer derfor, at studierne kan anvendes til besvarelsen af klinisk spørgsmål 2 men ikke af klinisk spørgsmål 4, da størstedelen af patienterne ikke har samtidig moderat til svær plaque psoriasis.
- Da der ikke findes direkte sammenlignende studier af tofacitinib og secukinumab, har ansøger lavet en indirekte sammenligning ved brug af Buchers metode, med placebo som fælles komparator, til besvarelse af klinisk spørgsmål 2 og 4 samlet.
- Ansøger har ikke leveret data på den samlede SF-36-score som ønsket, men kun på den fysiske komponent af scoren. Fagudvalget har derfor ikke vurderet dette effektmål, men udelukkende vurderet livskvalitet på baggrund af HAQ-DI.

9 Klinisk merværdi

9.1 Konklusion klinisk spørgsmål 1

Hvilken klinisk merværdi tilbyder tofacitinib til bionaive patienter med PsA uden samtidig moderat til svær plaque psoriasis, sammenlignet med adalimumab?

Fagudvalget vurderer, at tofacitinib til bionaive patienter med psoriasisartrit uden samtidig moderat til svær plaque psoriasis giver **ingen klinisk merværdi** sammenlignet med adalimumab (lav evidenskvalitet).

9.1.1 Gennemgang af studier

Ansøger identificerede ét studie af tofacitinib sammenlignet med adalimumab. Studiernes karakteristika og populationer er beskrevet nedenfor.

Karakteristika
OPAL BROADEN: OPAL BROADEN er et randomiseret, kontrolleret, dobbeltblindet studie publiceret i to artikler fra henholdsvis 2017 og 2019. Studiet har fem behandlingsarme, og patienterne blev randomiseret i ratioen 2:2:2:1:1. To af armene udgør grundlaget for vurderingsrapporten: en behandlingsarm (n = 107), hvor patienterne fik tofacitinib 5 mg to gange dagligt og en studiearm (n = 106), hvor patienterne fik adalimumab 40 mg hver 2. uge. Studiet var designet til at påvise en effekt af tofacitinib sammenlignet med placebo, mens adalimumab blev anvendt som en aktiv kontrol. Effekt- og sikkerhedsanalyser er baseret på alle randomiserede patienter, der modtog mindst én studiedosis. Data blev analyseret på baggrund af opfølgning efter hhv. 3 og 12 måneders behandling. Efter tre måneder blev patienter, der modtog placebo, re-randomiseret til tofacitinib 5 mg eller 10 mg. Studiets primære effektmål er ACR20 og studiets sekundære

effektmål af relevans er ACR50, behandlingsophør grundet uønskede hændelser, behandlingsophør grundet manglende effekt, HAQ-DI, mTSS, PASI75, SF-36 og alvorlige infektioner.

Population

Tabel 2. Baselinekarakteristika for populationerne OPAL BROADEN

	Tofacitinib 5 mg to gange dagligt (N=107)	Adalimumab 40 mg hver 2. uge (N=106)
Alder i år *gennemsnit ± SD*	49,4 ± 12,6	47,4 ± 11,3
Kvinder *n (procent)*	57 (53)	50 (47)
År siden PsA diagnose *gennemsnit ± SD*	7,3 ± 8,2	5,3 ± 5,3
Kropsoverflade berørt af psoriasis (BSA) ≥ 3 % *n (procent*)	82 (77)	78 (74)
Hævede led (af 66 led) *gennemsnit ± SD*	12,9 ± 9,9	9,8 ± 7,9

Fagudvalget finder, at der ikke er betydende forskelle i baselinekarakteristika mellem studiearmene. Fagudvalget vurderer, at patientkarakteristika i studiet ikke afviger væsentligt fra den danske patientpopulation, men bemærker at patienterne i studiet har flere hævede led ved studiestart end danske patienter.

9.1.2 Resultater og vurdering

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

Hvilken klinisk merværdi tilbyder tofacitinib til bionaive patienter med PsA uden samtidig moderat til svær plaque psoriasis, sammenlignet med adalimumab?

American College of Rheumatology response 50 % (ACR50) (kritisk)
Jf. protokollen er det primære mål for effekt ACR50. Dette er defineret som en 50 % forbedring i både ømme og hævede led, samt 50 % forbedring inden for mindst tre ud af følgende fem kategorier: patientens overordnede vurdering (Visual Assessment Scale (VAS) global), patientens vurdering af smerte, lægens overordnede vurdering (VAS doctor), HAQ-DI score og C-Reaktivt Protein (CRP). Fagudvalget vurderer, at en 50 % forbedring er et patientrelevant effektmål, og betragtes her som tilstrækkeligt for at definere respons.

Ansøger har rapporteret resultater vedrørende effekten af lægemidlerne efter 3 måneders behandling. Medicinrådets sekretariat har suppleret med analyser på data efter 12 måneders behandling.

Tabel 3. Vurdering af klinisk merværdi: ACR50

	Forhåndsdefineret grundlag for vurdering		Resultater, 3 måneder	Resultater, 12 måneder
Absolutte forskelle	15 procentpoint		-5,0 procentpoint [-17,3;7,4]	-4,0 procentpoint [-18,0; 9,0]
Relative forskelle	Stor merværdi	Nedre konf.gr. > 1,33		
	Vigtig merværdi	Nedre konf.gr. > 1,11		
	Lille merværdi	Nedre konf.gr. > 1,00		
	Ingen merværdi	Nedre konf.gr. < 1,00	0,85 [0,57;1,28]	0,93 [0,74; 1,17]
	Negativ merværdi	Øvre konf.gr. < 1,00		
Evidensens kvalitet	Lav			

Første kolonne indeholder de i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen. Anden og tredje kolonne indeholder data på de absolutte og relative værdier fra resultatafsnittet, som indgår i Medicinrådets vurdering.

Efter 3 måneders behandling med adalimumab (n = 106) havde 35 (33,0 %) patienter opnået ACR50, mens 30 (28,0 %) patienter havde respons på tofacitinib (n=107). Efter 12 måneders behandling med adalimumab (n = 106) havde 43 (40,6 %) patienter opnået ACR50, mens 48 (45,0 %) patienter havde respons på tofacitinib (n=107). Hverken de absolutte eller relative forskelle mellem de to arme er statistisk signifikante og indikerer dermed ingen merværdi.

Baseret på dette vurderer fagudvalget, at tofacitinib har **ingen klinisk merværdi** vedr. ACR50 sammenlignet med adalimumab (lav evidenskvalitet).

Behandlingsophør grundet uønskede hændelser (vigtig)

Det er fagudvalgets vurdering, at uønskede hændelser, der fører til ophør af behandlingen, er et brugbart surrogatmål for den samlede tyngde af bivirkninger.

Ansøger har rapporteret resultater vedrørende effekten af lægemidlerne efter 3 måneders behandling. Medicinrådets sekretariat har suppleret med analyser på data efter 12 måneders behandling.

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

	Forhåndsdefineret grundlag for vurdering		Resultater, 3 måneder	Resultater, 12 måneder
Absolutte forskelle	5 procentpoint		0,9 procentpoint [-3,00; 5,00]	2 procentpoint [-4,00; 8,00]
Relative forskelle	Stor merværdi	Øvre konf.gr. < 0,75		
	Vigtig merværdi	Øvre konf.gr. < 0,90		
	Lille merværdi	Øvre konf.gr. < 1,00		
	Ingen merværdi	Øvre konf.gr. > 1,00	1,49 [0,25;8,71]	1,49 [0,43; 5,12]
	Negativ merværdi	Nedre konf.gr. > 1,00		
Evidensens kvalitet	Lav			

Første kolonne indeholder de i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen. Anden og tredje kolonne indeholder data på de absolutte og relative værdier fra resultatafsnittet, som indgår i Medicinrådets vurdering.

Efter 3 måneders behandling med adalimumab (n = 106) ophørte 2 (1,9 %) patienter behandlingen grundet uønskede hændelser, mens dette var tilfældet for 3 (2,8 %) patienter på tofacitinib (n=107). Efter 12 måneders behandling med adalimumab (n = 106) ophørte 4 (3,8 %) patienter behandlingen grundet uønskede

hændelser, mens dette var tilfældet for 6 (5,6 %) patienter på tofacitinib (n=107). Hverken de absolutte eller relative forskelle mellem de to arme er statistisk signifikante og indikerer dermed ingen merværdi.

Baseret på dette vurderer fagudvalget, at tofacitinib har **ingen klinisk merværdi** vedr. behandlingsophør grundet uønskede hændelser sammenlignet med adalimumab (lav evidenskvalitet).

Behandlingsophør grundet manglende effekt (vigtig)

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

Ansøger har rapporteret resultater vedrørende effekten af lægemidlerne efter 3 måneders behandling. Medicinrådets sekretariat har suppleret med analyser på data efter 12 måneders behandling.

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

	Forhåndsdefineret grundlag for vurdering		Resultater, 3 måneder	Resultater, 12 måneder
Absolutte forskelle	10 procentpoint		0 procentpoint [-1,82;1,82]	-2 procentpoint [-5,00; 1,00]
Relative forskelle	Stor merværdi	Øvre konf.gr. < 0,75		
	Vigtig merværdi	Øvre konf.gr. < 0,90		
	Lille merværdi	Øvre konf.gr. < 1,00		
	Ingen merværdi	Øvre konf.gr. > 1,00		0,20 [0,01; 4,08]
	Negativ merværdi	Nedre konf.gr. > 1,00		
Evidensens kvalitet	Lav			

Første kolonne indeholder de i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen. Anden og tredje kolonne indeholder data på de absolutte og relative værdier fra resultatafsnittet, som indgår i Medicinrådets vurdering.

Efter 3 måneders behandling med adalimumab (n = 106) ophørte 0 (0 %) patienter behandlingen grundet manglende effekt, hvilket ligeledes var tilfældet for 0 (0 %) patienter på tofacitinib (n=107). Efter 12 måneders behandling med adalimumab (n = 106) ophørte 2 (1,9 %) patienter behandlingen grundet manglende effekt, mens dette var tilfældet for 0 (0 %) patienter på tofacitinib (n=107). Hverken de absolutte eller relative forskelle mellem de to arme er statistisk signifikante og indikerer dermed ingen merværdi.

Baseret på dette vurderer fagudvalget, at tofacitinib har **ingen klinisk merværdi** vedr. behandlingsophør grundet manglende effekt sammenlignet med adalimumab (lav evidenskvalitet).

SF-36

Studierne indeholder kun information om den fysiske komponent (SF36-PCS) af dette effektmål. Fagudvalget vurderer derfor, at tofacitinib har **ikkedokumenterbar merværdi** sammenlignet med adalimumab vedr. SF-36. Evidensens kvalitet kan ikke vurderes. Fagudvalget vurderer derfor livskvalitet på baggrund af HAQ-DI.

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

Dette er inkluderet som et mål for patienternes invaliditet/funktionstab. Det er et domænespecifikt instrument, der er pålideligt, velundersøgt og valideret [15]. HAQ-DI er valgt grundet stor relevans for patienter med PsA, og fordi det anvendes i dansk klinisk praksis og bl.a. registreres ved ambulante besøg.

Ansøger har indsendt data for andelen af patienter, der opnår en HAQ-DI ændring ≥ 0,35 point hos de patienter, der havde en baseline score ≥ 0,35 point. Fagudvalget havde ønsket andelen af patienter der opnår en ændring på 0,22, men vurderer at en ændring på ≥ 0,35 point også er relevant.

De anvendte data i tabel 6 vedrører effekten af lægemidlerne efter 3 måneders behandling. Det har ikke været muligt at finde data vedr. 12 måneders behandling.

Tabel 6. Vurdering af klinisk merværdi: HAQ-DI

	Forhåndsdefineret grundlag for vurdering		Resultater, 3 måneder
Absolutte forskelle	15 procentpoint		0 procentpoint [-14,1;14,1]
Relative forskelle	Stor merværdi	Nedre konf.gr. > 1,33	
	Vigtig merværdi	Nedre konf.gr. > 1,11	
	Lille merværdi	Nedre konf.gr. > 1,00	
	Ingen merværdi	Nedre konf.gr. < 1,00	1,00 [0,77;1,30]
	Negativ merværdi	Øvre konf.gr. < 1,00	
Evidensens kvalitet	Lav		

Første kolonne indeholder de i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen. Anden og tredje kolonne indeholder data på de absolutte og relative værdier fra resultatafsnittet, som indgår i Medicinrådets vurdering.

For adalimumab-gruppen (n = 96) opnåede 51 (53,1 %) patienter en HAQ-DI ændring ≥ 0,35 point, hvilket ligeledes var tilfældet for 51 (53,1 %) patienter i tofacitinib-gruppen (n = 96). Hverken de absolutte eller relative forskelle mellem de to arme er statistisk signifikante og indikerer dermed ingen merværdi.

Baseret på dette vurderer fagudvalget, at tofacitinib har **ingen klinisk merværdi** vedr. HAQ-DI (lav evidenskvalitet).

Modified Total Sharp Score (mTTS) (vigtig)

Fagudvalget ønsker at benytte et radiografisk effektmål, der kan tolkes som udtryk for leddestruktion og dermed sygdomsprogression. Fagudvalget ønsker at benytte en modificeret udgave af Total Sharp Score (mTSS) som er udviklet til scoring af patienter med PsA [16].

De anvendte data i tabel 7 vedrører effekten af lægemidlerne efter 12 måneders behandling hos patienter, hvor røntgendata var tilgængeligt. Progression er defineret som en ændring på 0,5 på mTSS, og andelen af patienter uden progression er dermed patienter med en stigning på mindre end 0,5 point på scoren.

Tabel 7. Vurdering af klinisk merværdi: mTSS

	Forhåndsdefineret grundlag for vurdering		Resultater, 12 måneder
Absolutte forskelle	10 procentpoint		2,0 procentpoint [-2,9;6,8]
Relative forskelle	Stor merværdi	Nedre konf.gr. > 1,33	
	Vigtig merværdi	Nedre konf.gr. > 1,11	
	Lille merværdi	Nedre konf.gr. > 1,00	
	Ingen merværdi	Nedre konf.gr. < 1,00	0,98 [0,93;1,03]
	Negativ merværdi	Øvre konf.gr. < 1,00	
Evidensens kvalitet	Lav		

Første kolonne indeholder de i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen. Anden kolonne indeholder data på de absolutte og relative værdier fra resultatafsnittet, som indgår i Medicinrådets vurdering.

For adalimumab-gruppen (n = 95) oplevede 93 (97,9 %) patienter en mTSS ændring mindre end 0,5, hvilket var tilfældet for 94 (95,9 %) patienter i tofacitinib-gruppen (n = 98). Hverken de absolutte eller relative forskelle mellem de to arme er statistisk signifikante og indikerer dermed ingen merværdi.

Baseret på dette vurderer fagudvalget, at tofacitinib har **ingen klinisk merværdi** vedr. HAQ-DI sammenlignet med adalimumab (lav evidenskvalitet).

Psoriatic Area and Severity Index 75 % (PASI75) (vigtig)

Fagudvalget ønsker at benytte et effektmål for hudaffektion på de populationer, hvor dette er relevant (klinisk spørgsmål 3 og 4). Her har fagudvalget valgt Psoriasis Area and Severity Index (PASI), som kombinerer størrelsen på det areal af huden, som er ramt, med alvorligheden heraf på en score fra 0 til 72, hvor 72 udtrykker maksimal sygdom. PASI75 afspejler det antal patienter, som opnår en 75 % reduktion i PASI score.

De anvendte data i tabel 8 vedrører effekten af lægemidlerne efter 3 måneders behandling hos de patienter, der har en kropsoverflade berørt af psoriasis (BSA) ≥ 3 %.

Tabel 8. Vurdering af klinisk merværdi: PASI75

	Forhåndsdefineret grundlag for vurdering		Resultater, 3 måneder	Resultater, 12 måneder
Absolutte forskelle	15 procentpoint		3,7 procentpoint [-11,6;19,0]	0,00 procentpoint [-15,0;16,0]
Relative forskelle	Stor merværdi	Nedre konf.gr. > 1,33		
	Vigtig merværdi	Nedre konf.gr. > 1,11		
	Lille merværdi	Nedre konf.gr. > 1,00		
	Ingen merværdi	Nedre konf.gr. < 1,00	1,1 [0,75;1,59]	1,00 [0,76;1,32]
	Negativ merværdi	Øvre konf.gr. < 1,00		
Evidensens kvalitet	Lav			

Første kolonne indeholder de i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen. Anden og tredje kolonne indeholder data på de absolutte og relative værdier fra resultatafsnittet, som indgår i Medicinrådets vurdering.

Efter 3 måneders behandling med adalimumab (n = 77) opnåede 30 (39,0 %) patienter en 75 % reduktion i PASI score, hvilket var tilfældet for 35 (42,7 %) patienter på tofacitinib (n = 82). Efter 12 måneders behandling med adalimumab (n = 77) opnåede 43 (55,8 %) patienter en 75 % reduktion i PASI score, hvilket var tilfældet for 46 (56,1 %) patienter på tofacitinib (n = 82). Hverken de absolutte eller relative forskelle mellem de to arme er statistisk signifikante og indikerer dermed ingen merværdi.

Baseret på dette vurderer fagudvalget, at tofacitinib har **ingen klinisk merværdi** vedr. PASI75 sammenlignet med adalimumab (lav evidenskvalitet).

Alvorlige infektioner (vigtig)

Fagudvalget finder, det er vigtigt for patienterne at undgå infektioner, hvorfor alvorlige infektioner indgår som et selvstændigt effektmål.

De anvendte data i tabel 9 vedrører effekten af lægemidlerne efter henholdsvis 3 og 12 måneders behandling. Analysen ved 12 måneder er baseret på poolede data for patienter på placebo, som er skiftet til tofacitinib ved 3 måneder, og patienter der har fået tofacitinib i alle 12 måneder.

Tabel 9. Vurdering af klinisk merværdi: Alvorlige infektioner

	Forhåndsdefineret grundlag for vurdering		Resultater, 3 måneder	Resultater, 12 måneder
Absolutte forskelle	5 procentpoint		0 procentpoint [-1,82;1,82]	0,31 procentpoint [-2,21;2,84]
Relative forskelle	Stor merværdi	Øvre konf.gr. < 0,75		
	Vigtig merværdi	Øvre konf.gr. < 0,90		
	Lille merværdi	Øvre konf.gr. < 1,00		
	Ingen merværdi	Øvre konf.gr. > 1,00		1,33 [0,12;14,52]
	Negativ merværdi	Nedre konf.gr. > 1,00		
Evidensens kvalitet	Lav			

Første kolonne indeholder de i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen. Anden og tredje kolonne indeholder data på de absolutte og relative værdier fra resultatafsnittet, som indgår i Medicinrådets vurdering.

Efter 3 måneders behandling med adalimumab (n = 106) oplevede 0 (0,0 %) patienter alvorlige infektioner, hvilket var tilfældet for 0 (0,0 %) patienter i tofacitinib-gruppen (n = 107).

Efter 12 måneders behandling med adalimumab (n = 106) oplevede 1 (0,9 %) patient alvorlige infektioner, hvilket var tilfældet for 2 (1,3 %) patienter i tofacitinib-gruppen (n = 159). Hverken de absolutte eller relative forskelle mellem de to arme er statistisk signifikante og indikerer dermed ingen merværdi.

Samlet set vurderer fagudvalget, at tofacitinib har **ingen klinisk merværdi** vedr. alvorlige infektioner sammenlignet med adalimumab (lav evidenskvalitet).

9.1.3 Evidensens kvalitet

Evidensens kvalitet for klinisk spørgsmål 1 (bionaive patienter med psoriasisartrit uden samtidig moderat til svær plaque psoriasis) er samlet set vurderet som værende **lav**. Overvejelser vedrørende evidensens kvalitet kan ses i bilag 1.

For alle effektmål blev der nedgraderet for ”Inconsistency”, da der kun ligger ét studie til grund for vurderingen, og for ”Imprecision”, da konfidensintervallet krydser den kliniske beslutningsgrænse for at anbefale eller ikke anbefale behandlingen.

9.1.4 Konklusion for klinisk spørgsmål 1

Fagudvalget vurderer, at tofacitinib giver en **ingen klinisk merværdi** for bionaive patienter med psoriasisartrit uden samtidig moderat til svær plaque psoriasis sammenlignet med adalimumab (lav evidenskvalitet).

Den samlede kategorisering af det kliniske spørgsmål er baseret på gennemgangen af de enkelte effektmål, som kan ses i afsnit 9.2.1, og som er opsummeret i nedenstående tabel.

Tabel 10. Samlet vurdering af klinisk værdi: Klinisk spørgsmål 1

Effektmål	Vigtighed	Merværdi	Evidenskvalitet
ACR50	Kritisk	Ingen	Lav
Behandlingsophør grundet uønskede hændelser	Vigtig	Ingen	Lav
Behandlingsophør grundet manglende effekt	Vigtig	Ingen	Lav
HAQ-DI	Vigtig	Ingen	Lav
mTSS	Vigtig	Ingen	Lav
PASI75	Vigtig	Ingen	Lav
SF-36	Vigtig	Ikkedokumenterbar	Kan ikke vurderes
Alvorlige infektioner	Vigtig	Ingen	Lav
Samlet		**Ingen**	**Lav**

Fagudvalget lægger i den samlede vurdering særligt vægt på, at det kritiske effektmål ACR50 giver ingen merværdi. Derudover lægger fagudvalget vægt på, at også alle de vigtige effektmål viser ingen merværdi.

9.2 Konklusion klinisk spørgsmål 2

Hvilken klinisk merværdi tilbyder tofacitinib til bioerfarne patienter med PsA uden samtidig moderat til svær plaque psoriasis, sammenlignet med secukinumab?

Fagudvalget vurderer, at tofacitinib til bioerfarne patienter med psoriasisartrit uden samtidig moderat til svær plaque psoriasis giver **ingen klinisk merværdi** sammenlignet med secukinumab (lav evidenskvalitet).

9.2.1 Gennemgang af studier

Ansøger identificerede ét studie af tofacitinib sammenlignet med placebo og tre studier af secukinumab sammenlignet med placebo.

Ansøger har anvendt data fra tre studier vedrørende secukinumab [17–20].Til effektmål, hvor data fra mere end et af disse studier indgår, er data først syntetiseret ved hjælp af metaanalyser (Mantel-Haenszel metoden), hvorefter de indgik i en indirekte sammenligning med tofacitinib (Bucher's metode). Resultater vedrørende behandling med secukinumab i en bioerfaren population er baseret på data fra subpopulationer i de inkluderede studier.

Studiernes karakteristika og populationer er beskrevet nedenfor.

Karakteristika
OPAL BEYOND: OPAL BEYOND er et randomiseret, kontrolleret, dobbeltblindet studie publiceret i to

artikler fra henholdsvis 2017 og 2019. Studiet har 4 behandlingsarme, og patienterne blev randomiseret 2.2:1:1. To af armene benyttes i vurderingen af klinisk spørgsmål 2: en behandlingsarm (n = 132), hvor patienterne fik tofacitinib 5 mg to gange dagligt og en placeboarm (n = 131), hvor patienterne efter 3 måneder blev skiftet til behandling med tofacitinib 5 mg eller 10 mg. Effekt- og sikkerhedsanalyser er baseret på alle randomiserede patienter, der modtog mindst én studiedosis. Studiets primære effektmål er ACR20 og HAQ-DI. Studiets sekundære effektmål af relevans er ACR50, behandlingsophør grundet uønskede hændelser, behandlingsophør grundet manglende effekt, PASI75, SF-36 og alvorlige infektioner.

FUTURE2: FUTURE 2 er et randomiseret, kontrolleret, dobbeltblindet studie [17,18]. I studiet indgår fire behandlingsarme, hvoraf to arme benyttes i vurderingen af klinisk spørgsmål 2: en behandlingsarm (n = 100), hvor patienterne fik secukinumab s.c. 300 mg uge 0,1,2,3,4 og herefter månedligt, og en kontrolarm (n = 98), hvor patienter fik placebo. Studiets blindede fase var 24 uger. Placebobehandlede patienter blev rerandomiseret til secukinumab ved uge 16 eller 24. Studiet inkluderede både bionaive og bioerfarne patienter, og randomiseringen var stratificeret i forhold til tidligere brug af TNF-hæmmere.

Følgende sekundære effektmål og safety-mål fra studiet, hvor der er publiceret subgruppeanalyser for bioerfarne patienter (n = 33 i behandlingsarmen og n = 35 i kontrolarmen), er relevante effektmål for vurderingen af klinisk spørgsmål 2:

- Andelen af patienter med ACR50-respons
- Andelen af patienter med PASI75-respons.

FUTURE3: FUTURE 3 er et randomiseret, kontrolleret, dobbeltblindet studie [19]. I studiet indgår tre behandlingsarme, hvoraf to arme benyttes i vurderingen af klinisk spørgsmål 2: en behandlingsarm (n = 139), hvor patienterne fik secukinumab s.c. 300 mg uge 0,1,2,3,4 og herefter månedligt, og en kontrolarm (n = 137), hvor patienterne fik placebo. Placebobehandlede patienter blev rerandomiseret til secukinumab 300 mg eller 150 mg ved uge 16 (ikke-respondenter) eller uge 24 (respondenter). Studiet inkluderede både bionaive og bioerfarne patienter, og randomiseringen var stratificeret i forhold til tidligere brug af TNF-hæmmere.

Følgende sekundære effektmål, hvor der er publiceret subgruppeanalyser for bioerfarne patienter (n = 44 i behandlingsarmen og n = 44 i kontrolarmen), er et relevant effektmål for vurderingen af klinisk spørgsmål 2:

- Andelen af patienter med ACR50-respons ved uge 24.

FUTURE5: FUTURE5 er et randomiseret, kontrolleret, dobbeltblindet studie [20]. I studiet indgår fire behandlingsarme, hvoraf to arme benyttes i vurderingen af klinisk spørgsmål 2: en behandlingsarm (n = 222), hvor patienterne fik secukinumab s.c. 300 mg uge 0,1,2,3,4 og herefter månedligt, og en kontrolarm (n = 332), hvor patienterne fik placebo. Placebobehandlede patienter blev rerandomiseret til secukinumab 300 mg eller 150 mg ved uge 16 (ikke-respondenter) eller uge 24 (respondenter). Studiet inkluderede både bionaive og bioerfarne patienter, og randomiseringen var stratificeret i forhold til tidligere brug af TNF-hæmmere.

Følgende sekundære effektmål, hvor der er publiceret subgruppeanalyser for bioerfarne patienter (n = 68 i behandlingsarmen og n = 98 i kontrolarmen), er et relevant effektmål for vurderingen af klinisk spørgsmål 2:

- Andelen af patienter med ACR50-respons ved uge 16.

Population
Tabel 11 indeholder udvalgte baselinekarakteristika for de to relevante arme i OPAL BEYOND med tofacitinib 5 mg to gange dagligt og placebo.

Tabel 11. Baselinekarakteristika for populationerne i OPAL BEYOND

	Tofacitinib (N=131)	Placebo (N=131)
Alder i år *gennemsnit ± SD*	49,5 ± 12,3	49,0 ± 12,6
Kvinder *n (procent)*	64 (49)	80 (61)
År siden PsA diagnose *gennemsnit ± SD*	9,6 ± 7,6	9,4 ± 8,1
Kropsoverflade berørt af psoriasis (BSA) ≥ 3 % *n (procent*)	80 (61)	86 (66)
Hævede led (af 66 led) *gennemsnit ± SD*	12,1 ± 10,6	10,5 ± 9,0

Tabel 12 indeholder baselinekarakteristika for de to relevante arme i henholdsvis FUTURE 2, FUTURE 3 og FUTURE 5 med secukinumab s.c. 300 mg uge 0,1,2,3,4 og herefter månedligt og placebo. Baselinekarakteristika er for den samlede population, dvs. både bionaive og -erfarne patienter. Studierne definerer bioerfarne patienter, som dem der tidligere har fejlet på en eller flere TNF-hæmmere. For alle tre studier er der taget højde for tidligere brug af TNF-hæmmere i randomiseringen, hvilket betyder, at fordelingen af patienter på betydende variable bør være den samme i den samlede population som i subpopulationerne af bionaive patienter.

Tabel 12. Baselinekarakteristika for populationerne i FUTURE 2, FUTURE 3 og FUTURE 5

	FUTURE 2		FUTURE 3		FUTURE 5	
	Secukinumab (n=100)	Placebo (n=98)	Secukinumab (n=139)	Placebo (n=137)	Secukinumab (n=222)	Placebo (n=332)
Alder i år *gennemsnit ± SD*	46,9 ± 12,6	49,9 ± 12,5	49,3 ± 12,9	50,1 ± 12,6	48,9 ± 12,8	49,0 ± 12,1
Kvinder *n (procent)*	51 (51)	39 (40)	67 (48,2)	59 (43,1)	108 (48,6)	161 (48,5)
År siden PsA diagnose *gennemsnit ± SD*	-	-	8,3 ± 9,2	6,6 ± 6,9	6,7 ± 8,3	6,6 ± 7,6
Kropsoverflade berørt af psoriasis (BSA) ≥ 3 % *n (procent*)	41 (41)	43 (44)	62 (44,6)	59 (43,1)	110 (49,5)	162 (48,8)
Hævede led (af 76 led) *gennemsnit ± SD*	11,2 ± 7,8	12,1 ± 10,7	8,9 ± 6,4	10,3 ± 8,6	10,0 ± 8,0	11,7 ± 10,8
DAS28-CRP *gennemsnit ± SD*	4,8 ± 1,0	4,7 ± 1,0	4,5 ± 1,0	4,7 ± 1,1	4,5 ± 1,0	4,6 ± 1,1

Fagudvalget finder, at der for de fire studier (tabel 11 og 12) ikke er betydende forskelle i baseline-karakteristika mellem studiearmene. Fagudvalget vurderer, at patienterne i studierne har flere hævede led og længere sygdomsvarighed end danske patienter, men at patientkarakteristika i studierne derudover ikke afviger væsentligt fra den danske patientpopulation.

9.2.2 Resultater og vurdering

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

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

Jf. protokollen er det primære mål for effekt ACR50. Dette er defineret som en 50 % forbedring i både ømme og hævede led, samt 50 % forbedring inden for mindst tre ud af følgende fem kategorier: patientens overordnede vurdering (Visual Assessment Scale (VAS) global), patientens vurdering af smerte, lægens overordnede vurdering (VAS doctor), HAQ-DI score og C-Reaktivt Protein (CRP). Fagudvalget vurderer, at en 50 % forbedring er et patientrelevant effektmål, og betragtes her som tilstrækkeligt for at definere respons.

De anvendte data i tabel 13 vedrører effekten af lægemidlerne efter 3 måneders behandling med tofacitinib og 16-24 uger med secukinumab.

Tabel 13. Vurdering af klinisk merværdi: ACR50

	Forhåndsdefineret grundlag for vurdering		Resultater
Absolutte forskelle	15 procentpoint		-16,9 procentpoint [-23,9;-1,5]
Relative forskelle	Stor merværdi	Nedre konf.gr. > 1,33	
	Vigtig merværdi	Nedre konf.gr. > 1,11	
	Lille merværdi	Nedre konf.gr. > 1,00	
	Ingen merværdi	Nedre konf.gr. < 1,00	
	Negativ merværdi	Øvre konf.gr. < 1,00	0,43 [0,19;0,95]
Evidensens kvalitet	Lav		

Første kolonne indeholder de i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen. Anden kolonne indeholder data på de absolutte og relative værdier fra resultatafsnittet, som indgår i Medicinrådets vurdering.

For secukinumab-gruppen (n = 145) havde 42 (29,0 %) patienter respons målt ved ACR50, mens 39 (29,8 %) patienter havde respons i tofacitinib-gruppen (n = 131). Både den absolutte og relative forskel mellem de to arme er statistisk signifikant i secukinumabs favør. Desuden overstiger den absolutte forskel den prædefinerede mindste klinisk relevante forskel.

Fagudvalget bemærker at samme andel patienter, der får henholdsvis tofacitinib og secukinumab, opnår ACR50. Der er dog samtidig stor forskel på, hvor mange patienter i placeboarmene der opnår effektmålet (15 % i OPAL BEYOND-studiet og 7,3 % i FUTURE-studierne). Dette kan medføre, at sammenligningerne er behæftet med særlig usikkerhed. Den høje placeboeffekt i OPAL BEYOND påvirker den indirekte sammenligning i retning af en negativ merværdi for tofacitinib, på trods af at den samme andel patienter opnår ACR50 på henholdsvis tofacitinib og secukinumab.

Baseret på den store forskel i placeboeffekt mellem studierne vurderer fagudvalget, at studierne ikke kan sammenlignes, hvad angår dette effektmål. Dermed har tofacitinib **ikkedokumenterbar merværdi** sammenlignet med secukinumab vurderet på effektmålet ACR50.

Behandlingsophør grundet uønskede hændelser (vigtig)

Studierne vedr. secukinumab indeholder ikke information om dette effektmål. Fagudvalget vurderer derfor, at tofacitinib har **ikkedokumenterbar merværdi** sammenlignet med secukinumab vedr. behandlingsophør grundet uønskede hændelser. Evidensens kvalitet kan ikke vurderes.

Behandlingsophør grundet manglende effekt (vigtig)

Studierne vedr. secukinumab indeholder ikke information om dette effektmål. Fagudvalget vurderer derfor, at tofacitinib har **ikkedokumenterbar merværdi** sammenlignet med secukinumab vedr. behandlingsophør grundet manglende effekt. Evidensens kvalitet kan ikke vurderes.

SF-36

Studierne indeholder ikke information om dette effektmål. Fagudvalget vurderer derfor, at tofacitinib har **ikkedokumenterbar merværdi** sammenlignet med secukinumab vedr. SF-36. Evidensens kvalitet kan ikke vurderes.

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

Studierne vedr. secukinumab indeholder ikke information om dette effektmål. Fagudvalget vurderer derfor, at tofacitinib har **ikkedokumenterbar merværdi** sammenlignet med secukinumab vedr. HAQ-DI. Evidensens kvalitet kan ikke vurderes.

Modified Total Sharp Score (mTTS) (vigtig)

Studierne vedr. secukinumab indeholder ikke information om dette effektmål. Fagudvalget vurderer derfor, at tofacitinib har **ikkedokumenterbar merværdi** sammenlignet med secukinumab vedr. mTSS. Evidensens kvalitet kan ikke vurderes.

Psoriatic Area and Severity Index 75 % (PASI75) (vigtig)

Fagudvalget ønsker at benytte et effektmål for hudaffektion på de populationer, hvor dette er relevant (klinisk spørgsmål 3 og 4). Her har fagudvalget valgt Psoriasis Area and Severity Index (PASI), som kombinerer størrelsen på det areal af huden, som er ramt, med alvorligheden heraf på en score fra 0 til 72, hvor 72 udtrykker maksimal sygdom. PASI75 afspejler det antal patienter, som opnår en 75 % reduktion i PASI score.

De anvendte data i tabel 14 vedrører effekten af lægemidlerne efter 3 måneders behandling med tofacitinib og 24 uger med secukinumab hos de patienter, der har en kropsoverflade berørt af psoriasis (BSA) ≥ 3 %.

Tabel 14. Vurdering af klinisk merværdi: PASI75

	Forhåndsdefineret grundlag for vurdering		Resultater
Absolutte forskelle	15 procentpoint		-51,8 procentpoint [-62,1; 28,2]
Relative forskelle	Stor merværdi	Nedre konf.gr. > 1,33	
	Vigtig merværdi	Nedre konf.gr. > 1,11	
	Lille merværdi	Nedre konf.gr. > 1,00	
	Ingen merværdi	Nedre konf.gr. < 1,00	0,19 [0,02; 1,44]
	Negativ merværdi	Øvre konf.gr. < 1,00	
Evidensens kvalitet	Meget lav		

Første kolonne indeholder de i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen. Anden kolonne indeholder data på de absolutte og relative værdier fra resultatafsnittet, som indgår i Medicinrådets vurdering.

PASI75 er kun rapporteret i ét af de tre secukinumab-studier (FUTURE2). For secukinumab-gruppen (n = 11) opnåede 7 (63,6 %) patienter en 75 % reduktion i PASI score, hvilket var tilfældet for 17 (21,3 %) patienter i tofacitinib-gruppen (n = 80). Hverken den absolutte eller relative forskel mellem de to arme er signifikant.

Baseret på dette vurderer fagudvalget, at tofacitinib har **ingen klinisk merværdi** vedr. PASI75 (meget lav evidenskvalitet).

Alvorlige infektioner (vigtig)

Studierne vedr. secukinumab indeholder ikke information om dette effektmål. Fagudvalget vurderer derfor, at tofacitinib har **ikkedokumenterbar merværdi** sammenlignet med secukinumab vedr. alvorlige infektioner. Evidensens kvalitet kan ikke vurderes.

9.2.3 Evidensens kvalitet

Evidensens kvalitet for klinisk spørgsmål 2 (bioerfarne patienter med psoriasisartrit uden samtidig moderat til svær plaque psoriasis) er samlet set vurderet som værende lav, da evidensens kvalitet for det lavest vurderede kritiske effektmål er lav. Overvejelser vedrørende evidensens kvalitet kan ses i bilag 1.

Indledningsvist blev lægemidlernes direkte sammenligninger med placebo vurderet.

- Overordnet var studiet af tofacitinib sammenlignet med placebo af moderat kvalitet. For både effektmålet ACR50 og PASI75 blev der nedgraderet for ”Inconsistency”, da der kun ligger ét studie til grund for vurderingen. For effektmålet PASI75 blev der derudover nedgraderet for ”Imprecision”, da konfidensintervallet krydser den kliniske beslutningsgrænse for at anbefale eller ikke anbefale behandlingen.
- Overordnet var studierne af secukinumab sammenlignet med placebo af høj kvalitet, da der for effektmålet ACR50 ikke blev nedgraderet for noget. For effektmålet PASI75 blev der nedgraderet for ”Inconsistency”, da der kun ligger ét studie til grund for vurderingen.

Da merværdien af tofacitinib sammenlignet med secukinumab er vurderet via indirekte sammenligninger med placebo som fælles komparator, er der for alle effektmål efterfølgende nedjusteret for ”Indirectness”. Herved er den samlede evidenskvalitet for klinisk spørgsmål 2 lav, baseret på det lavest vurderede kritiske effektmål (ACR50 ved tofacitinib sammenlignet med placebo). Se bilag 1 for uddybning heraf.

9.2.4 Konklusion for klinisk spørgsmål 2

Fagudvalget vurderer, at tofacitinib giver en **ingen klinisk merværdi** for bioerfarne patienter med psoriasisartrit uden samtidig moderat til svær plaque psoriasis (lav evidenskvalitet).

Den samlede kategorisering af det kliniske spørgsmål er baseret på gennemgangen af de enkelte effektmål, som kan ses i afsnit 9.2.2, og som er opsummeret i nedenstående tabel.

Tabel 15. Samlet vurdering af klinisk værdi: Klinisk spørgsmål 2

Effektmål	**Vigtighed**	**Merværdi**	**Evidenskvalitet**
ACR50	Kritisk	Ikkedokumenterbar	Lav
Behandlingsophør grundet uønskede hændelser	Vigtig	Ikkedokumenterbar	Kan ikke vurderes
Behandlingsophør grundet manglende effekt	Vigtig	Ikkedokumenterbar	Kan ikke vurderes
HAQ-DI	Vigtig	Ikkedokumenterbar	Kan ikke vurderes
mTSS	Vigtig	Ikkedokumenterbar	Kan ikke vurderes
PASI75	Vigtig	Ingen	Meget lav
SF-36	Vigtig	Ikkedokumenterbar	Kan ikke vurderes
Alvorlige infektioner	Vigtig	Ikkedokumenterbar	Kan ikke vurderes
Samlet		**Ingen**	**Lav**

Fagudvalget har kun modtaget anvendelige data på det vigtige effektmål PASI75, som er vurderet at have ingen klinisk merværdi. Ansøger har udført et studie med de relevante effektmål for tofacitinib (OPAL BEYOND), men det har ikke været muligt at finde resultater for secukinumab for alle effektmål. For de øvrige effektmål vurderer fagudvalget på baggrund af klinisk erfaring, at resultaterne fra klinisk spørgsmål 1 kan overføres til denne population af bioerfarne patienter.

9.3 Konklusion klinisk spørgsmål 3

Hvilken klinisk merværdi tilbyder tofacitinib til bionaive patienter med PsA og samtidig moderat til svær plaque psoriasis, sammenlignet med adalimumab?

Da det ikke har været muligt for ansøger at indsende en komparativ analyse for klinisk spørgsmål 3, kan fagudvalget ikke umiddelbart vurdere en eventuel merværdi baseret på effektestimater. Fagudvalget vurderer på den baggrund, at resultaterne fra klinisk spørgsmål 1 ikke kan overføres til denne population, og konkluderer derfor, at tofacitinib har **ikkedokumenterbar merværdi** sammenlignet med adalimumab til bionaive patienter med aktiv PsA og samtidig moderat til svær plaque psoriasis (evidensens kvalitet kan ikke vurderes).

9.4 Konklusion klinisk spørgsmål 4

Hvilken klinisk merværdi tilbyder tofacitinib til bioerfarne patienter med PsA og samtidig moderat til svær plaque psoriasis, sammenlignet med secukinumab?

Heller ikke for klinisk spørgsmål 4 har det været muligt for ansøger at indsende en komparativ analyse. Dermed kan fagudvalget ikke umiddelbart vurdere en eventuel merværdi baseret på effektestimater. Fagudvalget vurderer på den baggrund, at resultaterne fra klinisk spørgsmål 2 ikke kan overføres til denne population, og konkluderer derfor, at tofacitinib har **ikkedokumenterbar merværdi** sammenlignet med secukinumab til bioerfarne patienter med aktiv PsA og samtidig moderat til svær plaque psoriasis (evidensens kvalitet kan ikke vurderes).

10 Andre overvejelser

Fagudvalget er opmærksom på de af Det Europæiske Lægemiddelagentur (EMA) nyligt offentliggjorte bivirkningsdata vedrørende tofacitinib (https://www.ema.europa.eu/en/news/increased-risk-blood-clots-

lungs-death-higher-dose-xeljanz-tofacitinib-rheumatoid-arthritis). Patienter, der fik tofacitinib i en daglig dosis på 20 mg (2x10 mg dagligt) i et fase 4 sikkerhedsstudie (NCT02092467), havde øget risiko for at få blodpropper i lungerne og dø. Patienterne i studiet har kronisk leddegigt, er over 50 år og har i forvejen mindst en risikofaktor for hjertekarsygdom. EMA anbefaler, at alle patienter, der får tofacitinib, uanset indikationen, monitoreres for symptomer på blodpropper i lungerne.

Fagudvalget vurderer, at forskellene mellem populationen i sikkerhedsstudiet og populationen med psoriasisartrit, der potentielt vil få tofacitinib i Danmark, er væsentlige, da gennemsnitsalderen i studiet er højere end for en gennemsnitlig patient, og at patienterne i klinisk praksis ikke alle har risikofaktorer for hjertekarsygdom. Derudover er dosis, der gives til psoriasisartritpatienter, halvt så stor som den dosis, der var forbundet med øget risiko for blodprop i lungerne og død. Fagudvalget vurderer dermed, at de nye bivirkningsdata ikke påvirker kategoriseringen.

11 Fagudvalgets vurdering af samlet klinisk merværdi og samlet evidensniveau

Fagudvalget vurderer, at tofacitinib til psoriasisartrit giver **ingen klinisk merværdi** til patienter uden samtidig moderat til svær plaque psoriasis dvs.:

- **Ingen klinisk merværdi** for bionaive patienter med psoriasisartrit uden samtidig moderat til svær plaque psoriasis (lav evidenskvalitet).
- **Ingen klinisk merværdi** for bioerfarne patienter med psoriasisartrit uden samtidig moderat til svær plaque psoriasis (lav evidenskvalitet).

Til patienter med samtidig moderat til svær plaque psoriasis kan tofacitinibs merværdi ikke dokumenteres:

- **Ikkedokumenterbar merværdi** for bionaive patienter med psoriasisartrit med samtidig moderat til svær plaque psoriasis (evidensens kvalitet kan ikke vurderes).
- **Ikkedokumenterbar merværdi** for bioerfarne patienter med psoriasisartrit med samtidig moderat til svær plaque psoriasis (evidensens kvalitet kan ikke vurderes).

12 Rådets vurdering af samlet klinisk merværdi og samlet evidensniveau

Medicinrådet vurderer, at tofacitinib til psoriasisartrit giver ingen klinisk merværdi til patienter uden samtidig moderat til svær plaque psoriasis dvs.:

- **Ingen klinisk merværdi** for bionaive patienter med psoriasisartrit uden samtidig moderat til svær plaque psoriasis sammenlignet med adalimumab (lav evidenskvalitet).
- **Ingen klinisk merværdi** for bioerfarne patienter med psoriasisartrit uden samtidig moderat til svær plaque psoriasis sammenlignet med secukinumab (lav evidenskvalitet).

Til patienter med samtidig moderat til svær plaque psoriasis kan tofacitinibs merværdi ikke dokumenteres:

- **Ikkedokumenterbar merværdi** for bionaive patienter med psoriasisartrit med samtidig moderat til svær plaque psoriasis (evidensens kvalitet kan ikke vurderes).
- **Ikkedokumenterbar merværdi** for bioerfarne patienter med psoriasisartrit med samtidig moderat til svær plaque psoriasis (evidensens kvalitet kan ikke vurderes).

13 Relation til eksisterende behandlingsvejledning

Den eksisterende RADS behandlingsvejledning er opdelt på seks populationer og er dermed mere detaljeret end lægemidlernes EMA indikation for PsA (f.eks. indeholder behandlingsvejledningen populationen PsA med samtidig uveitis). Der er ikke evidens for lægemidlernes virkning til de populationer, der går ud over EMA indikationen, og lægemidlerne har delvist været anbefalet på baggrund af deres øvrige indikationer. Imidlertid finder Medicinrådets fagudvalg, at det på baggrund af den tilgængelige evidens ikke er muligt at relatere tofacitinib til den eksisterende behandlingsvejledning for de populationer, der går ud over EMA indikationen.

Der er evidens for tofacitinib til populationen af PsA patienter uden moderat til svær plaque psoriasis, og på den baggrund vurderer fagudvalget, at tofacitinib kan ligestilles med de eksisterende 1. linjebehandlinger.

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15 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende gigtsygdomme

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16 Versionslog

Version	Dato	Ændring
1.0	28. august 2019	Godkendt af Medicinrådet.

17 Bilag 1: GRADE-evidensprofiler

17.1 Cochrane Risk of Bias

Risiko for bias er vurderet for alle studier til besvarelse af det kliniske spørgsmål. Studiernes risiko for bias er vurderet ved brug af tjeklisten Cochrane Risk of Bias tool (Cochrane handbook version 5.1 del 2.8, se http://handbook-5-1.cochrane.org/).

Risiko for bias for studie: OPAL BROADEN

Risk of bias domæne	**Vurdering**	**Begrundelse**
Selection bias		
Random sequence generation	*Low risk*	*"A centralized automated randomization system was used to assign patients, in a 2:2:1:1 ratio"*
Allocation concealment	*Low risk*	*"The investigators , patients, and sponsor were unaware of the trial-group assignments for the duration of the trial."*
Performance bias: blinding of participants and personnel. Assessment made for class of outcomes.		
Performance bias	*Low risk*	*"Tofacitinib or placebo was administered orally at 12-hour intervals; matching placebo tablets were used to maintain the blinding."*
Detection bias: blinding of outcome assessment. Assessment made for class of outcomes.		
Detection bias	*Low risk*	*"Patients and investigators were masked to treatment assignment".* *"The investigators , patients, and sponsor were unaware of the trial-group assignments for the duration of the trial."* *"A contract research organization (ICON) collected the trial data; the data on outcomes and adverse events were analyzed by personnel from Pfizer and were interpreted by all the authors."*
Attrition bias: incomplete outcome data. Assessment made for class of outcomes.		
Attrition bias	*Unclear risk*	*"Patients who withdrew from the trial were considered to have no response at any visit after discontinuation. Continuous end points were analyzed with the use of a mixed model for repeated measures with trial group, visit, interaction of the trial group by visit, geographic location, and baseline value as fixed effects, without imputation for missing values"*
Reporting bias: selective reporting outcome data.		
Reporting bias	*Low risk*	Protokol er tilgængelig, og alle studiets præspecificerede effektmål af interesse er blevet rapporteret som beskrevet i protokollen.
Other bias	*Low risk*	
Overall bias	*Low risk*	Overall risk of bias judged low.

Risiko for bias for studie: OPAL BEYOND

Risk of bias domæne	**Vurdering**	**Begrundelse**
Selection bias		
Random sequence generation	*Low risk*	*"Eligible patients were randomly assigned in a 2:2:2:1:1 ratio, by means of an automated Web-based randomization system."*
Allocation concealment	*Unclear risk*	*"Eligible patients were randomly assigned in a 2:2:2:1:1 ratio, by means of an automated Web-based randomization system."*
Performance bias: blinding of participants and personnel. Assessment made for class of outcomes.		
Performance bias	*Unclear risk*	*"Potential opportunistic infections, cancers, gastrointestinal perforations, cardiovascular events, and hepatic events were adjudicated by independent expert committees whose members were unaware of the trial-group assignments."*
Detection bias: blinding of outcome assessment. Assessment made for class of outcomes.		
Detection bias	*Unclear risk*	*"Potential opportunistic infections, cancers, gastrointestinal perforations, cardiovascular events, and hepatic events were adjudicated by independent expert committees whose members were unaware of the trial-group assignments."*
Attrition bias: incomplete outcome data. Assessment made for class of outcomes.		
Attrition bias	*Low risk*	*"Of 546 patients screened, 395 underwent ran- domization, of whom 394 received at least one dose of tofacitinib or placebo"* *"Binary end points were compared with the use of the normal approximation for the difference in binomial proportions, with an imputation of no response for missing values (patients who withdrew from the trial were considered to have no response at any visit after discontinuation)."*
Reporting bias: selective reporting outcome data.		
Reporting bias	*Low risk*	Protokol er tilgængelig, og alle studiets præspecificerede effektmål af interesse er blevet rapporteret som beskrevet i protokollen.
Other bias	*Low risk*	
Overall bias	*Low risk*	Overall risk of bias judged low.

Risiko for bias for studie: FUTURE 2

Risk of bias domæne	**Vurdering**	**Begrundelse**
Selection bias		
Random sequence generation	*Low risk*	*"Randomisation was done with an interactive voice or web response system that assigned patients to randomisation numbers identifying assigned treatments and unique medication numbers for the packages of study treatment to be given".*
Allocation concealment	*Low risk*	*"Randomisation was done with an interactive voice or web response system that assigned patients to randomisation numbers identifying assigned treatments and unique medication numbers for the packages of study treatment to be given".*
Performance bias: blinding of participants and personnel. Assessment made for class of outcomes.		
Performance bias	*Low risk*	*"Patients and investigators were masked to treatment assignment. Doses were provided in identical prefilled syringes supplied by Novartis".*
Detection bias: blinding of outcome assessment. Assessment made for class of outcomes.		
Detection bias	*Low risk*	*"Patients and investigators were masked to treatment assignment".*
Attrition bias: incomplete outcome data. Assessment made for class of outcomes.		
Attrition bias	*Low risk*	*"For week 24 analyses of binary variables, patients who switched from placebo to secukinumab at week 16 because of non-response were imputed as nonresponders at week 24 (early escape penalty). Week 16 non-responders in the secukinumab groups were also imputed as non-responders at week 24. Patients with missing data or who had discontinued treatment early were imputed as non-responders".*
Reporting bias: selective reporting outcome data.		
Reporting bias	*Low risk*	Protokol er tilgængelig, og alle studiets præspecificerede effektmål af interesse er blevet rapporteret som beskrevet i protokollen.
Other bias	*Low risk*	
Overall bias	*Low risk*	Overall risk of bias judged low.

Risiko for bias for studie: FUTURE 3

Risk of bias domæne	**Vurdering**	**Begrundelse**
Selection bias		
Random sequence generation	*Low risk*	*"Eligible patients were randomized (1:1:1) by means of an interactive response technology".*
Allocation concealment	*Low risk*	*"Eligible patients were randomized (1:1:1) by means of an interactive response technology".*
Performance bias: blinding of participants and personnel. Assessment made for class of outcomes.		
Performance bias	*Low risk*	Tilsyneladende er det et dobbelt-blindet studie, men blindingen af deltagere og nøglepersoner beskrives ikke, og der er således utilstrækkelig information til at foretage en vurdering af risiko for bias.
Detection bias: blinding of outcome assessment. Assessment made for class of outcomes.		
Detection bias	*Low risk*	Tilsyneladende er det et dobbelt-blindet studie, men blindingen af deltagere og nøglepersoner beskrives ikke, og der er således utilstrækkelig information til at foretage en vurdering af risiko for bias.
Attrition bias: incomplete outcome data. Assessment made for class of outcomes.		
Attrition bias	*Low risk*	*"Missing values, including those due to discontinuation of study treatment, were imputed as failures to achieve the given response (nonresponses). Also, patients who did not achieve response based on joint count at week 16 were imputed as nonresponders at week 20 and week 24 (rescue penalty)".*
Reporting bias: selective reporting outcome data.		
Reporting bias	*Low risk*	Protokol er tilgængelig, og alle studiets præspecificerede effektmål af interesse er blevet rapporteret som beskrevet i protokollen.
Other bias	*Low risk*	
Overall bias	*Low risk*	Overall risk of bias judged low.

Risiko for bias for studie: FUTURE 5

Risk of bias domæne	**Vurdering**	**Begrundelse**
Selection bias		
Random sequence generation	*Low risk*	*"Interactive Response Technology was used to randomly assign eligible patients".*
Allocation concealment	*Low risk*	*"Interactive Response Technology was used to randomly assign eligible patients".*
Performance bias: blinding of participants and personnel. Assessment made for class of outcomes.		
Performance bias	*Low risk*	*"Patients, investigators and assessors remain masked to the treatment assignment until all patients reach week 52".*
Detection bias: blinding of outcome assessment. Assessment made for class of outcomes.		
Detection bias	*Low risk*	*"Patients, investigators and assessors remain masked to the treatment assignment until all patients reach week 52".*
Attrition bias: incomplete outcome data. Assessment made for class of outcomes.		
Attrition bias	*Low risk*	*"Missing values and placebo patients rescued at week 16 were imputed as non-responders for binary endpoints (rescue penalty), linear extrapolation was applied for radiographic data (if baseline and week 16 values were available) and the missing at random assumption of the MMRM analysis was applied for continuous endpoints".*
Reporting bias: selective reporting outcome data.		
Reporting bias	*Low risk*	Protokol er tilgængelig, og alle studiets præspecificerede effektmål af interesse er blevet rapporteret som beskrevet i protokollen.
Other bias	*Low risk*	
Overall bias	*Low risk*	Overall risk of bias judged low.

17.2 GRADE-evaluering af evidenskvaliteten til vurdering af den kliniske merværdi af tofacitinib

Klinisk spørgsmål 1 – Hvilken klinisk merværdi tilbyder tofacitinib til bionaive patienter med PsA uden samtidig moderat til svær plaque psoriasis, sammenlignet med adalimumab?

17.2.1 GRADE evidensprofil, tofacitinib vs. adalimumab

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**tofacitinib**	**adalimumab**	**Relative (95% CI)**	**Absolute (95% CI)**		
ACR 50 (follow up: 12 months)												
1	randomised trials	not serious	serious [a]	not serious	serious [b]	none	48/107 (44.9%)	43/106 (40.6%)	**RR 0.93** (0.74 to 1.17)	**28 fewer per 1.000** (from 105 fewer to 69 more)	⊕⊕◯◯ LOW	CRITICAL
Behandlingsophør grundet uønskede hændelser (follow up: 12 months)												
1	randomised trials	not serious	serious [a]	not serious	serious [b]	none	6/107 (5.6%)	4/106 (3.8%)	**RR 1.49** (0.43 to 5.12)	**18 more per 1.000** (from 22 fewer to 155 more)	⊕⊕◯◯ LOW	IMPORTANT
Behandlingsophør grundet manglende effekt (follow up: 12 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**tofacitinib**	**adalimumab**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	not serious	serious [a]	not serious	serious [b]	none	0/107 (0.0%)	2/106 (1.9%)	**RR 0.20** (0.01 to 4.08)	**15 fewer per 1.000** (from 19 fewer to 58 more)	⊕⊕◯◯ LOW	IMPORTANT
HAQ-DI (follow up: 3 months)												
1	randomised trials	not serious	serious [a]	not serious	serious [b]	none	51/96 (53.1%)	51/96 (53.1%)	**RR 1.00** (0.77 to 1.30)	**0 fewer per 1.000** (from 122 fewer to 159 more)	⊕⊕◯◯ LOW	IMPORTANT
mTSS (follow up: 12 months)												
1	randomised trials	not serious	serious [a]	not serious	serious [b]	none	94/98 (95.9%)	93/95 (97.9%)	**RR 0.98** (0.93 to 1.03)	**20 fewer per 1.000** (from 69 fewer to 29 more)	⊕⊕◯◯ LOW	IMPORTANT
PASI75 (follow up: 12 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**tofacitinib**	**adalimumab**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	not serious	serious [a]	not serious	serious [b]	none	46/82 (56.1%)	43/77 (55.8%)	**RR 1.00** (0.76 to 1.32)	**0 fewer per 1.000** (from 134 fewer to 179 more)	⊕⊕◯◯ LOW	IMPORTANT
Alvorlige infektioner (follow up: 12 months)												
1	randomised trials	not serious	serious [a]	not serious	serious [b]	none	2/159 (1.3%)	1/106 (0.9%)	**RR 1.33** (0.12 to 14.52)	**3 more per 1.000** (from 8 fewer to 128 more)	⊕⊕◯◯ LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

Forklaringer
a. Der foreligger kun ét studie

b. Konfidensintervallet krydser den kliniske beslutningsgrænse for at anbefale behandlingen

Klinisk spørgsmål 2 – Hvilken klinisk merværdi tilbyder tofacitinib til bioerfarne patienter med PsA uden samtidig moderat til svær plaque psoriasis, sammenlignet med secukinumab?

17.2.2 GRADE evidensprofil, tofacitinib vs. placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**tofacitinib**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
ACR50 (follow up: 3 months)												
1	randomised trials	not serious	serious [a]	not serious	not serious	none	39/131 (29.8%)	19/131 (14.5%)	**RR 0.43** (0.19 to 0.95)	**83 fewer per 1.000** (from 117 fewer to 7 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
PASI75 (follow up: 3 months)												
1	randomised trials	not serious	serious [a]	not serious	serious [b]	none	17/80 (21.3%)	12/86 (14.0%)	**RR 1.52** (0.78 to 2.99)	**73 more per 1.000** (from 31 fewer to 278 more)	⊕⊕◯◯ LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

Explanations
a. Der foreligger kun ét studie

b. Konfidensintervallet krydser den kliniske beslutningsgrænse for at anbefale behandlingen

17.2.3 GRADE evidensprofil, secukinumab vs. placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**secukinumab**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
ACR50 (follow up: 16-24 weeks)												
3	randomised trials	not serious	not serious	not serious	not serious	none	42/145 (29.0%)	4/63 (6.3%)	**RR 4.78** (2.56 to 8.93)	**240 more per 1.000** (from 99 more to 503 more)	⊕⊕⊕⊕ HIGH	CRITICAL
PASI75 (follow up: 3 months)												
1	randomised trials	not serious	serious [a]	not serious	not serious	none	7/11 (63.6%)	6/31 (19.4%)	**RR 4.25** (1.56 to 5.07)	**629 more per 1.000** (from 108 more to 787 more)	⊕⊕⊕◯ MODERATE	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio

Explanations
a. Der foreligger kun ét studie

Application for the assessment of clinically added value of Xeljanz® for Psoriatic Arthritis

Contents

Version 1.0 submitted 21 November 2018
Version 2.0 submitted 11 April 2019

The included analyses are conducted by Pfizer based on the request from the Medicines Council stipulated in the Protocol for Assessment of The Clinical Value of Tofacitinib for Psoriatic Arthritis. The analysis is a result of Pfizer's discretionary review hence Pfizer assumes no responsibility or liability for any errors or omissions in the content of this analysis.

General information

This is a template of the application form to be submitted to the Danish Medicines Council (*Medicinrådet*) for the assessment of the clinically added value of new medicines and new indications. The purpose of the form is to provide an overview of the basic information, literature search, study, and analysis results that will serve as the basis for the assessment. It indicates the minimum required information needed for the assessment.

The assessment of the pharmaceutical will be based on the outcomes defined in the protocol. Results for all critical and important outcomes (*kritiske og vigtige effektmål*) must be addressed in the application. The results of less important outcomes (*mindre vigtige effektmål*) do not need to be addressed. For all the data provided, a reference is mandatory.

During the completion of this form, elements should not be removed from the document. All sections should be filled in (if a section is not applicable, state "not applicable" and explain why). Table examples are provided in the form. Layout may deviate from the template to accommodate data; however, all requested information must be stated. We accept submission of appendices. Audits of data analyses and literature searches will occur.

In order to minimize any translation errors between the application and the assessment report, submission in the Danish language is preferred.

If confidential data are submitted, highlight the data in yellow and write the expected publication date in a comment. If confidential data are submitted in an appendix, the document must in addition be watermarked as "confidential."

The application will be published simultaneously with the final assessment and recommendation report on the Danish Medicines Council's web page (www.medicinraadet.dk). Any data that will be considered in the assessment report will be published with the final application.

Checklist before submitting the application form:

- Are all relevant fields in the application form filled in?
- Is the application explicit and self-explanatory?
- Does the application meet the general requirements defined in the *Process and Methods Guide* of the Danish Medicines Council for new medicines and new indications?
- Does the application meet the specific requirements in the protocol?
- Are deviation(s) from the protocol (if any) described?
- Are deviation(s) from the protocol (if any) justified?

Basic information

Table 1 Contact information

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Table 2 Overview of the pharmaceutical

Proprietary name	Xeljanz
Generic name	Tofacitinib
Marketing authorization holder in Denmark	Pfizer ApS
ATC code	L04AA29 (selective) immunosuppressive
Pharmacotherapeutic group	Immunosuppressive
Active substance(s)	Tofacitinib
Pharmaceutical form(s)	Film coated tablets
Mechanism of action	Janus Kinase Inhibitor
Dosage regimen	The recommended dosage is 5 mg twice daily
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	XELJANZ in combination with MTX is indicated for the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy
Other approved therapeutic indications	XELJANZ in combination with methotrexate (MTX) is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying antirheumatic drugs. XELJANZ can be given as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate. XELJANZ is indicated for the treatment of adults with moderate to severe active ulcerative colitis (UC) who have had an inadequate response, lost response or were intolerant to either conventional therapy or a biologic agent.

Will dispensing be restricted to hospitals?	No. Dispensing is hospitals and predefined specialists (NBS dispensing group)
Combination therapy and/or co-medication	Xeljanz is given in combination with Methotrexate (MTX)
Packaging – types, sizes/number of units, and concentrations	Packages with 56 5mg film-coated tablets
Orphan drug designation	No

Abbreviations

ACR	American College of Rheumatology criteria
ACR20/50/70	American College of Rheumatology criteria 20%/50%/70% improvement
AE	Adverse Event
BID	Bi-daily
Bio	Biological
BSA	Body Surface Area
CRP	C Reactive Protein
csDMARD	conventional synthetic Disease Modifying Anti-Rheumatic Drug
DAS28	28-joint Disease Activity Score
DMARD	Disease Modifying Anti-Rheumatic Drug
DSS	Dactylitis Severity Score
EOW	Every Other Week
EQ-5D	European Quality of life-5 Dimensions
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
HAQ-DI	Health Assessment Questionnaire – Disability Index
IV	Intravenous
JAK	Janus kinase
LEI	Leeds Enthesitis Score
LOCF	Last Observation Carried Forward
LSM	Least Square Mean
mTSS	modified Total Sharp Score

OR	Odds Ratio
PASI	Psoriasis Area and Severity Index
PGA-PsO	Physician's Global Assessment of Psoriasis
PsA	Psoriatic Arthritis
PsARC	Psoriatic Arthritis Response Criteria
RR	Relative Risk
SC	Subcutaneous
SE	Standard Error
SF-36	Short Form-36 health survey
SF-36 PCS	Short Form-36 health survey Physical Component Score
TNFi	Tumor Necrosis Factor inhibitor

Summary

XELJANZ in combination with MTX is indicated for the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant to a prior disease modifying anti-rheumatic drug (DMARD) therapy.

Tofacitinib, the active substance of Xeljanz, is a small molecule that exerts its anti-inflammatory action by binding to and inhibiting Janus kinases (JAK), known to be involved in inflammatory processes, and thus represents a new mode of action for treatment of psoriatic arthritis.

Tofacitinib has been investigated in both biological (bio)-naïve and -experienced PsA patients and accordingly can be used for treatment of bio-naïve as well as bio-experienced PsA patients.

In this application, the efficacy and safety of tofacitinib 5mg BID is compared to adalimumab 40 mg EOW in bio-naïve PsA patients and with secukinumab 300 mg (every week up to week 4 and then every 4 weeks) in bio-experienced patients.

A systematic literature search was carried out as specified in the protocol from the Medicine Council to identify relevant studies for this comparison and a total of 5 studies were included in the final analysis:

- 1 study investigating tofacitinib and adalimumab in the bio-naïve population
- 1 study investigating tofacitinib in bio-experienced patients and
- 3 studies investigating secukinumab in a mixed population of bio-naïve and -experienced patients.

For PsA **bio-naïve patients**:

Efficacy data for tofacitinib 5 mg BID- measured by the critical outcome of ACR50 and the important outcomes of HAQ-DI response rates, patients with radiographic non-progression (mTSS), PASI75 and SF-36 PCS - is significantly different from placebo and comparable, according to the pre-specified margins in the protocol, to adalimumab 40 mg EOW. The requested direct comparison between tofacitinib 5 mg BID and adalimumab 40 mg EOW did not demonstrate significant differences in ACR50, HAQ-DI, PASI75 at month 3 and mTSS non-progression at month 12. The observed small numerical differences for all variables tested are well within the predefined clinically relevant margins in the protocol. Similarly, safety data for tofacitinib 5 mg BID for the treatment of active PsA in adults - as measured by the important outcomes of discontinuations due to adverse events (AEs) and lack of efficacy as well as serious infection rates - is comparable to adalimumab 40 mg EOW as determined by the specified limits for these outcomes in the protocol.

For PsA **bio-experienced patients**:

Efficacy data for tofacitinib 5 mg BID - as measured by the critical outcome of ACR50 and the important outcomes of HAQ-DI responder rates and SF-36 PCS - has shown significant differences from placebo. The requested Bucher analysis favored secukinumab over Tofacitinib with regards to ACR50 (statistically significant) and PASI75 (statistically non-significant). However, the comparison is based on results reported at month 3 for tofacitinib and weeks 16 or 24 for secukinumab. In order to achieve a relevant comparison tofacitinib month 6 results relative to placebo rates (month 3, LOCF) were also compared to week 16-24 results of secukinumab, which yielded non-significant differences, within the prespecified 15 % margin with

regards to ACR50 and above the specified 15 % margin with regards to PASI75. Bucher analysis could not be performed for variables mTSS, HAQ-DI, discontinuation due to AEs and discontinuation due to loss of efficacy as these could not be identified for secukinumab TNFi experienced population in the FUTURE studies.

In addition, meta-analysis suggests that ACR50 and SF-36 PCS data are comparable to secukinumab as specified by the indicated clinical relevant differences. HAQ-DI responder rates could only be found for tofacitinib 5 mg BID but a meta-analysis of HAQ-DI changes from baseline showed comparable efficacy for tofacitinib 5mg BID and secukinumab 300 mg. The PASI75 responder rate was not significantly different for tofacitinib 5 mg BID compared to placebo and data for secukinumab were limited for the bio-experienced PsA sub-population with wide confidence intervals (CIs). Meta-analysis suggests that the rate could be in favor of secukinumab 300 mg but also in this case there are very limited data available and uncertainty in the estimates. There were no available data for the proportion of patients not progressing as measured by mTSS for either tofacitinib or secukinumab. Data for mTSS change from baseline for secukinumab were non-significant compared to placebo.

Finally, the tofacitinib 5 mg BID safety profile - as measured by the important outcomes of discontinuations due to AEs, discontinuations due to lack of efficacy, and patients with serious infections - show less discontinuations compared to placebo and zero serious infections at month 3. Comparison to secukinumab was not feasible as only mixed population (TNFi naïve and experienced) data were identified. In summary, tofacitinib 5 mg BID, as an oral therapy with a different mode of action and different pharmacokinetics compared to the comparators provides a new treatment opportunity for adult patients with active PsA with comparable efficacy and safety profile to existing selected treatment modalities.

Literature search

Databases and search strategy

Relevant searches were performed based on the requested search strings as described in the protocol. See appendix 1.1 and 1.5-1.7 for search strategy/databases and PRISMA schedules, respectively. The searches identified a total of 13 papers (after removal of duplications) for clinical question 1+3 and 345 papers (after removal of duplications) for clinical question 2+4. 2 reviewers independently reviewed all papers at abstract level and a total of 1 and 19 papers were reviewed in full text for clinical question 1+3 and 2+4, respectively. Following full review, 3 papers, representing 1 study, were included in the analysis of question 1+3 and 5 papers + 1 abstract, representing 4 studies, were included in the analysis of question 2+4.

Relevant studies

Table 3 Relevant studies included in the assessment (references in **bold** provided data to the analysis)

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question*
Tofacitinib or Adalimumab versus placebo for Psoriatic Arthritis, Mease et al., NEJM, 2017. **Tofacitinib or adalimumab versus placebo: patient-reported outcomes from OPAL Broaden-a phase III study of active psoriatic arthritis in patients with an inadequate response to conventional synthetic disease-modifying antirheumatic drugs, Strand V et al., RMD Open 2019;5(1):e000806.**	OPAL BROADEN	NCT01877668	Completed (study start 2013)	Clinical question1+3
Tofacitinib for Psoriatic Arthritis in Patients with an Inadequate Response to TNF Inhibitors, Gladman et al, NEJM, 2017 **Effect of tofacitinib on patient-reported outcomes in patients with active psoriatic arthritis and an inadequate response to tumour necrosis factor inhibitors in the phase III, randomised controlled trial: OPAL Beyond, Strand V et al., *RMD Open* 2019;5(1):e000808.**	OPAL BEYOND	NCT01882439	Completed (study start 2013)	Clinical question 2+4
Secukinumab, a human anti-interleukin-17A monoclonal	FUTURE 2	NCT01752634	2013-2019	Clinical question 2+4

antibody, in patients with psoriatic arthritis (FUTURE 2): a randomized, double-blind, placebo-controlled, phase 3 trial. McInnes et al, Lancet. 2015 Secukinumab sustains improvement in signs and symptoms of psoriatic arthritis: 2 year results from the phase 3 FUTURE 2 study. McInnes et al, Rheumatology (Oxford). 2017 Minimal Disease Activity among Active Psoriatic Arthritis Patients Treated with Secukinumab: 2-year Results from the FUTURE 2 Study. Coates et al, Arthritis Care Res (Hoboken). 2018. Secukinumab provides rapid and sustained pain relief in psoriatic arthritis over 2 years: results from the FUTURE 2 study. McInnes et al, Arthritis Res Ther. 2018 **Efficacy of subcutaneous Secukinumab in patients with active psoriatic arthritis stratified by prior TNF inhibitor use: results from the randomized placebo-controlled FUTURE 2 study, Kavanaugh et al, J Rheum, 2016**				
Efficacy and safety of secukinumab administration by autoinjector in patients with psoriatic arthritis: results from a randomized, placebo-controlled trial (FUTURE 3), Nash et al, Arthritis Research & Therapy, 2018	FUTURE 3	NCT01989468	Completed (start 2013)	Clinical question 2+4
Secukinumab improves active psoriatic arthritis symptoms and inhibits radiographic progression: primary results from the randomized, double-blind, phase III FUTURE 5 study, Mease et al, BMJ, 2018	FUTURE 5	NCT02404350	2015- 2019	Clinical question 2+4
*when multiple clinical questions are defined in the protocol				

Main characteristics of included studies

The main characteristics for each of the included studies are described in table A2.

A total of 5 studies were identified. Two studies include tofacitinib (OPAL BROADEN and OPAL BEYOND), one study includes adalimumab (OPAL BROADEN) and 3 studies (FUTURE 2, 3 and 5) investigate secukinumab at the requested dose. All studies are randomized, controlled, double blind, clinical trials.

Selected baseline characteristics of included patients across the studies can be seen in table 4. For detailed information see appendix 1.2, tables A2a-e.

Across the studies baseline characteristics for age, gender distribution and weight are comparable between the studies.

One major difference between the studies however, is the inclusion criteria of csDMARD and TNFi experienced responders. Accordingly, all studies involving secukinumab have a mixed population of TNFi naïve and TNFi experienced PsA patients, with the majority (approx. 2/3rd) being TNFi naïve. In contrast OPAL BROADEN included only TNFi naïve patients whereas OPAL BEYOND included only bio- experienced (TNFi and other biologics) PsA patients. This latter may account for slightly longer disease duration and a higher mean HAQ-DI score in the OPAL BEYOND study compared to the other studies. Mean tender and swollen joints were calculated in different manners in the secukinumab studies (78/76 joint count) compared to the tofacitinib studies (68/66 joint count). Average PASI score at baseline varied slightly across studies from 8.3-10 in OPAL BROADEN to 11.6-16.2 in FUTURE 2.

Table 4: Selected average baseline characteristics for patients with active PsA included in the studies

Baseline characteristic	OPAL BROADEN	OPAL BEYOND	FUTURE 2	FUTURE 3	FUTURE 5
Mean Age (years)	46.9- 49.4	49-51.3	46.5- 49.9	49.3- 50.1	48.4- 49.0
Gender (% female)	47-60	49-61	45-60	51.8-56.9	45.9-51.5
Time since diagnosis (years)	5.3- 7.3	9.1- 9.6	NA	6.6 -8.3	6.2 – 6.7
Weight (mean, kg)	82.1 – 83.7 (BMI 28.8-29.3)	82.1 – 87.9 (BMI 29.5-31)	85.4-91.2	87.1 - 82.6	81.9 - 84.1
Mean Swollen joint count (66 joints)	9.8– 12.9	10.5– 12.8	10.8– 12.1 (76 joint)	8.9– 11.2 (76 joints)	10.0– 12.1 (76 joints)
Mean Tender/painful Joint count (68 joints)	17.1 – 20.6	19.8– 25.5	20.2– 24.1 (78 joints)	19.7 – 23.3 (78 joints)	19.8 – 21.8 (78 joints)
Mean HAQ-DI score	1.1 - 1.2	1.3- 1.4	1.2 - 1.3	1.1 - 1.2	1.2 - 1.3
PASI score (in patients with PsO on at least 3% Body Surface Area)	5.6 – 7.8 (median) 8.3- 10 (mean)	7.1 – 8.8 (median) 9.8-11.1 (mean)	11.6 – 16.2 (mean)	8.8 – 10.4 (mean)	NA
Previous treatment	csDMARD	TNFi	64-67 % csDMARDs 33-37% TNFi	67.9-68.3% csDMARD 31.7-32.1% TNFi	70.4% csDMARD 29.6% TNFi

Clinical questions

Clinical question 1 and 3: What is the added value of tofacitinib for bio-naive patients with PsA without (question 1) or with (question 3) moderate to severe plaque psoriasis?

Moderate to severe psoriasis can be defined in different ways. In a recent Nordic study, PsA patients with psoriasis (n =184) were asked to define the severity of their psoriasis from “not severe at all” to “extremely severe”. According to this definition, 30.4% and 11.4% reported moderate and severe disease respectively (1). When patients were asked to define their psoriasis severity based on Body Surface Area (BSA), with BSA from 4-10% defined as moderate, the corresponding values were 17.8% and 8.4% (1). In the latest report from Rådet for anvendelse af dyr Sygehusmedicin (RADS) for psoriasis and in the national society of dermatology guidelines, moderate to severe psoriasis is defined as PASI≥10(-12), BSA≥10 and DLQI≥10 (2, 3).

In the study that was identified to answer question 1 (what is the added value of tofacitinib in bio-naïve PsA patients without moderate to severe psoriasis) and 3 (what is the added value of tofacitinib in bio-naïve PsA patients with moderate to severe psoriasis) , moderate to severe psoriasis was defined as PGA-PsO≥3, PASI≥12 and BSA≥10. 12 subjects receiving tofacitinib 5 mg BID and 12 subjects receiving adalimumab 40 mg EOW had moderate to severe psoriasis according to this definition (see also (4), table 8). Due to these low numbers, the current available data does not allow for a subgroup division into PsA patients with or without moderate to severe psoriasis. Clinical question 1 and 3 is therefore addressed as one question.

Full Analysis Set is used for efficacy endpoints and Safety Analysis Set is used for safety endpoints. Analyses for PASI75 included subjects with Baseline BSA≥3% and Baseline PASI>0. Analysis for HAQ-DI response included subjects with Baseline HAQ-DI≥0.35. Presentation of relevant studies

One relevant study, OPAL BROADEN, was identified using the search string specified in the protocol.

Opal BROADEN is a phase 3 randomized, controlled study, investigating the efficacy and safety of tofacitinib in patients with active PsA and naïve to biological treatment. At study entry, a total of 422 patients were randomized 1:1:1:1 to oral tofacitinib 5 mg or 10 mg BID, an active control arm (adalimumab subcutaneous (SC) 40 mg EOW) or placebo. Enrolled subjects were followed for 12 months and the co-primary endpoints were ACR20 and HAQ-DI at week 12 after which patients randomized to placebo would enter the 5 mg BID or the 10 mg BID tofacitinib arm for the remaining 9 months. The study was not designed or powered to determine non-inferiority/superiority between tofacitinib and adalimumab.

Results per study

Both efficacy and safety analysis included all patients that were randomized and received at least one dose of study drug.

To control for type 1 error at the 5% level, a sequential hierarchical approach was used where tofacitinib 10 mg BID was compared to placebo before the 5 mg tofacitinib dose was compared to placebo. For the 2 primary endpoints at month 3 the sequence was: tofacitinib 10 mg BID ACR20 versus placebo before tofacitinib 5 mg BID ACR20 versus placebo, then tofacitinib 10 mg BID versus placebo for HAQ-DI change before tofacitinib 5 mg BID versus placebo for HAQ-DI.

Secondary endpoint included: ACR50, ACR70, components of the ACR response criteria, PASI75 (among patients with at least 3% BSA), Leeds enthesitis index score (LEI) & spondyloarthritis research consortium of Canada enthesitis index score (among patients with enthesitis at baseline), the dactylitis severity score (DSS) (among patients with dactylitis at baseline), PsARC and DAS28-CRP. Radiographic changes (and % progressors) were assessed by means of van der Heijde modified total sharp score at month 12. Patient reported outcomes included FACIT-F for measurement of Fatigue, SF-36 and EQ5D.

A step-down approach was also applied to certain secondary efficacy endpoints as follows: PASI75, ΔLEI, ΔDSS, ΔPhysical Functioning Domain of SF-36 and FACIT-F at month 3. In order to strongly protect the study-wise Type I error rate at the 0.05 (2-sided) level with respect to these key secondary endpoints and the primary endpoints, these endpoints were tested only if all endpoints/doses for the primary endpoints were statistically significant.

Safety data was recorded throughout the study.

An overview of absolute difference from placebo for tofacitinib 5 mg BID and adalimumab 40 mg EOW can be seen in table 5A. The requested direct comparison between tofacitinib 5 mg BID and adalimumab 40 mg EOW is shown in table 5B. Detailed information regarding the results can be found in appendix 1.3, table A3a.

Table 5A: Absolute difference from placebo for selected outcomes for tofacitinib and adalimumab in bio-naïve patients (see also appendix 1.3, table A3a)

Outcome at week 12 (except mTSS)	Tofacitinib 5 mg BID vs. placebo	Adalimumab 40 mg EOW vs. placebo
% ACR50 (95% CI)	18.5 (8.3;28.7)**	23.5 (12.9;34)***
% Discontinuation due to AEs	1.8 (-2.8;7.03)	0.9 (-3.53;5.73)
% Discontinuation due to lack of efficacy	0	0
% HAQ-DI response (≥ 0.35) (95% CI)	22.3 (8.6;35.9)**	22.3 (8.6;35.9)**
Number of patients with mTSS <0.5 (% non-progression) at month 12†	2.5	4.5
% PASI75 (95% CI)	28.1 (14.9;41.2)***	24.3 (11;37.6)**
SF-36- PCS mean change (95% CI)	2.83 (0.9;4.7)**	3.55 (1.6;5.4)**
% Serious infections	0	0

ACR50: defined as 50% or greater reduction from baseline in the numbers of tender or painful joints (of 68 assessed) and swollen joints (of 66 assessed and an improvement of 50% or more in at least 3 of: patient global assessment of arthritis, physician global assessment of arthritis, patient assessment of pain, HAQ-DI or CRP. PASI75: 75% or more improvement from baseline in psoriasis area and severity index. *p≤0.05, **p< 0.001, ***p<0.0001. †Note: All placebo patients were re-randomized to active treatment (tofacitinib 5 and 10 mg BID) at month 3. Comparison for non-progression is between group receiving active treatment for 12 months versus 9 months

Table 5B: Treatment comparison including selected Efficacy and Safety Binary Endpoints - OPAL Broaden

			Treatment Comparison				
Endpoint	Visit	Treatment	OR (95 % CI)*	RR (95 % CI)**	P-value	Absolute difference (%) (95 % CI)	P-value
ACR50	Month 3	Tofa 5 mg BID vs. ADA 40 mg EOW	**0.79 (0.44; 1.42)**	0.85 (0.57;1.28)	0.43	-4.98 (-17.33 - 7.37)	0.429
HAQ-DI Response (Decrease from Baseline ≥ 0.35)	Month 3	Tofa 5 mg BID vs. ADA 40 mg EOW	**1.00 (0.57; 1.76)**	1.00 (0.77;1.30)	1.00	0.00 (-14.12 - 14.12)	1.000
PASI75	Month 3	Tofa 5 mg BID vs. ADA 40 mg EOW	**1.17 (0.62; 2.20)**	1.10 (0.75;1.59)	0.63	3.72 (-11.55 - 18.99)	0.633
mTSS, Non-Progression (Change from Baseline ≤ 0.5)	Month 12	Tofa 5 mg BID vs. ADA 40 mg EOW	**0.51 (0.09; 2.83)**	0.98 (0.93;1.03)	0.43	1.98 (-2.89 - 6.84)	0.426
Discontinuation Due to Adverse Events	Up to Month 3	Tofa 5 mg BID vs. ADA 40 mg EOW	**1.50 (0.25; 9.16)**	1.49 (0.25;8.71)	0.66	0.9 (-1.4 – 14.6)	NS
Discontinuation Due to Loss of Efficacy	Up to Month 3	Tofa 5 mg BID vs. ADA 40 mg EOW	0 events	N/A	N/A	N/A	N/A
Serious Infections	Up to Month 3	Tofa 5 mg BID vs. ADA 40 mg EOW	0 events	N/A	N/A	N/A	N/A

Full Analysis Set is used for efficacy endpoints and Safety Analysis Set is used for safety endpoints. Analysis for PASI75 included subjects with Baseline BSA≥3% and Baseline PASI>0. Analysis for HAQ-DI response included subjects with Baseline HAQ-DI≥0.35. For ACR50, HAQ-DI response and PASI75, missing response is imputed as non-response; for mTSS, linear extrapolation is used to impute missing response at Month 12. *A logistic regression model is used to model the probability of response with treatment (classification variable) as the only explanatory variable. The estimated rate is based on the maximum likelihood estimation of the logistic regression model. The p-value is based on Wald test testing if the odds ratio is equal to 1. For an endpoint, when there is no subject meeting criterion (n=0) across all treatment groups, logistic regression model is not performed. ** Relative risk is calculated by dividing the event rates, active vs. comparator. P-values are calculated using unadjusted Chi-Square test.

No (0) events were reported for Discontinuation due to lack of efficacy and Serious Infections at month 3

Comparative analyses

The OPAL BROADEN study was, as previously mentioned, neither designed nor powered to compare tofacitinib 5 mg BID with adalimumab 40 mg EOW in bio-naïve patients with active PsA (5). Medicines Council requested additional analysis comparing tofacitinib 5 mg vs adalimumab 40 mg EOW for endpoints ACR50, HAQ-DI, PASI 75 and mTSS. This was performed by calculating relative risk for selected endpoints (Table 5B). In the trial, both tofacitinib and adalimumab statistically significantly improved signs and symptoms of PsA as measured by ACR50 response rate, HAQ-DI response, SF-36 PCS change as well as PASI75 at month 3 (5) compared with placebo at month 3.

ACR50 (critical importance)

The absolute difference of ACR50 response over placebo was comparable for the 2 treatment arms and the difference between the treatment arms was within the 15% margin specified to be clinically relevant in the protocol. The absolute difference in ACR50 response was 18.5% (CI 95%: 8.3;28.7) over placebo in the tofacitinib 5 mg BID arm and 23.5% (CI 95%: 12.9;34) in the adalimumab 40 mg EOW arm (appendix 1.3, table A3a). The relative difference from placebo (RR) for ACR50 response was 2.94 (CI 95%: 1.51;5.71) for tofacitinib and 3.47 (CI 95%: 1.81;6.63) for adalimumab and not significant different between the 2 active

arms. The requested direct comparison of efficacy endpoint ACR50 between tofacitinib 5 mg BID vs. adalimumab 40 mg EOW was non-significant and within the predefined 15 % margin of clinically relevant absolute difference .The estimated absolute difference between tofacitinib 5 mg and adalimumab 40 mg is -4.98 % (-17.33 - 7.37) (Table 5B). .

Patient reported outcomes (HAQ-DI and SF-36) (important outcome)

The absolute difference in HAQ-response rates were 22.3% (CI 95%: 8.6;35.9) in both the tofacitinib and adalimumab group and accordingly the difference between the treatment arms was less than the 15% specified in the protocol to be a clinical relevant difference (appendix 1.3, table A3a). For HAQ-DI the reported clinical relevant change was 0.35 or more in OPAL BROADEN. This value is higher than the 0.22 suggested in the protocol. However, a study by Mease and coworkers (6) suggests that for PsA the minimal clinical important difference may be higher than the 0.22 used in RA. They identified the minimal important difference to be 0.35 and this cut off was consequently used for the OPAL BROADEN HAQ-DI responder analysis. Additional analysis with a cut off of 0.30 did not change the outcome (4). The requested direct comparison of efficacy endpoint HAQ-DI between tofacitinib 5 mg BID vs. adalimumab 40 mg EOW was non-significant and within the predefined 15 % margin clinically relevant absolute difference. The estimated absolute difference between tofacitinib 5 mg and adalimumab 40 mg is 0.00 % (-14.12 - 14.12) (Table 5B).

The absolute difference in SF36 PCS least square mean (LSM) change from baseline was 5.51 (SE 0.73) in patients treated with tofacitinib 5 mg BID and 6.23 (SE 0.75) in the adalimumab treated patient group - again with overlapping confidence intervals (appendix 1.3, table A3a). Patients receiving all active treatments reported improved SF-36v2 PCS scores compared with placebo at month 1, maintained to month 3 (all $p<0.05$). No improvements in SF-36v2 MCS were reported at month 3 versus placebo. Significant improvements in SF-36v2 PF, BP and VT domain scores following treatment with both Tofacitinib doses, compared with placebo, were reported at month 3 (all $p<0.05$). Improvements in SF domain scores were reported following tofacitinib 5 mg twice daily at month 3, versus placebo ($p<0.05$). Compared with placebo, patients receiving adalimumab reported significant improvements in SF-36v2 PF, BP and GH domains (all $p<0.05$) at month 3. Responses reported by patients receiving tofacitinib or adalimumab were generally maintained to month 12. In this application, SF36- PCS is provided for consistency rather than the total SF-36 which has not been reported in most of the studies. However, each of the individual domains including SF-36 physical functioning, SF role physical functioning, SF-36 general health, SF bodily pain, SF-36 vitality and SF-social functioning have been reported for OPAL BROADEN (7). For each of these individual domains, comparable (less than 0.5 SD) changes were seen for tofacitinib and adalimumab, and all but role physical + social functioning (adalimumab and tofacitinib) as well as vitality (adalimumab) and general health (tofacitinib) were statistically significant from placebo (7).

PASI75 (important outcome)

The absolute difference over placebo for the PASI75 response rate was 28.1% (95% CI: 14.9;41.2) for tofacitinib 5 mg BID which is 3.8% higher than for adalimumab but again with overlapping confidence intervals (appendix 1.3, table A3a) and within the 15% margin specified by the Medicines Council. Post hoc analysis showed that the relative differences to placebo was RR 2.92 (95% CI: 1.63; 5.21) for tofacitinib and 2.66 (95% CI: 1.47;4.82) for adalimumab and not statistical significant between the 2 groups. The requested direct comparison of efficacy endpoint PASI75 between tofacitinib 5 mg BID vs. adalimumab 40 mg EOW was non-significant and within the predefined 15 % margin of clinically relevant absolute difference. The estimated absolute difference between tofacitinib 5 mg and adalimumab 40 mg is 3.72 % (-11.55 - 18.99) (Table 5B).

Proportion of patients without radiographic progression (mTSS)

Although OPAL BROADEN included measurement of radiographic progression, the study was not designed as a radiographic study. The study therefore did not specifically recruit patients based on radiographic prognosis and the study design only included a short placebo controlled period of 3 months (which is likely a too short period of time to impact significantly on radiographic progression). After 3 months the placebo patients were switched to active treatment for the remaining 9 months before radiographic progression (mTSS) was measured at month 12.

Accordingly, the vast majority of included patients in the trial did not experience progression of structural damage as measured by modified TSS (mTSS) at 12 months. With the switch of placebo into active treatment already at month 3, it has not been possible to compare tofacitinib or adalimumab to placebo for radiographic progression at month 12. However, comparing tofacitinib 5 mg BID and Adalimumab 40 mg EOW with the group of patients that received placebo for the first 3 months and hence active treatment for only 9 months, 2.5% more patients in the tofacitinib (12 months treatment) arm and 4.5% more patients in the adalimumab (12 months treatment) arm were non-progressors at month 12 (appendix 1.3, table A3a) which is within the limit of the 10% difference provided by the Medicines Council to be a clinical relevant difference. The requested direct comparison of efficacy endpoint mTSS between tofacitinib 5 mg BID vs. adalimumab 40 mg EOW was non-significant and within the predefined 10 % margin of clinically relevant absolute difference. The estimated absolute difference between tofacitinib 5 mg and adalimumab 40 mg is 1.98 % (-2.89 - 6.84) (Table 5B).

Safety outcomes (discontinuations and serious infections) (important outcomes)

At month 3 (the placebo controlled period) there were no discontinuations due to lack of efficacy (appendix 1.3, table A3a). In the complete study period of 12 months a total of 2 discontinuations due to insufficient response were reported in the adalimumab arm. Two participants discontinued due to insufficient response in the group of patients that moved from placebo to 5 mg tofacitinib BID at month 3. No discontinuations were reported in the group that received tofacitinib 5 mg BID throughout the study.

Safety events as measured by discontinuation due to AEs and serious infections rates at month 3 were comparable between active treatments with 1.8% (95% CI: -2.8;7.03) and 0 over placebo in the tofacitinib arm and 0.9% (95% CI: -3.53;5.73) and 0 over placebo in the adalimumab arm reporting discontinuation due to AEs and serious infections respectively (appendix 1.3, table A3a). This is within the specified border of 5% reported to be a clinical relevant difference. At month 12, 1% reported serious infection in the adalimumab group and 1.3% in the tofacitinib group. RR for discontinuation due to AEs relative to placebo was 2.94 (95% CI: 0.31;27.85) for tofacitinib and 1.98 (95% CI: 0.18;21.52) for adalimumab. However, only very few events were reported and accordingly the statistical certainty is low as indicated by the very broad confidence interval of these RR. For discontinuations due to AEs and serious infections no events were reported at month 3. There were also very few reported events for discontinuation due to AEs at month 3. The low number of events does not allow viable direct comparison between tofacitinib 5 mg and adalimumab 40mg EOW. However, the requested direct comparison of discontinuation due to AEs between tofacitinib 5 mg BID vs adalimumab 40 mg EOW was non-significant and within the predefined 5 % margin of clinically relevant absolute difference (Table 5B).

SUMMARY

In summary, efficacy data for tofacitinib 5 mg BID for the treatment of active PsA in adults naïve to biological treatment, measured by the critical outcome of ACR50 and the important outcomes of HAQ-DI

response rates, mTSS non-progression, PASI75 and SF-36 PCS is significant from placebo and comparable, according to the specified limits in the protocol, to adalimumab 40 mg EOW. Similarly, safety data for tofacitinib 5 mg BID for the treatment of active PsA in adults as measured by the important outcomes of discontinuations due to AEs and lack of efficacy as well as serious infection rates is comparable to adalimumab 40 mg EOW as determined by the specified limits for these outcomes in the protocol.

Clinical question 2 and 4: Which clinical added value does tofacitinib offer for bioexperienced patients with PsA without (question 1) or with (question 3) moderate to severe plaque psoriasis.

Analysis of tofacitinib data based on whether patients had moderate to severe psoriasis was not feasible due to a small sample size of patients (18 in each group) with moderate to severe psoriasis (as indicated by baseline PGA-PsO≥3, PASI≥12 and BSA≥10) in the OPAL BEYOND trial (ref (4), table 28). Therefore, clinical question 2 and 4 are answered as one question.

In addition, although secukinumab 300 mg is specifically indicated for patients with prior TNF inadequate response and patients with moderate to severe psoriasis (see (8)), it has not been possible to find subgroup data that explore any of the requested outcomes based on whether the PsA patients have moderate to severe psoriasis or not. However, data from psoriasis trials support a higher PASI and HAQ-DI response in patients with moderate to severe psoriasis (ref (8), table 17).

Presentation of relevant studies

Four relevant multicenter, randomized, placebo controlled and double blinded studies were identified: OPAL BEYOND investigating tofacitinib, FUTURE 2, 3 and 5 investigating secukinumab. All studies included patients with active PsA that were experienced to biological/TNFi therapies. Of note, in FUTURE 2, 3 and 5 the included population was a mixed population of both TNFi-naïve and TNFi-experienced patients. Approximately 30% of included patients in the studies were TNFi-experienced (in FUTURE 2: 35 %). For OPAL BEYOND, bio-experience was an inclusion criterion. Overall the reported disease duration in the FUTURE trials was shorter (6.2-8.3 years) compared to the OPAL BEYOND trial (9-9.6 years) (see table 4). However, it is not specified how long the disease duration was for the subgroup of bio-experienced patients making comparison difficult.

In addition to the difference in patient population between tofacitinib and secukinumab studies, also the time point of primary endpoint varied between the studies. Accordingly, primary endpoint was recorded at week 12 in tofacitinib trials whereas primary endpoint was recorded at week 24 in the secukinumab trials.

OPAL BEYOND included 395 patients with active PsA randomized 1:1:1 to either placebo, tofacitinib 5 mg BID or tofacitinib 10 mg BID (9). Patients were followed for 6 months and primary outcomes were ACR20 response and HAQ-DI change at month 3. At month 3, patients in the placebo group moved to active treatment with either 5 or 10 mg tofacitinib BID. At entry into the trial patients had received on average of 1.5-1.7 TNF inhibitors. In addition, 8-11% had received other biologics in addition to TNF inhibitors (9).

In FUTURE 2 a total of 397 (TNFi naïve and experienced) patients with active PsA were randomized 1:1:1:1 to 4 treatment groups: secukinumab 75 mg, 150 mg, 300 mg or placebo (10, 11). Patients were stratified according to previous anti-TNF experience. Secukinumab was given subcutaneously weekly up to week 4 followed by every 4 weeks. Patients are followed for 5 years and primary efficacy outcome was ACR20 response at week 24. At week 16, patients were classified as responders or non-responders (20% reduction in tender and swollen joints). Non-responder placebo patients were re-randomized to active treatment at week 16 and placebo responders were re-randomized to active treatment at week 24. At entry, 33-37% were bio-experienced patients of which approximately 50% in the 300 mg and placebo group had received 1 TNF inhibitor and 50 % 2 TNF inhibitors ((8), table 11).

FUTURE 3 included 414 (TNFi naïve and experienced) patients with active PsA randomized 1:1:1 to subcutaneous secukinumab 300 mg, 150 mg or placebo once weekly up to week 4 followed by treatment every 4 weeks (12). Patients were followed for 52 weeks and primary outcome was ACR20 response at week 24. As for FUTURE 2, patients treated with placebo were either re-randomized to active treatment at week 16 (non-responders) or week 24 (responders).

FUTURE 5 included 996 (TNFi naïve and experienced) patients with active PsA randomized 2:2:2:3 to 4 different groups: secukinumab 300 mg every week up to week 4 followed by every 4 weeks, 150 mg secukinumab with loading dose, 150 mg without loading dose or placebo (13). Primary endpoint was ACR20 response at week 16. Additionally radiographic progression at week 24 was a key secondary endpoint. As for FUTURE 2 and 3, placebo patients were re-randomized to active treatment according to whether they were non-responders (less than 20% reduction in tender and swollen joint count, week 16) or not (week 24).

Results per study

OPAL BEYOND:

Both efficacy and safety analysis in the study included all patients that were randomized and received at least one dose of study drug (9).

To control for type 1 error at the 5% level, a sequential hierarchical approach was used where tofacitinib 10 mg BID was compared to placebo before the 5 mg tofacitinib dose was compared to placebo. For the 2 primary endpoints at month 3 the sequence was: tofacitinib 10 mg BID ACR20 versus placebo before tofacitinib 5 mg BID ACR20 versus placebo, then tofacitinib 10 mg BID versus placebo for HAQ-DI change before tofacitinib 5 mg BID versus placebo for HAQ-DI (9).

Secondary endpoint included: ACR50, ACR70, components of the ACR response criteria, PASI75 (among patients with at least 3% BSA), Leeds enthesitis index score (LEI) & spondyloarthritis research consortium of Canada enthesitis index score (among patients with enthesitis at baseline), the dactylitis severity score (DSS) (among patients with dactylitis at baseline), PsARC and DAS28-CRP. Patient reported outcomes included FACIT-F for measurement of Fatigue, SF-36 and EQ5D.

FUTURE 2

Safety analysis is reported for week 16 and across the entire study period for all patients that received at least one dose of study drug (10, 11).

A sequential hierarchical test was used to maintain family wise type 1 error rate at 5% across the primary and ranked secondary endpoints. If the primary endpoint was significant, secondary outcomes were completed as follows: ACR20, PASI75, PASI90, DAS28-CRP, SF36-PCS, HAQ-DI, ACR50, dactylitis and enthesitis. For week 24 analyses of binary endpoints, non-responder patients in the placebo who switched to secukinumab at week 16 were imputed as non-responders at week 24. Week 16 non-responders in the secukinumab group were also imputed as non-responders at week 24 (10, 11).

FUTURE 3

Evaluation of efficacy was performed on the full analysis set, comprising all patients randomized and assigned to a treatment. Safety analysis is reported for week 16 and across the entire study period for all patients that received at least one dose of study drug (12).

The hypotheses for the primary objective in either the secukinumab treatment arm (300 mg or 150 mg) versus placebo were tested simultaneously at the p=0.025 level. Based on the rejection of 1 or both hypotheses, secondary endpoint analysis was completed according to the following pre-specified hierarchy sequence at p=0.025 level: ACR50, DAS28-CRP, PASI 75, SF-36 PCS, PASI 90, HAQ-DI, dactylitis, and enthesitis (12). If all secondary endpoints were rejected for one of the secukinumab arms vs. placebo the testing strategy allowed for its assigned alpha of 2.5% to be transferred to the testing sequence for the other arm. Hence, the hypotheses for that secukinumab arm vs. placebo could then be tested at 5% level (if not already rejected at 2.5% level).

For the primary analyses, all patients who were non-responders based on the joint count at Week 16 were imputed as non-responders at Week 20 and Week 24 for all binary variables (rescue penalty). This was done also for secukinumab patients although they continued on the same dose of secukinumab (12).

FUTURE 5

Safety analysis is reported for all patients that received at least one dose of study drug (13).

Sample sizes were calculated based on an overall two-sided 5% type I error rate. As three secukinumab regimens were tested versus placebo for ACR20, the type I error was separated into a 1.67% two-sided for each comparison. A sequential hierarchical testing method was used to maintain the familywise type I error rate at 5% across the primary and ranked secondary specified endpoints: ACR20, mTSS change, PASI75, PASI90, ACR50 response, HAQ-DI change, DAS28-CRP, enthesitis and dactylitis (13).

RESULTS

An overview of the absolute differences over placebo for each of the outcomes in each of the studies can be seen in table 6A below. For detailed information, see appendix 1.3, table A3b-e. Of note, The FUTURE trials, investigating the comparator secukinumab, included a mixed population of TNFi-naïve and TNFi experienced patients and secukinumab data for all requested outcomes could not be identified in the EPAR or in papers for the sub-population of TNFi experienced patients specifically. The requested indirect Bucher analysis comparing tofacitinib 5 mg BID and secukinumab 300 mg is shown in table 6B. ACR50 META for Secukinumab 300 mg is based on relative differences in ACR50 response rates in TNFi experienced patients on secukinumab and control group in FUTURE 2, FUTURE 3 and FUTURE 5 studies.

Table 6A: Absolute difference from placebo on selected outcomes for tofacitinib and secukinumab in bio-experienced patients (see also appendix 1.3, A3b-e)

Outcome at month 3 (tofacitinib)/ 16-24 weeks (Secukinumab)	Tofacitinib 5 mg BID	Secukinumab 300 mg FUTURE 2	Secukinumab 300 mg FUTURE 3	Secukinumab 300 mg FUTURE 5
% ACR50 (95%CI)	15 (5-25)*	18.7 (0.3;36.5)*	18.2(4.9;32.4)*	29.7 (17;42)***
% Discontinuation due to AEs (95% CI)	-2.3 (-3.5;3.9)			
% Discontinuation due to lack of efficacy (95% CI)	-2.3(-1.6;6.87)			
% HAQ-DI response (≥ 0.35) (95% CI)	22.4 (10-35)*			
Number of patients with mTSS <0.5 (non-progression)				
% PASI75 (95% CI)	7.3 (-4;19)	55.3 (16;78)*		
SF-36- PCS mean change	3.4 (1.5-5.3)**	3.9		
% Serious infections	0			

ACR50: defined as 50% or greater reduction from baseline in the numbers of tender or painful joints (of 68 assessed) and swollen joints (of 66 assessed and an improvement of 50% or more in at least 3 of: patient global assessment of arthritis, physician global assessment of arthritis, patient assessment of pain, HAQ-DI or CRP. PASI75: 75% or more improvement from baseline in psoriasis area and severity index. *p≤0.05, **p< 0.001, ***p<0.0001.

Table 6B: Bucher analysis tofacitinib 5mg BID (OPAL Beyond) vs. secukinumab 300mg META (FUTURE studies)

Secukinumab 300 mg sc + optional csDMARD (FUTURE Studies)	**Study population**	**Relative difference vs. Control**
ACR50 (Week 24)	FUTURE 2 TNF experienced patients	3.182
ACR50 (Week 24)	FUTURE 3 TNF experienced patients	9.000
ACR50 (Week 16)	FUTURE 5 TNF experienced patients	5.147
META ACR50 Secukinumab*	**META FUTURE studies**	**4.78 [2.56; 8.93]**
Tofacitinib 5mg BID ACR50 (Month 3)	Opal Beyond TNF experienced patients	2.053

Indirect comparison (Bucher analysis)	**RR (95 % CI)**	**P-value (two sided)**	**Absolut difference % (95% CI)**
Tofacitinib 5mg BID ACR50 (Month 3) vs Secukinumab 300mg ACR50 META (week 16-24)	0.43 (0.19 -0.95)	0.037	-16.9% (-23.9% - -1.5%)
Tofacitinib ACR50 (Month 6**) vs Secukinumab 300mg ACR50 META (week 16-24)	0.55 (0.25 – 1.20)	0.134	-13.3% (-22.2% - 6.0%)
Tofacitinib PASI75 (Month 3) vs Secukinumab 300mg PASI75 (Month 3), FUTURE 2	0.19 (0.02-1.44)	0.108	-51.8% (-62.1% - 28.2%)

*Inverse variance method was used to combine results from 2 or more studies. Review Manager v5.3 was used for the calculation. 95% Confidence intervals were calculated in SAS or Review Manager v5.3.

**There was no placebo group after Month 3. For comparison, relative difference between tofacitinib 5 mg BID Month 6 vs. placebo was calculated using Month 3 placebo rates carried forward (LOCF).

Bucher analysis could not be performed for variables mTSS, HAQ-DI, discontinuation due to AEs and discontinuation due to loss of efficacy as these could not be identified for secukinumab TNFi experienced population in the FUTURE studies.

ACR50

ACR50 was reported in all 4 studies. The placebo response varied between the studies, from 2.3% in FUTURE 3 over 7.1% and 8.6% in FUTURE 2 and 5 respectively to 15% in OPAL BEYOND.

For OPAL BEYOND, the absolute difference from placebo was 15% (95% CI 5;25) for tofacitinib 5 mg BID at week 12 (see appendix 1.3, table A3b). The RR was 2.05 (95% CI 1.26;3.36).

The absolute ACR50 response rates recorded 4-12 weeks later (week 16-24) for secukinumab over placebo in FUTURE 2, 3 and 5 varied from 18.2% (95% CI 4.9;32.4) over 18.7% (95% CI 0.3;36) to 29.7% (95% CI 17;42) (see table 6 and appendix 1.3, table A3c-e).

HAQ-DI

The rate of HAQ-DI response as measured by patients achieving a change of 0.35 or more was only reported for tofacitinib and was significantly higher than for placebo at week 12 (absolute difference of 22.4% (95% CI 10.2;34.6)) (appendix 1.3, table A3c-e). In contrast, the mean change in HAQ-DI from baseline for bio/TNFi-experienced patients has been reported for both tofacitinib in OPAL BEYOND and secukinumab in FUTURE 2 (9, 10). For tofacitinib the LSM change at week 12 was -0.39 (SE 0.05) for tofacitinib 5 mg BID versus -0.14 (0.05) for placebo (9). For secukinumab 300 mg in FUTURE 2 the LSM change was -0.53 (SE 0.09) versus -0.23 (0.11) for placebo at week 24 (10).

PASI75

PASI75% response was reported for the TNFi experienced patients in 2 studies: OPAL BEYOND and FUTURE 2. For tofacitinib the absolute difference was 7.3 (95% CI -4;19) (appendix 1.3, table A3b). For secukinumab the difference from placebo was 55.3% (95% CI 16; 78) (appendix 1.3, table A3c). Of note, the sample size for secukinumab was very low in FUTURE 2 with evaluation of 12 TNFi experienced patients in the placebo arm and 11 patients in the secukinumab arm, which may explain the broad confidence interval (10).

SF-36

The change in SF-36 was provided only for the physical component score (PCS) for secukinumab 300 mg. A total change in SF-36 PCS of 3.4 (95% CI 1.5; 5.3) over placebo was observed for tofacitnib 5 mg BID at week 12 and 3.9 for secukinumab 300 mg at week 24. Descriptive statistics for tofacitinib 5 mg BID showed a mean change for tofacitinib of 4.96 with an SD of 8.65 (Pfizer, data on file).

mTSS progression

The percentage of patients that does not progress radiographically has not been identified for tofacitinib or secukinumab in the bio-experienced subpopulation. However, data does exist for secukinumab 300 mg for the mean change in mTSS (13). Mean change from baseline in mTSS at week 24 for the TNFi experienced subgroup is reported to be 0.23 for secukinumab 300 mg (n:65) and 0.54 for placebo (n:82) (13).

Safety

Regarding safety it was not possible to identify data specific for the TNFi experienced patient population for secukinumab in the three FUTURE trial publications. In the secukinumab EPAR it is noted that the incidence rate (IR)/100 patient years of serious infections in the TNFi experienced population is 7.2 for patients treated with secukinumab 300 mg versus 0 in the placebo group (8). This is in contrast to the TNFi naïve population where the IR for secukinumab 300 mg is 3.3 versus 4.1 for placebo (8), suggesting that there may be a difference between TNFi naïve patients and TNFi experienced patients. For tofacitinib 5 mg BID, the rate of serious infections was low with no reported events within the placebo controlled period (3 months) and 2% at 6 months follow-up (appendix 1.3, table A3b).

In OPAL BEYOND, the rate of discontinuation due to AEs at month 3 were higher in the placebo group than the tofacitinib 5 mg group with an RR of 0.4 and an absolute difference of -2.3% (95% CI: -3.5;3.9) with 4% in the placebo group and 2% in the tofacitinib group (appendix 1.3, table A3b). Similarly, at month 3, discontinuations due to lack of efficacy was observed only for 1 patients (0.8%) in the tofacitinib group compared to 6 (4.6%) in the placebo group, resulting in a total difference of -3.8% (95% CI: -0.4;8.9) and an RR for discontinuation due to lack of efficacy of -2.3% (95% CI: -3.0;3.7) (appendix 1.3, table A3b).

Within the placebo- controlled period of FUTURE 2 there were 2% overall (TNFi naïve and experienced) discontinuation due to AEs in the secukinumab 300 mg group versus 3% in the placebo group at month 6 (11). There were no recorded discontinuation due to lack of efficacy in the secukinumab 300 mg mixed group (TNFi naïve and experienced) versus 3.1% in the placebo group up until week 24 (11). Of note the majority of patients were TNFi naïve patients (65%) which could potentially influence the profile.

In FUTURE 3 and 5, a total of 2.2% (week 16) and 1.4% (week 24) discontinued due to AEs in comparison to 3.6% and 2.1% respectively in the placebo arm (12). Discontinuations due to lack of efficacy was reported for the 300 mg secukinumab group at 2.2% at week 24 (12). No data was provided for the placebo group at week 24. For FUTURE 5 there were no reported discontinuations due to lack of efficacy in the secukinumab 300 mg group and 3 patients out of 332 (0.9%) in the placebo group up until week 24 (13). However, the patient disposition was similar to that observed in FUTURE 2 with the population being a mix of TNFi naïve and TNFi experienced patients and the majority being TNFi naïve (68.1% and 70.4% respectively) which could potentially influence the profile (see discussion in comparative analysis).

Comparative analyses

Due to the paucity of available data for secukinumab 300 mg in the TNFi-experienced population the comparison of most outcomes is not feasible for this subpopulation. For two of the included studies, FUTURE 3 and 5, it was only possible to identify ACR50 response (critical outcome) in the bio-experienced population specifically. For FUTURE 2 additionally data are available for PASI75 and SF-36 PCS in TNFi experienced population. Hence comparison can be made on these three requested outcomes.

ACR50

The protocol specifies that a clinical relevant difference between tofacitinib and comparator for the critical outcome of ACR50 response rate should be 15% or more. The absolute difference in ACR50 response rate at week 12 reported for patients treated with 5 mg tofacitinib BID was 15.3% (95% CI: 5.4;25.2) (appendix 1.3, table A3b). In comparison the response rates at week 16-24 were 18.7% (week 24), 18.2% (week 24) and 29.7% (week 16) for secukinumab 300 mg in FUTURE 2, 3 and 5 respectively (appendix 1.3, table A3c-e). 95% confidence intervals were broad: 0.3;36; 4.9;32.4; 17;43 and overlapping with tofacitinib confidence intervals. Thus, although the studies cannot be directly compared due to different designs including timing of endpoint measurement, the difference was not above 15% for any of the studies.

The requested comparison of efficacy endpoint ACR50 between tofacitinib 5 mg BID (month 3) vs secukinumab 300 mg (week 16-24) by Bucher analysis was significantly different and marginally above the predefined clinically relevant 15 % margin in favor of secukinumab with RR 0.43 (0.19 -0.95), p=0.037, and absolute difference of -16.9% (-23.9% - -1.5%) (Table 6B). However, tofacitinib 5 mg BID month 6 ACR50 response rate (relative to month 3 placebo LOCF) vs secukinumab 300 mg was not significant and within the predefined 15 % margin of clinically relevant difference (Table 6B). Considering the differences in time points for ACR50 response measurements in tofacitinib and secukinumab, difference in disease duration and no placebo control after month 3 for tofacitinib, this difference can be considered as borderline.

Pfizer recently also performed a meta-analysis of randomized controlled trials (RCTs) enrolling patients with active PsA (see appendix 1.4 and 1.5). Interventions of interest included conventional synthetic and biologic DMARDs. The searches were conducted up to October 2017, and identified a total of 43 unique RCTs (bio-naïve and experienced). Only 11 RCTs reported data for the TNFi inadequate responder population. The majority of trials reported data for ACR responses and ΔHAQ-DI but there was a paucity of data reported

for, for example, ΔSF-36 (PCS or PF) across eligible RCTs and therefore only sparse networks were available for these outcomes (Pfizer, data on file). However, for the ACR50 response the meta-analysis showed an odds ratio (OR) of 0.43 (95% CI: 0.1;1.76) for tofacitinib versus secukinumab 300 mg suggesting comparable efficacy as measured by ACR50 response rate (Pfizer data on file) (appendix 1.4 and 1.5). Of note, FUTURE 3 and 5 were published after the meta-analysis was performed and hence are not a part of this analysis. In the protocol it is recommended to calculate an absolute value based on the calculated relative difference and an assumed number of occurrences for the comparator in the Danish population. We have not been able to find data on the occurrence rate for ACR50 in secukinumab treated TNFi experienced Danish patients. Instead, as only one secukinumab study was included in the network meta- analysis the absolute difference can be calculated using ACR50 data from this study. THE ACR50 responder rate in FUTURE 2 was 27.3%. Thus the calculated absolute difference with an OR of 0.43 would be 15.56%. However, considering the wide 95% confidence intervals on the ACR50 rate (13.3;45.5) the absolute difference vary from 7.78% to 25.93% using this calculation. In addition the credible intervals for the calculated OR varies from 0.10 to 1.76. Using the lower confidence interval and an assumed ACR50 rate of 27.3%, the lower credible interval suggest an absolute difference of 24.57% whereas the higher confidence interval suggest an absolute difference of -20.75%. Thus, based on the current available evidence the absolute difference may be somewhere between -20.75% and +24.93%.

Patient reported outcomes (HAQ-DI and SF-36)(important outcome)

We were not able to identify HAQ-DI data for secukinumab regarding proportion of patients that obtain a clinical response (change beyond 0.22, 0.3 or 0.35). For tofacitinib 5 mg BID the proportion of bio-experienced patients that achieved a HAQ-DI response (>0.35) was 22.4% (10;35) over placebo and statistically significant higher than placebo (appendix 1.3, table A3b). As noted in the result per study, change from baseline in HAQ-DI is reported for both tofacitinib (OPAL BEYOND) and secukinumab in FUTURE 2 (9, 10). For tofacitinib the LSM change at week 12 was -0.39 (SE 0.05) (n=131) for tofacitinib 5 mg BID versus -0.14 (0.05) for placebo (n=131) (14). For secukinumab 300 mg in FUTURE 2 the LSM change was -0.53 (SE 0.09 SE) (n=33) versus -0.23 (0.11)(n=35) for placebo at week 24 (10). Thus the absolute difference from placebo in HAQ-DI change from baseline is -0.26 for tofacitinib 5 mg BID at week 12 and -0.30 for 300 mg secukinumab 12 weeks later, at week 24. Network meta-analysis performed by Pfizer on the mean changes from baseline of HAQ-DI showed a mean difference of 0.05 (Crl -0.26;0.36) between tofacitinib 5 mg BID and secukinumab 300 mg suggesting comparable efficacy on the change in HAQ-DI from baseline (Pfizer, data on file) (see appendix 1.4 and 1.5).

SF-36 data was identified for SF-36 PCS only for both tofacitinib in OPAL BEYOND and secukinumab in FUTURE 2 (9, 10, 14). A total change in SF-36 PCS of 3.4 (CI 1.5; 5.3) over placebo was observed for tofacitinib 5 mg BID and 3.9 for secukinumab 300 mg at week 12 and 24 respectively (see table A3b and c). Descriptive statistics for tofacitinib 5 mg BID showed a mean change for tofacitinib of 4.96 with an SD of 8.65. Although the 2 studies cannot be directly compared and for example, the time point of reporting differs, the difference between the 2 products is less than the 0.5 standard deviation that is described in the protocol as minimal relevant difference.

Radiographic data (mTSS) (important outcome)

None of the studies report on the rate of TNFi experienced patients that do not progress as measured by mTSS. FUTURE 5 reports on radiographic data measured by change in mTSS from baseline at week 24 for TNFi experienced patients and report a change of 0.23 for secukinumab 300 mg and 0.54 for placebo which at this time point is non-significant (ns) (13).

PASI75 (Important outcome)

The requested comparison of efficacy endpoint PASI75 at month 3 between tofacitinib 5 mg BID vs secukinumab 300 mg by Bucher analysis was non-significant (RR 0.19 (0.02-1.44), p=0.108) but above the predefined 15 % margin of clinically relevant absolute difference in favor of secukinumab (-51.8% (-62.1% - 28.2%) (Table 6B).

PASI75 response in bio/TNFi-experienced patients with an affected BSA>3 is reported for tofacitinib 5 mg BID in OPAL BEYOND and secukinumab 300 mg in FUTURE 2 (9, 10). For tofacitinib the absolute difference from placebo is 7.3% with CI of -4% to 19% (appendix 1.3, table A3b). For secukinumab the difference from placebo was 55.3% with CI range from 16% to 78% (appendix 1.3, table A3c). The difference between the absolute values (not considering the CI) is bigger than the 15% stated in the protocol. However, as noted in the result per study section, the sample size in the secukinumab study is limited (11-12 patients) which may explain the large confidence interval and which makes it challenging to draw final conclusion on the comparability between tofacitinib and secukinumab on PASI75 despite the difference in absolute value. In the meta-analysis performed by Pfizer (data on file) the OR for PASI75 for tofacitinib 5 mg BID versus secukinumab 300 mg is 0.06 (95% Crl: 0;0.66) suggesting that there could be a difference in favor of secukinumab on this outcome in patients with more than 3% of their body surface area affected by psoriasis (Pfizer data on file) (appendix 1.4 and 1.5). However, as noted previously, the meta-analysis was performed prior to the publication of FUTURE 3 and 5 and therefore contains the same limited data from FUTURE 2 for secukinumab 300 mg.

Safety (discontinuations and serious infections) (important outcomes)

The rate of discontinuation due to AEs at month 3 were higher in the placebo group than the tofacitinib 5 mg group with an OR of 0.39 and an absolute difference of -2% (CI -2.15;7.22) (appendix 1.3, table A3b). Similarly, at month 3, discontinuations due to lack of efficacy was observed only for 1 patients (0.8%) in the tofacitinib group compared to 6 (4.6%) in the placebo group resulting in a total difference of -3.8% (-0.4;8.9) and an OR of 0.24 (appendix 1.3, table A3b). Thus the discontinuation rates due to AEs and lack of efficacy were overall lower in tofacitinib 5 mg BID treated patients than placebo.

We were not able to identify discontinuation data for secukinumab 300 mg in the subpopulation of TNFi-experienced patients. Only data for the mixed subgroups of TNFi naïve and experienced patients is provided in the identified publications and no additional data was found in the EPAR. However, even though TNFi experienced patients makes up only approximately 1/3rd of the included study population in FUTURE 2, it is noted by Kavanaugh and coworkers (10), that more than half of those patients that discontinued due to lack of efficacy (13/19, 68.4%) at week 52 across all secukinumab doses belonged to the TNFi experienced group. Thus comparison of tofacitinib 5 mg in TNF exposed patients only (as is the study population of OPAL BEYOND) to the mixed TNFi naïve and experienced study population of FUTURE 2, 3 and 5 is not appropriate since the inclusion of the TNF naïve patient population potentially changes the discontinuation profile. However, as noted in the “result per study section”, in general discontinuations due to AEs or lack of efficacy were low also for the secukinumab 300 mg mixed population.

Similar to discontinuations, data for serious infections is reported for the mixed subgroup population including both TNFi naïve and TNFi experienced patients for secukinumab 300 mg and as noted in the result section the events of serious infections may vary between TNFi naïve and experienced patients. For tofacitinib 5 mg BID, the rate of serious infections was low with no reported events within the placebo controlled period (3 months) and 2% at 6 months follow-up.

SUMMARY

In summary, Bucher analysis provided mixed results with regard to ACR50, marginally in favor of secukinumab when compared to tofacitinib month 3 ACR50 and non-significant and within the predefined margin when compared to tofacitinib month 6 ACR50. With regard to PASI75, secukinumab sample size was too small. However, secukinumab had a favorable PASI75 response, although not significant. Bucher analysis could not be performed for variables mTSS, HAQ-DI, discontinuation due to AEs and discontinuation due to loss of efficacy as these could not be identified for secukinumab TNFi experienced population in the FUTURE studies

However,bio-experienced adult patients with active PsA efficacy data for tofacitinib 5 mg BID measured by the critical outcome of ACR50 and the important outcomes of HAQ-DI responder rates, and SF-36 PCS has shown significant difference from placebo. ACR50 and SF-36 PCS data for tofacitinib and secukinumab was within the interval suggested to constitute a comparable efficacy (less than 15% difference). HAQ-DI responder rates could only be found for tofacitinib 5 mg BID but a meta-analysis of HAQ-DI changes from baseline showed comparable efficacy for tofacitinib 5mg BID and secukinumab 300 mg. PASI75 responder rates were not significant for tofacitinib 5 mg BID over placebo. The network meta-analysis suggest that the PASI75 responder rate may be in favor of secukinumab 300 mg but further data are warranted to draw final conclusions as this analysis is based on very limited number of patients. There were no available data for the proportion of patients not progressing as measured by mTSS for either tofacitinib or secukinumab. Data for mTSS change from baseline was presented for secukinumab and were non-significant. Finally, the tofacitinib 5 mg BID safety profile, as measured by the important outcomes of discontinuations due to AEs and lack of efficacy as well as serious infections shows less discontinuations compared to placebo, zero infections within the placebo controlled 3 months and 2% serious infections at month 6. Comparison to secukinumab was not feasible as only mixed population (TNF naïve and experienced) data were identified.

Other considerations

In this application, comparable tofacitinib efficacy and safety data for the treatment of active PsA has been shown and discussed for different outcomes in relation to two comparators, adalimumab in bio-naïve patients and secukinumab 300 mg in bio-experienced patients.

In addition to the assessment of these data for evaluation of tofacitinib as standard treatment in active PsA we would like to encourage the consideration of some additional parameters for added value for patients with active PsA.

Tofacitinib is drug with a new mode of action and may be able to treat patients that would not respond to or tolerate current available treatments. It is noteworthy that data from the Danish registry, Danbio, has shown that approximately 45% of patients started on TNFi therapy maintain an ACR50 response after 2 years and if there is a switch to a second TNFi this rate decreases to 32% leaving 55% and 68% respectively not achieving this critical outcome (15, 16) after 2 years. Thus new treatment options with a different mode of action could potentially be of added clinical value to some of these patients.

Overall, the data from Danbio showed that a short drug survival for the first TNFi was associated with female sex, a high VAS global health score at baseline, a low CRP level at baseline, and lack of concomitant MTX use. Switchers to a second TNFi were more frequently women, had shorter disease duration, more swollen/tender joints, had higher HAQ, DAS28, and fatigue and pain scores at the start of the first TNFi. Predictors of response to the second TNFi was low HAQ and tender joint count as well as low fatigue score which also predicted longer drug survival. These data suggest that the general health and patient reported

outcomes such as pain and fatigue, in addition to disease activity and HAQ, influence the treatment outcomes for advanced therapies in PsA.

An additional parameter to consider is the pharmacokinetics of tofacitinib which differ from the comparators. For example, the short half-life could potentially have value for some patients (17). Finally, as discussed in the early application, tofacitinib is an oral drug- a route of administration that may be a preference to some patients such as those that are not interested in going to hospital for infusions or perform sc injections (18).

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Appendices

1.1 Literature search

Literature search was performed in MEDLINE and CENTRAL according to the protocol. Both free text and indexed search using MeSH terms were used. In addition to the literature identified, the EPAR has been consulted for exploration of additional data.

Table A1.1 Inclusion and exclusion criteria for literature search to answer clinical question 1 and 3

Inclusion criteria	Population: Patients with psoriatic arthritis (PsA) Intervention(s): tofacitinib/Xeljanz 5 mg BID Comparator(s): 40 mg eow Adalimumab Outcomes: ACR50, HAQ-DI, discontinuations due to AEs, Discontinuations due to lack of efficacy, SF-36, PASI75, serious infections., mTSS Settings (if applicable): Study design: Randomized controlled trials Language restrictions: English Other search limits or restrictions applied: NA
Exclusion criteria	Population: primary diagnosis other than PsA Intervention(s): Comparator(s): Outcomes: other than those described in inclusion Settings (if applicable): Study design: other than RCTs Language restrictions: other than English Other search limits or restrictions applied: NA

Table A1.2 Inclusion and exclusion criteria for literature search to answer clinical question 2 and 4

Inclusion criteria	Population: Patients with psoriatic arthritis (PsA) Intervention(s): tofacitinib/Xeljanz 5 mg BID Comparator(s): placebo or subcutaneous (sc) secukinumab/Cosentyx 300 mg week 0,1,2,3,4 and then every 4 weeks Outcomes: ACR50, HAQ-DI, discontinuations due to AEs, Discontinuations due to lack of efficacy, SF-36, PASI75, serious infections., mTSS Settings (if applicable): Study design: Randomized controlled trials Language restrictions: English Other search limits or restrictions applied: NA
Exclusion criteria	Population: primary diagnosis other than PsA Intervention(s): Comparator(s): Outcomes: other than those described in inclusion Settings (if applicable): Study design: other than RCTs Language restrictions: other than English Other search limits or restrictions applied: NA

1.2 Main characteristics of included studies

Study characteristics

Table A2 Main study characteristics
(Complete this table for each included study.)

Trial name	*OPAL BROADEN*
NCT number	*NCT01877668*
Objective	*Evaluation of the efficacy and safety of tofacitinib and an active control, adalimumab, in altering signs and symptoms of PsA, physical function and progression of structural damage over a period of 12 months in patients with active PsA and inadequate response to at least one conventional DMARD.*
Publications – title, author, journal, year	*Tofacitinib or Adalimumab versus placebo for psoriatic arthritis, Mease et al, NEJM, 2017* *Strand et al*
Study type and design	*Completed double-blinded, active-controlled and placebo-controlled phase 3 study. Eligible patients were randomly assigned in a 2:2:2:1:1 ratio by means of automated web based randomization system to receive the following regimens: tofacitinib 5 mg BID, Tofacitinib 10 mg BID, Adalimumab 40 mg eow, placebo with switch to 5 mg BID at month 3 and placebo with switch to tofacitinib 10 mg BID at month 3. The study was patient-, investigator-, and sponsor-blinded.*
Follow-up time	*Controlled period: 3 months, additional data for 12 months reported. Further follow up is ongoing in OPAL Balance study (NCT01976364)*
Population (inclusion and exclusion criteria)	*Inclusion Criteria:* • *Males or females, aged >= 18 years at time of consent.* • *Have a diagnosis of Psoriatic arthritis (PsA) of >= 6 months* • *Meet the Classification Criteria of PsA (CASPAR) at time of screening* • *Must not have been adequately treated with a a traditional non-biologic disease modifying anti-rheumatic drug (DMARD).* • *Concurrent treatment with methotrexate, leflunomide, or sulfasalazine allowed and required* • *Must not have taken a biologic Tumour Necrosis Factor Inhibitor* • *Must have 3 or more swollen joints AND 3 or more tender joints* • *Must have active psoriasis skin lesions* *Exclusion Criteria:* • *Have non-plaque forms of psoriasis, eg erythrodermic, guttate or pustular, with the exception of nail psoriasis which is allowed* • *Pregnant or breast feeding, females of child-bearing potential not using highly effective contraception* • *New York Heart Association Class III and IV congestive heart failure* • *History of hypersensitivity or infusion reaction to biologic agents* • *Infection with HIV, hepatitis B virus, hepatitis C virus, or other chronic infection*

Intervention	*Placebo (with switch to 5 mg BID tofactinib at month3)N=52* *Placebo (With switch to 10 mg BID tofacitinib at month 3):N=53* *Tofacitinib 5 mg BID N=107* *Tofacitinib 10 mg BID N=104* *Adalimumab 40 mg eow N=106* *All patients received their intervention on a stable background dose of a single conventional synthetic DMARD (MTX, Sulfasalazine or leflunomide)*
Baseline characteristics	*- age(years): 46.9±12.4- 49.4±12.6* *- gender distribution: 47-60% female* *- duration of disease (Years): 5.3±5.3- 7.3±8.2* *- Mean BMI, kg/m2 (SD): 28.8 (5.8)- 29.3 (5.5)* *- mean weight in kg: 82.1±18.1 – 83.7±16.6* *- performance status:* • *Swollen joint count (of 66 joints): 9.8±7.9 – 12.9±9.9* • *Tender/painful joint count (of 68 joints): 17.1±11.2 – 20.6±14.4* • *CRP (% with elevation): 60-64%* • *PASI score in patients with PsO on at least 3% BSA (median and range): 5.6 (0.4-60) – 7.8 (0.3-24.3); mean (SD): 8.28(8.3)-9.42(8.8)* • *HAQ-DI score: 1.1±0.6 - 1.2±0.6* • *Dactylitis severity score (mean): 8.0±7.4 - 9.9±8.4* • *Leeds enthesitis index score (mean): 2.3±1.2 - 3.0±1.6* • *mTSS (mean score): 10.4±18.4 - 17.6±43.4* • *SF36 PCS: 35.35±7.87 – 36.37±7.58* *- previous treatments: Conventional synthetic DMARDs (MTX, Sulfazalazine, leflunomide. All are TNFi naive*
Primary and secondary endpoints	*The two primary end points, assessed at month 3, were the proportion of patients who had an American College of Rheumatology 20 (ACR20) response and the change from baseline in the Health Assessment Questionnaire–Disability Index (HAQ-DI) score.* *Secondary efficacy end points included: ACR50 and ACR70 responses; components of the ACR response criteria; PASI75 among patients who had at least 3% of their body-surface area affected at baseline and patients who met Psoriatic Arthritis Response Criteria. In patients with enthesitis or dactylitis at baseline, improvements were assessed using Leeds Enthesitis Index score; the SPARCC enthesitis index score and the Dactylitis Severity Score. The proportion of patients with minimal disease activity and DAS28-CRP were also assessed as secondary outcomes. Radiographic progression was assessed using van der Heijde–modified total Sharp score at month 12. SF36v2, EQ-5D and FACIT-F were also secondary efficacy outcomes*
Method of analysis	*The trial was designed to show the superiority of tofacitinib over placebo. Adalimumab was used as an active control. The trial was not designed and was not powered to evaluate the noninferiority or superiority of tofacitinib as compared with adalimumab* *Efficacy analyses included all the patients who underwent randomization and received at least one dose of tofacitinib, adalimumab, or placebo (full analysis set). To control for type I error at the 5% level, a sequential hierarchical testing method was used: for all end points, the 10-mg dose of tofacitinib was compared with placebo before the 5-mg dose of tofacitinib was compared with placebo. For the two primary end points, the fixed sequence for testing the superiority of each tofacitinib dose versus placebo at month 3 was the following: ACR20 response rate in the 10-mg tofacitinib group vs placebo group; ACR20 response rate in the 5-mg tofacitinib group vs placebo group; change from baseline in HAQ-DI score in the 10-mg tofacitinib group vs the placebo*

	group; and change from baseline in the HAQ-DI score in the 5-mg tofacitinib group vs the placebo group. *Binary end points were analyzed with the use of the normal approximation for the difference in binomial proportions with an imputation of no response for missing values. Continuous end points were analyzed with the use of a mixed model for repeated measures with trial group, visit, interaction of the trial group by visit, geographic location, and baseline value as fixed effects, without imputation for missing values*
Subgroup analyses	*PASI75 was analyzed only among patients who had at least 3% of their body-surface area affected at baseline as pre-specified in the protocol.67-78% of the included patients had at least 3% of their body surface area affected*

Trial name	*OPAL BEYOND*
NCT number	*NCT01882439*
Objective	*A phase 3 trial to investigate the efficacy and safety of tofacitinib in patients with active psoriatic arthritis who have had an inadequate response to at least one TNF inhibitor*
Publications – title, author, journal, year	*Tofacitinib for Psoriatic Arthritis in Patients with an Inadequate Response to TNF Inhibitors, Gladman et al, NEJM, 2017*
Study type and design	*A completed 6-month randomized, placebo-controlled, double-blind, multicenter, phase 3 trial. A centralized automated randomization system was used to assign patients, in a 2:2:1:1 ratio, to one of the following regimens: 5 mg tofacitinib BID for 6 months; 10 mg tofacitinib BID for 6 months; placebo, with a switch to 5 mg of tofacitinib BID at 3 months; or placebo, with a switch to 10 mg of tofacitinib BID at 3 months. The switch from placebo to the preassigned dose of tofacitinib at 3 months was made in a blinded manner. The investigators, patients, and sponsor were unaware of the trial-group assignments for the duration of the trial.*
Follow-up time	*Controlled period: 3 months, additional data for 6 months reported. Further follow up is ongoing in OPAL Balance study*
Population (inclusion and exclusion criteria)	*Inclusion Criteria:* • *Active arthritis at screening/baseline as indicated by >/= 3 tender/painful and 3 swollen joints* • *Active plaque psoriasis at screening* • *Inadequate efficacy or lack of toleration to previously administered TNF inhibitor* *Exclusion Criteria:* • *Non-plaque forms of psoriasis (with exception of nail psoriasis)* • *History of autoimmune rheumatic disease other than PsA; also prior history of or current, rheumatic inflammatory disease other than PsA*
Intervention	*Placebo (with switch to 5 mg BID tofactinib at month3)N=66* *Placebo (With switch to 10 mg BID tofacitinib at month 3):N=65* *Tofacitinib 5 mg BID N=131* *Tofacitinib 10 mg BID N=132* *All patients received their intervention on a stable background dose of a single conventional synthetic DMARD.*
Baseline characteristics	*age(years): 49±12.6- 51.3±10.9* *- gender distribution: 49-61% female*

	- duration of disease (Years): 9.1±6.8- 9.6±7.6 *- Mean BMI, kg/m2 (SD): 29.5 (5.5)- 31.0 (6.7)* *-weight in kg: 82.1±16.2 – 87.9±22.9* *- performance status:* • *Swollen joint count (of 66 joints): 10.5±9.0 – 12.8±11.2* • *Tender/painful joint count (of 68 joints): 19.8±14.9 – 25.5±17.5* • *CRP (% with elevation): 61-65%* • *PASI score in patients with PsO on at least 3% BSA (median and range): 7.1 (1.6-66) – 8.8 (0.8-41.6); mean(SD): 9.8(7.3)-11.11(10.9)* • *HAQ-DI score: 1.3±0.8 - 1.4±0.6* • *Dactylitis severity score (mean): 6.8±5.7 - 9.5±8.2* • *Leeds enthesitis index score (mean): 2.8±1.6 - 3.4±1.8* • *mTSS (mean score): NA* • *SF36 (PCS): 32.1±9.9 – 34.0± 11.0* *- previous treatments:* • *Conventional synthetic DMARDs (MTX, Sulfazalazine, leflunomide, Other)* • *All required to have tried TNF inhibitors: Average no: 1.5±0.8 -1.7±1* • *% of patients who have tried other biologics in addition to TNFi: 8-11%*
Primary and secondary endpoints	*State the primary and secondary outcomes of the study.* *E.g.: The primary endpoint was progression-free survival as assessed by the investigator, according to RECIST version 1.1. Secondary endpoints were overall survival, confirmed objective response according to RECIST version 1.1, response duration, progression-free survival assessed by an independent review facility, health-related quality of life (HRQoL) as assessed by QLQ-C30, and safety.*
Method of analysis	*Efficacy analyses included all patients who underwent randomization and received at least one dose of tofacitinib or placebo (full analysis set). To control for type I error at the 5% level, sequential hierarchical testing was performed; for all end points, the comparison of the 10-mg dose of tofacitinib with placebo was performed before the comparison of the 5-mg dose of tofacitinib with placebo.* *Binary end points were compared with the use of the normal approximation for the difference in binomial proportions, with an imputation of no response for missing values (patients who withdrew from the trial were considered to have no response at any visit after discontinuation). Continuous end points were analyzed with the use of a repeated-measures model that included trial group, visit, interaction of the trial group by visit, geographic location, and baseline value as fixed effects. The model used a common unstructured variance–covariance matrix, without imputation for missing data.*
Subgroup analyses	*PASI75 was analyzed only among patients who had at least 3% of their body-surface area affected at baseline as prespecified in the protocol.61-66% of the included patients had at least 3% of their body surface area affected*

Trial name	*FUTURE 2*
NCT number	*NCT01752634*
Objective	*Investigate the efficacy and safety of subcutaneous loading and maintenance dosing of secukinumab versus placebo in patients with psoriatic arthritis.*
Publications – title, author, journal, year	• *Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomized, double-blind, placebo-controlled, phase 3 trial. McInnes et al, Lancet. 2015*

	• *Secukinumab sustains improvement in signs and symptoms of psoriatic arthritis: 2 year results from the phase 3 FUTURE 2 study. McInnes et al, Rheumatology (Oxford). 2017* • *Minimal Disease Activity among Active Psoriatic Arthritis Patients Treated with Secukinumab: 2-year Results from the FUTURE 2 Study. Coates et al, Arthritis Care Res (Hoboken). 2018.* • *Secukinumab provides rapid and sustained pain relief in psoriatic arthritis over 2 years: results from the FUTURE 2 study. McInnes et al, Arthritis Res Ther. 2018* • *Efficacy of subcutaneous Secukinumab in patients with active psoriatic arthritis stratified by prior TNF inhibitor use: results from the randomized placebo-controlled FUTURE 2 study, Kavanaugh et al, J Rheum, 2016*
Study type and design	*An ongoing randomized, double-blind, placebo-controlled phase 3 trial. Patients were randomly assigned in a 1:1:1:1 ratio to receive subcutaneous secukinumab 300 mg, 150 mg, 75 mg, or placebo once a week from baseline to week 4 and then every 4 weeks thereafter. Placebo-treated patients were randomly assigned again in a 1:1 ratio to receive subcutaneous secukinumab 300 mg or 150 mg every 4 weeks from week 16 (non-responders) or week 24 (responders). Randomisation was done with an interactive voice or web response system and stratified according to previous anti-TNF therapy use, with patients being anti-TNF-naive (planned enrolment about 60%) or anti-TNF-IR. Patients and investigators were masked to treatment assignment*
Follow-up time	*Placebo controlled period: 16-24 weeks, study ongoing for up to 5 years- long term follow up data published for 2 years*
Population (inclusion and exclusion criteria)	*Inclusion Criteria:* • *Diagnosis of PsA classified by CASPAR criteria and with symptoms for at least 6 months with moderate to severe PsA who must have at Baseline ≥3 tender joints out of 78 and ≥3 swollen out of 76 (dactylitis of a digit counts as one joint each)* • *Rheumatoid factor and anti-CCP antibodies negative at screening* • *Diagnosis of active plaque psoriasis or nail changes consistent with psoriasis or documented history of plaque psoriasis* • *Subjects with PsA should have taken NSAIDs for at least 4 weeks prior to randomization with inadequate control of symptoms or at least one dose if stopped due to intolerance to NSAIDs* • *Subjects taking corticosteroids must be on a stable dose of ≤10 mg/day prednisone or equivalent for at least 2 weeks before randomization and should remain on a stable dose up to Week 24* • *Subjects taking MTX (≤ 25 mg/week) are allowed to continue their medication if the dose is stable for at least 4 weeks before randomization and should remain on a stable dose up to Week 52.* *Exclusion Criteria:* • *Chest X-ray or chest MRI with evidence of ongoing infectious or malignant process, obtained within 3 months prior to screening and evaluated by a qualified physician* • *Subjects taking high potency opioid analgesics (e.g. methadone, hydromorphone, morphine)* • *Previous exposure to secukinumab or other biologic drug directly targeting IL-17 or IL-17 receptor* • *Ongoing use of prohibited psoriasis treatments / medications (e.g., topical corticosteroids, UV therapy) at randomization. The following wash out periods need to be observed:* • *Oral or topical retinoids 4 weeks*

	• *Photochemotherapy (e.g. PUVA) 4 weeks* • *Phototherapy (UVA or UVB) 2 weeks* • *Topical skin treatments (except in face, scalp and genital area during screening, only corticosteroids with mild to moderate potency) 2 weeks* • *Subjects who have ever received biologic immunomodulating agents except for those targeting TNFα, investigational or approved* • *Previous treatment with any cell-depleting therapies including but not limited to anti-CD20, investigational agents (e.g., CAMPATH, anti-CD4, anti-CD5, anti-CD3, anti-CD19)*
Intervention	• *subcutaneous secukinumab 300 mg, once a week from baseline to week 4 and then every 4 weeks N=100* • *subcutaneous secukinumab 150 mg, once a week from baseline to week 4 and then every 4 weeks N=100* • *subcutaneous secukinumab 75 mg, once a week from baseline to week 4 and then every 4 weeks N=99* • *Subcutaneous placebo once a week from baseline to week 4 and then every 4 weeks until week 16 (non-responders) or week 24 (responders) where placebo patients are randomly assigned to either the 300 mg or 150 Secukinumab group N=98*
Baseline characteristics	*age(years): 46.5±11.7- 49.9±12.5* *- gender distribution: 45-60% female* *- duration of disease (Years): NA* *- Mean weight (kg): 85.4 (18.4)- 91.2 (19.8)* *- performance status:* • *Swollen joint count (of 76 joints): 10.8±9.2 – 12.1±10.7* • *Tender/painful joint count (of 78 joints): 20.2±13.3 – 24.1±19.4* • *CRP (% with elevation): NA* • *PASI score in patients with PsO on at least 3% BSA(mean and SD): 11.6 (8.3) – 16.2 (14.3)* • *HAQ-DI score: 1.2±0.7 - 1.3±0.6* • *Dactylitis count (mean): 2.7±2.2 - 4.5±5.1* • *Leeds enthesitis index score (mean): 2.8±1.7 - 3.2±1.7* • *mTSS (mean score): NA* • *SF36 PCS: 36.2±8.1 – 37.4±8.8* *- previous treatments:* • *Conventional synthetic DMARDs,* • *NSAIDs* • *TNF inhibitors: 33-37% of patients had previous anti-TNF treatment*
Primary and secondary endpoints	*The primary endpoint was the proportion of patients achieving an ACR20 response at week 24* *Secondary endpoints at week 24 were the proportion of patients achieving PASI75 and PASI90, change from baseline in DAS28-CRP, change from baseline in SF36-PCS score; change from baseline in HAQ-DI score, proportion of patients achieving ACR50; resolution of dactylitis and enthesitis; and overall safety and tolerability. PASI75 and PASI90 responses were assessed in patients with at least 3% of their body surface area affected by psoriasis at baseline. Resolution of dactylitis and enthesitis was assessed in patients with these characteristics at baseline, using pooled data (all secukinumab groups combined) for analysis.*
Method of analysis	*The primary and secondary and relevant pre-specified exploratory endpoints were analyzed according to the pre-specified analysis plan with SAS software (version 9.3).*

	Safety data are presented for week 16, when all patients remained in the originally randomized groups, and across the entire study period; efficacy was assessed at week 24 (primary analysis) and up to week 52. A sequential hierarchical testing method was used to maintain the family wise type 1 error rate at 5% across the primary and ranked secondary endpoints. *For week 24 analyses of binary variables, patients who switched from placebo to secukinumab at week 16 because of non-response were imputed as non-responders at week 24 (early escape penalty). Week 16 non-responders in the secukinumab groups were also imputed as non-responders at week 24. Patients with missing data or who had discontinued treatment early were imputed as non-responders* *Odds ratios (ORs), 95% CIs, and p values were computed for comparisons of secukinumab doses versus placebo from a logistic regression model with treatment and previous anti-TNF use as factors and baseline weight as a covariate. Baseline PASI score was a covariate in PASI75 and PASI90 analyses.* *For analyses of continuous variables at week 24, a mixed-effects model with treatment regimen, analysis visit, and previous anti-TNF use as factors, and weight and baseline score as continuous covariates was used. Treatment by analysis visit and baseline score by analysis visit were interaction terms, and an unstructured covariance structure was assumed*
Subgroup analyses	• *Assessment of efficacy in TNFi-naive and TNFi-exposed patients was prespecified, with analyses performed by intent-to-treat. Exploratory posthoc analyses were performed in TNFi-naive and TNFi-exposed patients based on concomitant MTX use, baseline weight (≥ 90 kg and < 90 kg), and disease activity (DAS28-CRP > 5.1 and ≤ 5.1). For binary variables, patients with missing values and those with < 20% improvement in tender and swollen joint counts at Week 16 were imputed as nonresponders in the Week 24 analyses (nonresponder imputation). P values were computed for comparisons of secukinumab doses versus placebo from a logistic regression model with treatment and previous TNFi use as factors and the covariate being baseline weight. Baseline PASI score was a covariate in PASI75 and PASI90 analyses. For continuous variables at Week 24, a mixed-effect model repeated measures model was used, with treatment regimen, analysis visit, and previous TNFi use as factors, and weight and baseline score as continuous covariates.* *258 (65%) patients were TNFi naïve and 139 (35%) were TNFi experienced.* • *PASI75 was analyzed only among patients who had at least 3% of their body-surface area affected at baseline as prespecified in the protocol.41-58% of the included patients had at least 3% of their body surface area affected*

Trial name	*FUTURE 3*
NCT number	*NCT01989468*
Objective	*To investigate the efficacy and safety results over a 52-week period from the FUTURE 3 study which involves subcutaneous (s.c.) self-administration of secukinumab via auto injector in patients with active PsA*
Publications – title, author, journal, year	*Efficacy and safety of secukinumab administration by auto injector in patients with psoriatic arthritis: results from a randomized, placebo-controlled trial (FUTURE 3), Nash et al, Arthritis Research & Therapy2018*

Study type and design	*FUTURE 3 is an ongoing, multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel-group, 3-year study assessing the use of s.c. secukinumab self-administration with an auto injector in patients with active PsA* *Following a 10-week screening period, eligible patients were randomized (1:1:1) by means of an interactive response technology (IRT) to one of two secukinumab dose groups (secukinumab 300 mg or 150 mg) or placebo*
Follow-up time	*Placebo-controlled period: 16-24 weeks, 52 week data reported, further long term follow up is ongoing*
Population (inclusion and exclusion criteria)	*Inclusion Criteria:* • *Diagnosis of Psoriatic Arthritis (PsA) classified by ClASsification criteria for Psoriatic ARthritis (CASPAR) criteria.* • *Rheumatoid factor and anti-cyclic citrullinated peptide (CCP) antibodies negative.* • *Diagnosis of active plaque psoriasis or nail changes consistent with psoriasis.* • *Inadequate control of symptoms with NSAID.* *Exclusion Criteria:* • *Chest X-ray or chest magnetic resonance imaging (MRI) with evidence of ongoing infectious or malignant process.* • *Subjects taking high potency opioid analgesics.* • *Previous exposure to secukinumab or other biologic drug directly targeting interleukin-17 (IL-17) or IL-17 receptor.* • *Ongoing use of prohibited psoriasis treatments / medications.* • *Subjects who have ever received biologic immunomodulating agents except for those targeting TNFα.* • *Previous treatment with any cell-depleting therapies.*
Intervention	1. *s.c. secukinumab at a dose of 300 mg (2 × 1.0 ml auto injector) at baseline, weeks 1, 2, 3, and 4, and every 4 weeks thereafter* 2. *150 mg (1.0 ml auto injector + 1.0 ml placebo auto injector) at baseline, weeks 1, 2, 3, and 4, and every 4 weeks thereafter.* 3. *placebo (2 × 1.0 ml placebo auto injector) were treated according to the same administration schedule as the active drug until week 16-24 after which they switched to active treatment* *Concomitant steroid (no more than 10 mg/day prednisone or equivalent) and MTX (no more than 25 mg/week) was allowed*
Baseline characteristics	*age(years): 49.3±12.9- 50.1±12.6* *- gender distribution: 51.8-56.9% female* *- duration of disease (Years): 6.6±6.9 -8.3±9.2* *- Mean weight (kg): 87.1 (20.0)- 82.6 (18.5)* *- performance status:* • *Swollen joint count (of 76 joints): 8.9±6.4 – 11.2±9.2* • *Tender/painful joint count (of 78 joints): 19.7±14.8 – 23.3±18.1* • *CRP (% with elevation): NA* • *PASI score in patients with PsO on at least 3% BSA (mean and SD): 8.8 (6.4) – 10.4 (9.0)* • *HAQ-DI score: 1.1±0.7 - 1.2±0.6* • *Presence of Dactylitis (%): 26.1-33.1%* • *Presence of enthesitis (%): 63.3-71.5%* • *mTSS (mean score): NA* • *SF36 PCS: 37.4±8.5 – 39.2±8.4* *- previous treatments:* • *Conventional synthetic DMARDs,*

	• *NSAIDs* • *TNF inhibitors: 31.7-32.1% of patients had previous anti-TNF treatment*
Primary and secondary endpoints	*The primary efficacy endpoint was the proportion of patients achieving ACR20 response at week 24.* *Secondary endpoints assessed as part of a predefined hierarchical hypothesis-testing strategy at week 24 included: proportion of patients with an ACR50 response; change from baseline in DAS28-CRP; proportion of patients achieving PASI75 response in patients with psoriasis affecting ≥ 3% of body surface area; change from baseline in score of SF-36 PCS; PASI 90 response; change from baseline in HAQ-DI score; and resolution of dactylitis and enthesitis.*
Method of analysis	*Evaluations of efficacy were performed on the full analysis set (FAS), which comprised all randomized patients to whom treatment had been assigned. Closed testing procedures were used to maintain a family-wise error rate of 5% across the secukinumab groups and endpoints.* *Primary and other binary endpoints were evaluated by means of logistic regression, with treatment and anti-TNF response status as factors and weight as a covariate. Baseline PASI score was a covariate in PASI 75 and PASI 90 analyses. Missing values, including those due to discontinuation of study treatment, were imputed as failures to achieve the given response (nonresponses). Also, patients who did not achieve response based on joint count at week 16 were imputed as non-responders at week 20 and week 24 (rescue penalty).* *Between-group differences in continuous variables were evaluated with the use of a mixed-model repeated-measures (MMRM) approach, with missing data assumed to be missing at random, with treatment, assessment visit, and anti-TNF response status as factors. Weight and baseline values of endpoints were included in the model as continuous covariates*
Subgroup analyses	*Subgroup analyses were carried out on the basis of previous anti-TNF therapy or concomitant MTX treatment. 39 and 44 patients in the Secukinumab 300 mg group and placebo group respectively had received previous anti-TNF treatment*

Trial name	*FUTURE 5*
NCT number	*NCT02404350*
Objective	*The study was designed to evaluate the impact of s.c. secukinumab 300 and 150 mg on clinical signs and symptoms and radiographic progression as well as evaluating the short-term benefit of the loading regimen. This trial is ongoing and will provide long-term data out to 2 years*
Publications – title, author, journal, year	*Secukinumab improves active psoriatic arthritis symptoms and inhibits radiographic progression: primary results from the randomized, double-blind, phase III FUTURE 5 study, Mease et al, BMJ, 2018*
Study type and design	*A randomized, double-blind, placebo-controlled, parallel-group phase III trial* *Following a screening period of up to 10 weeks, Interactive Response Technology was used to randomly assign eligible patients in a 2:2:2:3 ratio to one of four treatment groups: secukinumab 300 mg with loading dose (LD), secukinumab 150 mg with LD, secukinumab 150 mg without LD or placebo, all administered s.c. Randomization was stratified according to previous anti-TNF therapy use, with patients being anti-TNF-naïve (planned enrolment about 70%) or anti-TNF-IR. Patients, investigators and*

	assessors remain masked to the treatment assignment until all patients reach week 52
Follow-up time	*Controlled period: 16-24 week. Additionally follow-up for up to 2 years is ongoing*
Population (inclusion and exclusion criteria)	*Inclusion Criteria:* *Diagnosis of PsA classified by CASPAR criteria and with symptoms for at least 6 months with moderate to severe PsA who must have at BSL ≥3 tender joints out of 78 and ≥3 swollen joints out of 76 (dactylitis of a digit counts as one joint each). - Rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibodies negative at screening. - Diagnosis of active plaque psoriasis or nail changes consistent with psoriasis or a documented history of plaque psoriasis. - Subjects with PsA should have taken NSAIDs for at least 4 weeks prior to randomization with inadequate control of symptoms or at least one dose if stopped due to intolerance to NSAIDs.-Subjects who are regularly taking NSAIDs as part of their PsA therapy are required to be on a stable dose for at least 2 weeks before study randomization and should remain on a stable dose up to Week 24. - Subjects taking corticosteroids must be on a stable dose of ≤10 mg/day prednisone or equivalent for at least 2 weeks before randomization and should remain on a stable dose up to Week 24. - Subjects taking MTX (≤ 25 mg/week) are allowed to continue their medication if the dose is stable for at least 4 weeks before randomization and should remain on a stable dose up to Week 52. - Subjects on MTX must be on folic acid supplementation at randomization. - Subjects who are on a DMARD other than MTX must discontinue the DMARD 4 weeks prior to randomization visit except for leflunomide, which has to be discontinued for 8 weeks prior to randomization unless a cholestyramine wash-out has been performed.* • *Subjects who have been on a TNFα inhibitor must have experienced an inadequate response to previous or current treatment with a TNFα inhibitor given at an approved dose for at least 3 months or have stopped treatment due to safety/tolerability problems after at least one administration of a TNFα inhibitor.* • *Subjects who have previously been treated with TNFα inhibitors (investigational or approved) will be allowed entry into study after appropriate wash-out period prior to randomization* *Exclusion Criteria:* *Chest X-ray or chest MRI with evidence of ongoing infectious or malignant process. - Subjects taking high potency opioid analgesics. - Previous exposure to secukinumab or other biologic drug directly targeting IL-17 or IL-17 receptor. - Ongoing use of prohibited psoriasis treatments / medications (e.g., topical corticosteroids, UV therapy) at randomization. - Any intramuscular or intravenous or intra-articular corticosteroid treatment within 4 weeks before randomization. - Subjects who have ever received biologic immunomodulating agents except for those targeting TNFα (investigational or approved). - Previous treatment with any cell-depleting therapies including but not limited to anti- CD20, investigational agents - Other protocol-defined exclusion criteria do apply*
Intervention	• *sc secukinumab 300 mg at baseline, week 1,2,3 and then every 4 weeks* • *sc secukinumab 150 mg week at baseline, 1,2,3 and then every 4 weeks* • *sc secukinumab 150 mg at baseline and then every 4 weeks* • *sc placebo* *Concomitant steroid (no more than 10 mg/day prednisone or equivalent), NSAIDs and MTX (no more than 25 mg/week) was allowed*
Baseline characteristics	*age(years): 48.4±12.9- 49.0±12.1* *- gender distribution: 45.9-51.5 % female*

	- duration of disease (Years): 6.2±6.1 – 6.7±8.3 *- Mean weight (kg): 81.9 (16.9)- 84.1 (20.5)* *- performance status:* • *Swollen joint count (of 76 joints): 10.0±8.0 – 12.1±10.5* • *Tender/painful joint count (of 78 joints): 19.8±15.1 – 21.8±16.0* • *CRP (% with elevation): NA* • *PASI score (mean and SD): NA* • *HAQ-DI score: 1.2±0.6 - 1.3±0.7* • *Dactylitis count (mean): NA* • *Leeds enthesitis index score (mean): NA* • *mTSS (mean score): 12.9±23.7 – 15.3±37.5* *- previous treatments:* • *Conventional synthetic DMARDs,* • *Steroids, NSAIDs* • *TNF inhibitors: 29.6% of patients had previous anti-TNF treatment*
Primary and secondary endpoints	*The primary efficacy endpoint was the proportion of patients with an ACR20 response at week 16. The key secondary hierarchical endpoint was radiographic structural progression at week 24, as measured by change from baseline in vdH-mTSS. Other hierarchical secondary endpoints were assessed at week 16 and included: proportion of patients achieving PASI75 and PASI90, proportion of patients with an ACR50 response; change from baseline in HAQ-DI scores, change from baseline in DAS28-CRP and resolution of enthesitis and dactylitis.* *Pre-specified exploratory endpoints of ACR70 response, the proportion of patients with no structural progression (change from baseline in vdH-mTSS ≤0.5) at week 24 and both the primary endpoint (ACR20 at week 16), change from baseline vdH-mTSS at week 24 by prior use of anti-TNF therapy and the proportion of patients achieving minimal disease activity (MDA)were also reported. Disease Activity index for PSoriatic Arthritis (DAPSA) was analyzed posthoc*
Method of analysis	*Statistical analyses were based on logistic regression for binary efficacy variables (eg, ACR20/50/70 and so on), non-parametric analysis of covariance for radiographic data (if baseline and ≥1 post baseline radiographic assessments were available) and mixed-effects models for repeated measures (MMRM) for continuous variables (eg, DAS28-CRP, HAQ-DI). All models fitted included anti-TNF status, weight and the corresponding baseline value as a covariate as well as treatment as a factor (time, treatment by time and baseline by time interaction were also used for MMRM models). Missing values and placebo patients rescued at week 16 were imputed as non-responders for binary endpoints (rescue penalty), linear extrapolation was applied for radiographic data (if baseline and week 16 values were available) and the missing at random assumption of the MMRM analysis was applied for continuous endpoints.* *A sequential hierarchical testing method was used to maintain the familywise type I error rate at 5% across the primary and ranked secondary specified endpoints. P values were calculated as 2-sided. Patients were analyzed according to randomized treatment.*
Subgroup analyses	*the primary endpoint (ACR20 at week 16) and change from baseline in vdH-mTSS at week 24 by prior use of anti-TNF therapy and the proportion of patients achieving minimal disease activity (MDA)were also reported.*

1.3 Results per study

Table A3a Results of study OPAL BROADEN

Trial name:	*OPAL BROADEN (TNFi naive patients)*										
NCT number:	*NCT01877668*										
					Estimated absolute difference from placebo in effect			Estimated relative difference from placebo in effect			Description of methods used for estimation
Outcome	Study arm	n/N	Result(%)	95%CI	Difference	95% CI	*P* value	Relative Risk (RR)	95% CI	*P* value	
ACR50 (%) Month 3	Placebo+ csDMARD	10/105	9.52	4.7;16.8							*Relative risk is calculated by dividing the event rates, active vs. comparator. P-values are calculated using unadjusted Chi-Square test.*
	Tofacitinib 5 mg BID +csDMARD	30/107	28.04	19.8;37.3	18.51	8.32–28.71	0.0004	2.94	1.52;5.71	p<0.001	
	Adalimumab 40 mg eow + csDMARD	35/106	33.02	24;42.8	23.5	12.93-34.06	<0.0001	3.47	1.81;6.63	p<0.001	
Discontinuations due to AEs (%) Month 3	Placebo+ csDMARD	1/105	1	0;5.2							*CI on absolute difference calculated with no continuity correction*
	Tofacitinib 5 mg BID +csDMARD	3/107	2.8	0.6;8	1.8	-2.78;7.03	-	2.94	0.31;27.85	p=0.32	*Note: numbers are very small. 3 discontinued due to AEs in tofacitinib 5 mg BID, 2 in Adalimumab 40 mg eow and 1 in placebo*
	Adalimumab 40 mg eow + csDMARD	2/106	1.9	0.2;6.7	0.9	-3.53;5.73	-	1.98	0.18;21.52	p=0.57	

	Placebo+ csDMARD	105	0							*There were no discontinuations during the placebo controlled period (3 months) due to lack of efficacy. After 12 months, at total of 2 discontinued in the adalimumab arm due to insufficient response and 2 discontinued in the group of patients that moved from placebo to 5 mg tofacitinib BID. No discontinuations were reported in the group that received tofacitinib 5 mg BID throughout the study.*
Discontinuations due to lack of efficacy (%) Month 3	Tofacitinib 5 mg BID +csDMARD	107	0	N/A			N/A			
	Adalimumab 40 mg eow + csDMARD	106	0	N/A			N/A	0	0	
Number of patient achieving HAQ-DI	Placebo+ csDMARD	29/94	30.85 (4.76)	22.3	8.6-35.9	0.0014	1.72	1.21;2.46	p<0.01	* Among patients with

*change of ≥0.35 (for absolute values; % (SE))Month 3**	Tofacitinib 5 mg BID +csDMARD	51/96	53.13 (5.09)						baseline score ≥0.35.
	Adalimumab 40 mg eow + csDMARD	51/96	53.13 (5.09)	22.3	8.6-35.9	0.0014	1.72	1.21;2.46	P<0.01	
Number of patients without structural progression (mTSS change less than 0.5)(%) Month 12	Placebo+ csDMARD	N/A	N/A						*. *mTSS was assessed at week 52- all placebo controlled patients were switched to active treatment (tofacitinib 5mg or 10 mg) at week 12- hence patients in this arm has received active treatment for 9 out of 12 months.*
	Tofacitinib 5 mg BID +csDMARD	94/98	96	2.5	-4.4;9.75	NS	0.96	0.92;1.0	NA	
	Adalimumab 40 mg eow + csDMARD	93/95	98	4.5	-1.9;11.43	NS	0.98	0.95;1.0	NA	*Data provided for patients with eligible X-ray data only*
*Number of patients achieving PASI75(% (SE)) Month 3***	Placebo+ csDMARD	12/82	15 (3.9)						*Note PASI 75 is only assessed in patients with BSA ≥3%- hence lower number of patients evaluated*
	Tofacitinib 5 mg BID +csDMARD	35/82	43 (5.46)	28.1	14.9-41.2	<0.0001	2.92	1.63;5.21	p<0.001	

	Adalimumab 40 mg eow + csDMARD	30/77	39 (5.56)	24.3	11.0-37.6	0.0003	2.66	1.47;4.82	P<0.001	
Mean change in SF-36-PSC (LSM(SE))/mean(SD) Month 3	Placebo+ csDMARD	105	Strand 2.68 (0.79) 5.51 (0.73)/2.12(6.169)							*Also SF-36 physical functioning, SF role functioning, SF-36 general health, SF-36 vitality and SF-social functioning has been reported. SF-36 PCS has been included for consistency in outcome reporting throughout the report.SF-36 data are from the latest publication by Strand et al. summarizing PROOs from Opal Broaden and Opal Beyond studies.*
	Tofacitinib 5 mg BID +csDMARD	107	Strand 5.51 (0.73) 6.23 (0.75)/5.01(6.881)	2.83/NA	0.94-4.73	0.0035	NA			
	Adalimumab 40 mg eow + csDMARD	106	6.23 (0.75) 2.68 (0.79)/5.80(7.572)	3.55/NA	1.66-5.44	0.0003	NA			
Number of patients with serious infections	Placebo+ csDMARD	105	0/NA	0	NA		N/A			*pooled group of 52 entering 5 mg tofacitinib
	Tofacitinib 5	107/159*	0/2(1.3)(0.2;4.5)							

Month3/month 12 (n(%))	mg BID +csDMARD						at month 3 and 107 who have been continuously on 5 mg tofacitinib
	Adalimumab 40 mg eow + csDMARD	106	0/1(1) (0;5.1)	0	NA	N/A	

Table A3b Results of study OPAL BEYOND

Trial name:	*OPAL BEYOND (TNFi experienced patients)*									
NCT number:	*NCT01882439*									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	n/N	Result(%) 95%CI	Difference	95% CI	*P* value	Relative Risk	95% CI	*P* value	
ACR50 (%) Month 3	Placebo+ CDMARD	19/131	15 9;21.7	15.3	5.4- 25.2	0.0025	2.05	1.26;3.36	0.003	*Relative risk is calculated by dividing the event rates, active vs. comparator. P-values are calculated using unadjusted Chi-Square test.*
	Tofacitinib 5 mg BID	39/131	30 22.1;38.4							
Discontinuations due to AEs (n (%) Month 3	Placebo+ CDMARD	5/131	5(4) (1.3;8.7)	-2.3%	-3.5;3.9	NS	0.40	0.08;2.03	0.250	*CI absolute value calculated with Wilson procedure, uncorrected continuity*
	Tofacitinib 5 mg BID	2/131	2(2) (0.2;5.4)							
Discontinuations due to lack of efficacy (n (%)) Month 3	Placebo+ CDMARD*	4/131	4 (3.05) (0.8;7.6)	- 2.3%	-3.0;3.7	NS	0.25	0.03;2.21	0.176	*CI for absolute difference calculated with Wilson procedure with uncorrected continuity*
	Tofacitinib 5 mg BID	1/131	1 (0.8) (0;4.2)							
Number of	Placebo+	32/116	27.6 (4.15)	22.4	10.2-34.6	0.0003	1.81	1.28;2.56	0.0005	Among patients with baseline

patient achieving HAQ-DI change of ≥0.35 (% (SE) Month 3	CDMARD Tofacitinib 5 mg BID	58/116	50 (4.64)							score ≥0.35.
Number of patients without structural progression (mTSS change less than 0.5)	Placebo+ CDMARD	NA	NA	NA	NA	NA	NA	NA		
	Tofacitinib 5 mg BID	NA	NA							
Number of patients achieving PASI75(%) Month 3	Placebo+ CDMARD	12/86	13.95 (3.74)	7.3	-4.3- 18.9	NS (p=0.22)	1.52	0.78;2.99	0.216	*Results were assessed among patients who had an affected body-surface area of 3% or more at baseline and who had a baseline PASI score of more than*
	Tofacitinib 5 mg BID	17/80	21.25 (4.57)							
Mean change in SF-36 PSC (LSM (SE)) Month 3	Placebo+ CDMARD	131	1.77 (0.69)	3.41	1.52-5.32	0.0005	NA	NA	NA	*Also SF-36 physical functioning, SF role functioning, SF-36 general health, SF-36 vitality and SF-36 social functioning has been reported. SF-36 PCS has been included for consistency in outcome reporting throughout the report.* *SF-36 data are from the latest publication by Strand et al. addressing PROs from Opal Broaden and Opal Beyond studies.*
	Tofacitinib 5 mg BID	131	5.18 (0.68)							
Number of patients with serious infections (n (%))	Placebo+ CDMARD*	0/131	0/NA	0/NA	-3.47;3.53/NA	NS	N/A			Following 3 months, all placebo patients were re-grouped into active arms
	Tofacitinib 5 mg BID	0/131	0/2(2)							

3/6 months			

Table A3c Results of study FUTURE 2

Trial name:	*FUTURE 2 (TNF experienced arm only)*									
NCT number:	*NCT01752634*									
				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	Odds ratio	95% CI	*P* value	
ACR50 (%) Week 24	Placebo + Optional csDMARD	35	8.6 (1.8;23.1)	18.7	0.3;36.5	<0.05	4·37 (1·05–18·26)	1.016	0·0431	
	Secukinumab 300 mg sc + optional csDMARD	33	27.3 (13.3;45.5)							
Discontinuations due to AEs	Placebo + Optional csDMARD	NA	NA	NA			NA			*Only provided for the overall group*
	Secukinumab 300 mg sc+ optional csDMARD	NA	NA							
Discontinuations due to lack of efficacy	Placebo + Optional csDMARD		NA	NA			NA			*As above*
	Secukinumab 300 mg sc+ optional csDMARD		NA							
Number of patient	Placebo + Optional		NA							Only provide change in HAQ-DI : -0.53 +/- 0.09 vs -0.23 +/- 0.11

achieving HAQ-DI change of ≥0.35	csDMARD Secukinumab 300 mg sc+ optional csDMARD		NA						(p<0.05)
Number of patients with structural progression (mTSS change less than 0.5)	Placebo + Optional csDMARD Secukinumab 300 mg sc+ optional csDMARD	NA NA	NA NA	NA			NA		
Number of patients achieving PASI75(%) at week 24	Placebo + Optional csDMARD Secukinumab 300 mg sc+ optional csDMARD	12 11	8.3 (0.2;38.5) 63.6 (30;89)	55.3	16;78	<0.05	19.25	1.8-209.6 0.0152	*PASI estimated among patients with BSA ≥ 3% at baseline. CI calculated with Wilson not corrected for continuity*
Mean change in SF-36 PSC (LSM (SE)) Week 24	Placebo + Optional csDMARD Secukinumab 300 mg sc+ optional csDMARD	35 33	2.65 (1.66) 6.56 (1.20)	3.91	NA	NA			
Number of patients with serious infections	Placebo + Optional csDMARD Secukinumab 300 mg sc+ optional csDMARD								provided only for overall population (naive and experienced)

Table A3d Results of study FUTURE 3

Trial name:	*FUTURE 3*									
NCT number:	*NCT01989468*									
				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	Odds ratio	95% CI	*P* value	
ACR50 (%) at week 24	Placebo + Optional csDMARD	44	2.3 0.1;12	18.2	4.9;32.4	<0.05	11	1.3;91.5	0.03	*Note: number of TNiF-IR patients calculated based on table 1 in Nash et al, 2017 and number of responders calculated based on % responders indicated in figure 3*
	Secukinumab 300 mg sc+ optional csDMARD	44	20.5 9.8;35.3							
Discontinuations due to AEs	Placebo + Optional csDMARD	NA		NA			NA			
	Secukinumab 300 mg sc+ optional csDMARD	NA								
Discontinuations due to lack of efficacy	Placebo + Optional csDMARD	NA		NA			NA			
	Secukinumab 300 mg sc+ optional csDMARD	NA								
Number of patient achieving HAQ-DI change of ≥0.35	Placebo + Optional csDMARD	NA		NA			NA			
	Secukinumab 300 mg sc+	NA								

	optional csDMARD			
Number of patients with structural progression (mTSS change less than 0.5)	Placebo + Optional csDMARD	NA	NA	NA	
	Secukinumab 300 mg sc+ optional csDMARD	NA		
Number of patients achieving PASI75(%)	Placebo + Optional csDMARD	NA	NA	NA	
	Secukinumab 300 mg sc+ optional csDMARD	NA		
Mean change in SF-36 (PSC)	Placebo + Optional csDMARD	NA	NA	NA	
	Secukinumab 300 mg sc+ optional csDMARD	NA		
Number of patients with serious infections	Placebo + Optional csDMARD	NA	NA	NA	
	Secukinumab 300 mg sc+ optional csDMARD	NA		

Table A3e Results of study FUTURE 5

Trial name:	*FUTURE 5*									
NCT number:	*NCT02404350*									
				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	Odds ratio	95% CI	*P* value	
ACR50(%) Week 16	Placebo + Optional csDMARD	98	7.1 (2.9;14,2)	29.7	17;42	<0.0001	7.6	3;18.8	P<0.0001	As for FUTURE 3, number of TNFi experienced patients calculated from table 1 and number of responders calculated based on % response in figure 1
	Secukinumab 300 mg sc+ optional csDMARD	68	36.8 (25.4;49.3)							
Discontinuations due to AEs	Placebo + Optional csDMARD				NA					
	Secukinumab 300 mg sc+ optional csDMARD									
Discontinuations due to lack of efficacy	Placebo + Optional csDMARD				NA					
	Secukinumab 300 mg sc+ optional csDMARD									
Number of patient achieving HAQ-DI change of ≥0.35	Placebo + Optional csDMARD				NA					
	Secukinumab 300 mg sc+									

	optional csDMARD				
Number of patients with structural progression (mTSS change less than 0.5)	Placebo + Optional csDMARD	82	NA		Only change in mTSS is reported in subgroups. The proportion of patients with no radiographic structural progression at week 24, defined as ≤0.5 change from baseline in vdH-mTSS, was higher across all secukinumab dose regimens than placebo: 191/217 (88.0%) patients in the secukinumab 300 mg (naïve and experienced) with LD group versus 218/296 (73.6%) in the placebo group
	Secukinumab 300 mg sc+ optional csDMARD	65			
Number of patients achieving PASI75(%)	Placebo + Optional csDMARD		NA		
	Secukinumab 300 mg sc+ optional csDMARD				
Mean change in SF-36 (PSC)	Placebo + Optional csDMARD		NA		
	Secukinumab 300 mg sc+ optional csDMARD				
Number of patients with serious	Placebo + Optional csDMARD		NA		

infections	Secukinumab 300 mg sc+ optional csDMARD			

1.4 Results per PICO (clinical question)

Table A4a Results referring to clinical question 1&3: Biological naïve patients with and without moderate to severe PsO

Results per outcome	*Attach forest plots and statistical results as a separate file.* *Results from the comparative analysis should be given in the table below, if possible.*							
		Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies of relevance included in the analysis	Difference (%)	CI (%)	*P* value		Credible intervals (95%	*P* value	
ACR50 Month 3 Tofacitinib 5 mg BID vs Adalimumab 40 mg EOW	OPAL BROADEN	-4.98	-17.33 - 7.37	0.4293	0.85	0.57 – 1.28	0.43	Normal Approximation to ACR50 Response Rates Up to Month 3 (FAS, Missing Response = Non-response) - Treatment Comparisons. Two-sided 95% CI and p-value are based on the normal approximation for the difference in binomial proportions. Relative risk is calculated by dividing the event rates, active vs. comparator. P-values are calculated using unadjusted Chi-Square
HAQ-DI change (mean treatment difference) Month 3 Tofacitinib 5 mg BID vs Adalimumab 40 mg EOW	OPAL BROADEN	0.00	-14.12 - 14.12	1.0000	1.00	0.77 – 1.30	1.0	Normal Approximation to HAQ-DI Response Rates (Decrease from Baseline >=0.35) Up to Month 3. Two-sided 95% CI and p-value are based on the normal approximation for the difference in binomial proportions. Subjects with baseline HAQ-DI>=0.35 were included in the analysis. Relative risk is calculated by dividing the event rates, active vs. comparator. P-values are calculated using unadjusted Chi-Square
PASI75 Month 3 Tofacitinib 5 mg BID vs Adalimumab 40 mg EOW	OPAL BROADEN	3.72	-11.55 - 18.99	0.6329	1.1	0.75 – 1.59	0.63	Normal Approximation to PASI75 Response Rates Up to Month 3. Only Subjects with baseline BSA affected >=3% (per study protocol) and baseline PASI>0 are considered. Two-sided 95% CI and p-value are based on the normal approximation for the difference in binomial proportions. Relative risk is calculated by dividing the event rates, active vs. comparator. P-values are calculated using unadjusted Chi-Square

mTSS Month 12 Tofacitinib 5 mg BID vs Adalimumab 40 mg EOW	OPAL BROADEN	1.98	-2.89 - 6.84	0.4260	0.98	0.93 – 1.03	N/A	Progressor is defined as a >0.5 increase fom baseline in mTSS. The linearly extrapolated value of mTSS at Month 12 is calculated as Y=B+((X - B)/(date of assessment - date of baseline + 1)) x 337, where X is the value obtained prior to Month 12 and B is the baseline value.Two-sided 95% CI and p-value are based on the normal approximation for the difference in binomial proportions. Relative risk is calculated by dividing the event rates, active vs. comparator. P-values are calculated using unadjusted Chi-Square

Table A4b Results referring to clinical question 2&4: Biological experienced patients with and without moderate to severe PsO

Results per outcome	*Attach forest plots and statistical results as a separate file.* *Results from the comparative analysis should be given in the table below, if possible.*							
		Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies of relevance included in the analysis	Difference	CI	*P* value		Credible intervals (95%	*P* value	
ACR50 Tofacitinib 5mg BID (Month 3) vs Secukinumab 300mcg (week 16-24)	OPAL BEYOND META FUTURE Studies	-16.9%	-23.9% - -1.5%	0.04	0.43	0.19 -0.95	0.037	Bucher analysis FUTURE META: Inverse variance method was used to combine results from 2 or more studies (FUTURE studies). Review Manager v5.3 was used for the calculation. 95% Confidence intervals were calculated in SAS or Review Manager v5.3
ACR50 Tofacitinib 5mg BID (Month 6) vs Secukinumab 300mcg (week 16-24)	OPAL BEYOND META FUTURE Studies	-13.3%	-22.2% - 6.0%	0.13	0.55	0.25 – 1.20	0.134	
PASI75 Month 3 Tofacitinib 5mg BID vs Secukinumab 300mcg	OPAL BEYOND FUTURE 2	-51.8%	-62.1% - 28.2%	0.11	0.19	0.02-1.44	0.108	

1.5 Literature search for the referenced meta-analysis

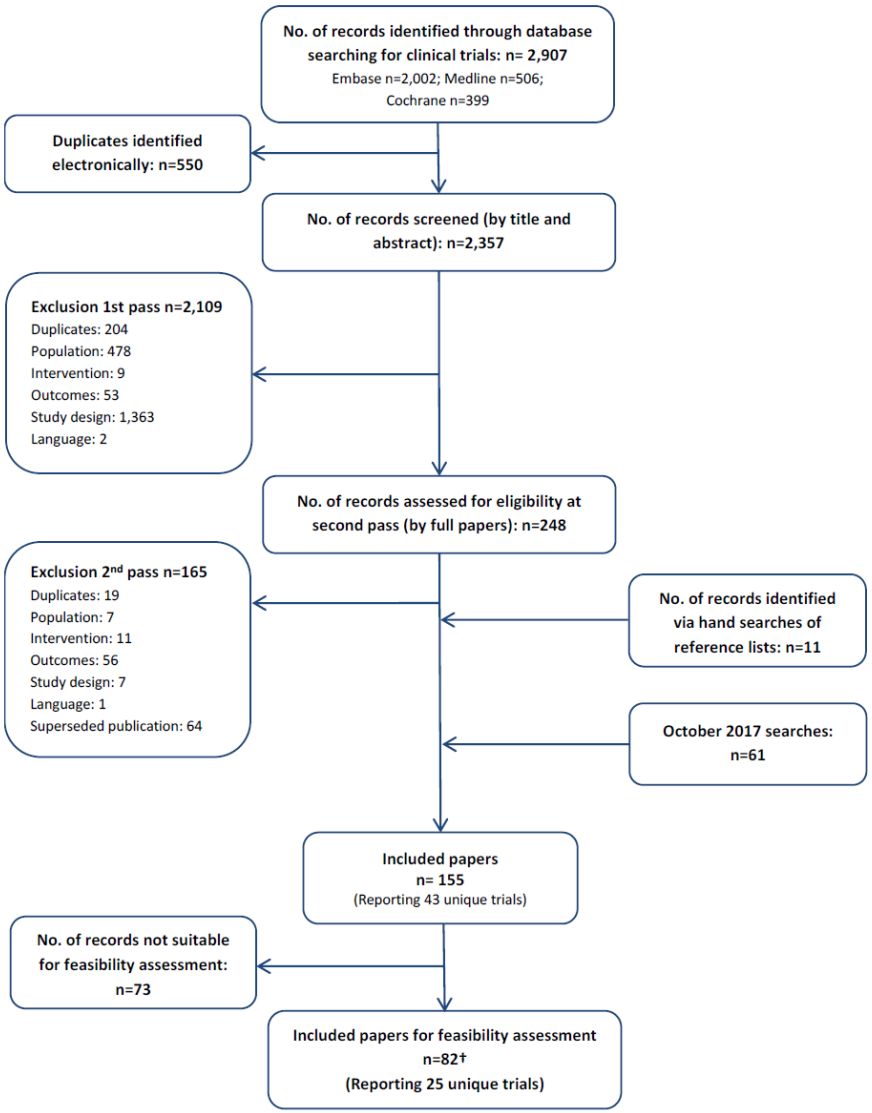
The following electronic databases, for the time period 1980-2017, were searched via the OVID platform:

- MEDLINE® In-Process & Other Non-Indexed Citations
- MEDLINE, 1946 to present
- Embase, 1980 to present
- The Cochrane Library, incorporating;
    - the Cochrane Database of Systematic Reviews (Cochrane Reviews)
    - the Database of Abstracts of Reviews of Effects (DARE)
    - the Cochrane Central Register of Controlled Trials (CENTRAL)
    - the Health Technology Assessment Database (HTA)
    - the NHS Economic Evaluation Database (NHS EED)

The SLR identified randomized controlled clinical trials (RCTs) evaluating tofacitinib, bDMARDs, csDMARDs or apremilast for the treatment of PsA. Eligible RCTs identified for inclusion were Phase 1–4, that evaluated adult patients with PsA. Treatments could be used as monotherapy or in combination with csDMARDs. Clinical outcomes included American College of Rheumatology 20 response, (ACR20), change from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI), Dactylitis Severity Score (DSS) and Leeds Enthesitis Index (LEI).

A total of 11 studies were identified for the TNFi-IR population.

PRISMA flow diagram



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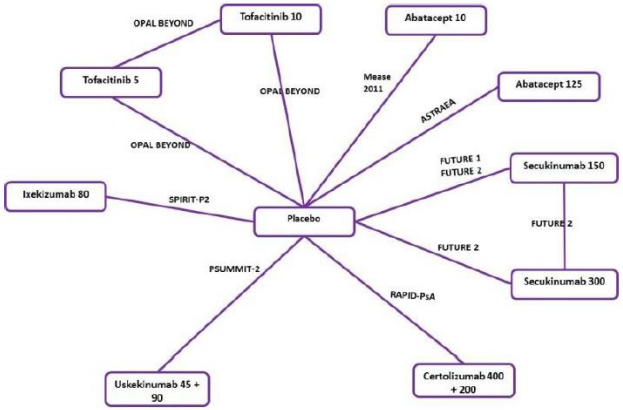
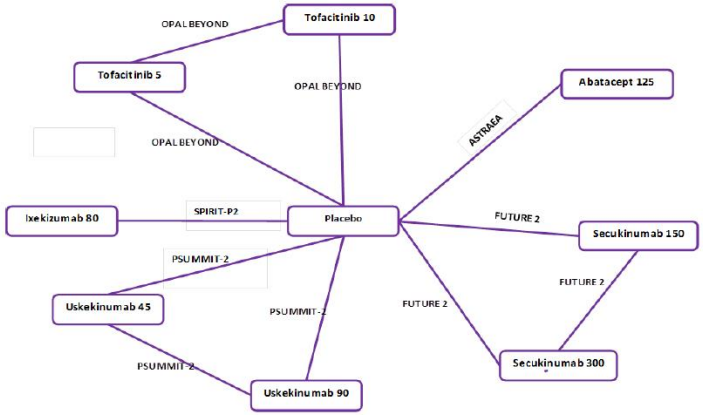
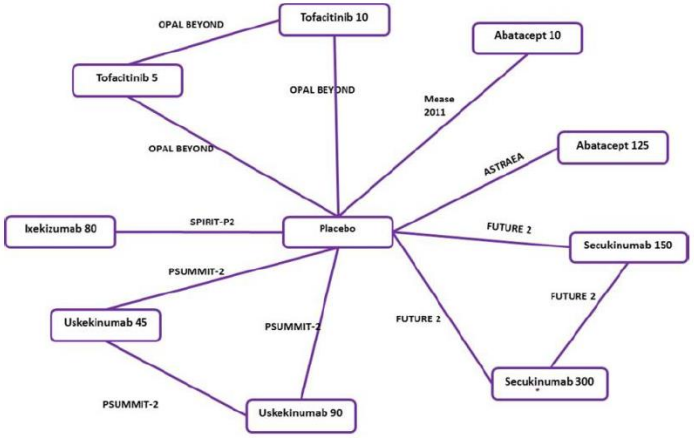
Evidence network for ACR50 in the TNFi-IR population



Evidence network foR HAQ-DI in the TNFi-IR population



Evidence network for PASI75 in the TNFi-IR population



Studies included in meta-analysis performed October 2017:
ASTRAEA (NCT01860976),
FUTURE 1 (NCT01392326)
FUTURE 2 (NCT01752634)
Mease 2011 (NCT00534313)
OPAL BEYOND (NCT01882439)
PALACE 1 (NCT01172938)
PALACE 2 (NCT01212757)
PALACE 3 (NCT01212770)
PSUMMIT 2 (NCT01077362)
RAPID-PsA (NCT01087788)
SPIRIT-P2 (NCT02349295)

Study design for studies included in NMA:

Trial	Treatment arms	Number of patients randomized	Duration of randomized treatment	Rescue therapy/details of cross-over/treatment details post placebo controlled phase	Duration of follow up	Reference
ASTRAEA (NCT01860976) Phase III, double-blind RCT	Abatacept ABA 125 mg SC weekly	213	24 weeks	Patients who had not achieved ≥20% improvement in swollen and tender joint counts from baseline to week 16 were switched to open-label abatacept weekly (early escape (EE)) for 28 weeks	52 weeks	Mease PJ, Gottlieb AB, van der Heijde D, FitzGerald O, Johnsen A, Nys M, et al. Efficacy and safety of abatacept, a T-cell modulator, in a randomized, double-blind, placebo-controlled, phase III study in psoriatic arthritis. Annals of the Rheumatic Diseases. 2017;76(9):1550-8
	Placebo	211				
FUTURE 1 (NCT01392326) Double-blind RCT 104 sites in Asia, Australia, Middle East, North America, South America, and Europe	Secukinumab 10 mg/kg at baseline, week 2, and week 4 then 75 mg SC every 4 weeks	202	52 weeks (16 weeks placebo controlled)	Patients originally randomized to placebo were randomized to secukinumab 150 mg or 75 mg at week 16 (non- responders) or 24 (responders)	52 weeks (16 weeks for the placebo controlled period)	Mease PJ, McInnes IB, Kirkham B, Kavanaugh A, Rahman P, van der Heijde D, et al. Secukinumab Inhibition of Interleukin-17A in Patients with Psoriatic Arthritis. The New England journal of medicine. 2015 01 Oct;373(14):1329-39
	Secukinumab 10 mg/kg at baseline, week 2, and week 4 then 150 mg SC every 4 weeks	202				
	Placebo	202				
FUTURE 2 (NCT01752634) Double-blind RCT 76 sites in Asia, Australia, North America, and Europe	Secukinumab 75 mg SC weekly for 4 weeks then every 4 weeks	99	52 weeks (16 weeks placebo controlled)	Patients originally randomized to placebo were randomized to secukinumab 300 or 150 mg at week every 4 weeks from week 16 (non-responders) or 24 (responders)	52 weeks	McInnes IB, Mease PJ, Kirkham B, Kavanaugh A, Ritchlin CT, Rahman P, et al. Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomized, double-blind, placebo-controlled, phase 3 trial. Lancet. 2015 Sep 19;386(9999):1137-46
	Secukinumab 150 mg SC weekly for 4 weeks then every 4 weeks	100				
	Secukinumab 300 mg SC weekly for 4 weeks then every 4 weeks	100				
	Placebo	98				

Trial	Treatment arms	Number of patients randomized	Duration of randomized treatment	Rescue therapy/details of cross-over/treatment details post placebo controlled phase	Duration of follow up	Reference
GO-REVEAL (NCT00265096) Phase III, double-blind RCT 58 sites in USA, UK, and Canada	Golimumab 50 mg SC at week 0, 4, 8, 12, 16 and 20	146	24 weeks	After 16 weeks patients with <10% improvement in both swollen and tender joint counts entered early escape with dose escalations	24 weeks (active treatment for all patients provided at 24 weeks)	Kavanaugh A, McInnes IB, Krueger GG, Gladman D, Beutler A, Gathany T, et al. Patient-reported outcomes and the association with clinical response.. Arthritis care & research. 2013 Oct;65(10):1666-73.
	Golimumab 100 mg at week 0, 4, 8, 12, 16 and 20	146				Kavanaugh A, McLnnes I, Mease P, Krueger GG, Gladman D, Gomez-Reino J, et al. Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis. Arthritis and Rheumatism. 2009 April;60(4):976-86
	Placebo	113				
Mease 2011 (NCT00534313) Phase II, double-blind RCT	Abatacept 3 mg/kg as 30-minute IV infusions on days 1, 15, and 29, and every 28 days thereafter	45	6 month	Patients across all treatment arms who completed the 6-month double-blind period were given the weight-tiered dose of 10 mg/kg, administered monthly starting on day 169, for the duration of the 18-month open label period.	18 months	Mease P, Genovese MC, Gladstein G, Kivitz AJ, Ritchlin C, Tak PP, et al. Abatacept in the treatment of patients with psoriatic arthritis: results of a six-month, multicenter, randomized, double-blind, placebo-controlled, phase II trial. Arthritis and Rheumatism. 2011 Apr;63(4):939-48.
	Abatacept ABA 10 mg/kg as 30-minute IV infusions on days 1, 15, and 29, and every 28 days thereafter	40				
	Abatacept 30/10 mg/kg as 30-minute IV infusions on days 1, 15, and 29, and every 28 days thereafter	43				
	Placebo as 30-minute IV infusions on days 1, 15, and 29, and every 28 days thereafter	42				

Trial	Treatment arms	Number of patients randomized	Duration of randomized treatment	Rescue therapy/details of cross-over/treatment details post placebo controlled phase	Duration of follow up	Reference
PALACE 1 (NCT01172938) Phase III, double-blind RCT 83 sites in 13 countries	Apremilast 20 mg oral twice daily	168	4.5 years (24 weeks for placebo controlled period)	After week 16 patients without ≥20% reduction in swollen and tender joint counts were required to be re-randomized equally to either apremilast dose if initially randomized to placebo or remained on their initial apremilast dose	5 years (as per the trial design but available data up to 24 weeks)	Kavanaugh A, Mease PJ, Gomez-Reino JJ, Adebajo AO, Wollenhaupt J, Gladman DD, et al. Treatment of psoriatic arthritis in a phase 3 randomized, placebo-controlled trial with apremilast, an oral phosphodiesterase 4 inhibitor. Annals of the Rheumatic Diseases. 2014 Jun;73(6):1020-6.
	Apremilast 30 mg oral twice daily	168				
	Placebo	168				
PALACE 2 (NCT01212757) Phase III	Apremilast 20 mg twice daily	163	52 weeks (24 weeks placebo controlled)	At week 16, pts with <20% reduction in swollen and tender joint counts qualified for protocol-defined early escape; those on placebo were re-randomized to apremilast and those on apremilast remained on the initial dose. At week 24, all remaining placebo patients were re-randomized to apremilast through week 52.	52 weeks	Cutolo M, Myerson GE, Fleischmann RM, Liote F, Diaz-Gonzalez F, Van Den Bosch F, et al. Long-term (52-week) results of a phase 3, randomized, controlled trial of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with psoriatic arthritis (PALACE 2). Arthritis and Rheumatism. 2013;65(25).
	Apremilast 30 mg twice daily	162				
	Placebo	159				
PALACE 3 (NCT01212770) (19) Phase III, double-blind RCT	Apremilast 20 mg twice daily	169	52 weeks (16 weeks placebo controlled)	Patients whose swollen and tender joint counts had not improved by ≥ 20% at week 16 were randomized to apremilast 20 or 30 mg BID if originally randomized to placebo or continued on their initial apremilast dose. At 24 weeks the remaining placebo patients were randomized to active treatments.	52 weeks (16 week placebo controlled period)	Edwards CJ, Blanco FJ, Crowley J, Birbara CA, Jaworski J, Aelion J, et al. Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with psoriatic arthritis and current skin involvement: a phase III, randomized, controlled trial (PALACE 3). Annals of the Rheumatic Diseases. 2016 Jun;75(6):1065-73
	Apremilast 30 mg twice daily	167				
	Placebo	169				

Trial	Treatment arms	Number of patients randomized	Duration of randomized treatment	Rescue therapy/details of cross-over/treatment details post placebo controlled phase	Duration of follow up	Reference
PSUMMIT 2 (NCT01077362) (20) Double-blind RCT 104 sites in Australia, Europe, and North America	Ustekinumab 45 mg SC at baseline, week 4 and then every 12 weeks	103	52 weeks (16 weeks placebo controlled)	At week 16, patients with <5% improvement in tender and swollen joints entered blinded early escape; patients receiving placebo switched to ustekinumab 45 mg, those receiving ustekinumab 45 mg increased to 90mg and patients receiving ustekinumab 90mg continued with blinded 90 mg dosing. Placebo patients who did not EE crossed over to receive ustekinumab 45 mg at week 24, week 28 and week 40.	60 weeks	Ritchlin C, Rahman P, Kavanaugh A, McInnes IB, Puig L, Li S, et al. Efficacy and safety of the anti-IL-12/23 p40 monoclonal antibody, ustekinumab, in patients with active psoriatic arthritis despite conventional non-biological and biological anti-tumor necrosis factor therapy. Annals of the Rheumatic Diseases. 2014 Jun;73(6):990-9
	Ustekinumab 90 mg SC at baseline, week 4 and then every 12 weeks†	105				
	Placebo	104				
RAPID-PsA (NCT01087788) Double-blind RCT to week 24, dose-blind to week 48, and then open-label to week 216 92 Sites in Europe, North America, and Latin America	Certolizumab 400 mg SC at week 0, 2, and 4 then 200 mg SC every 2 weeks	138	216 weeks (16 weeks placebo controlled)	Placebo patients who failed to achieve a 10% improvement from baseline in both swollen and tender joints at weeks 14 and 16 underwent mandatory escape to active treatment in a blinded manner. These patients were re-randomized to active treatment at week 16 in a 1:1 ratio, receiving loading doses at weeks 16, 18 and 20. All CZP patients continued to receive the initially assigned dose.	216 weeks (16 weeks placebo controlled)	Mease PJ, Fleischmann R, Deodhar AA, Wollenhaupt J, Khraishi M, Kielar D, et al. Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24-week results of a Phase 3 double-blind randomized placebo-controlled study (RAPID-PsA). Annals of the Rheumatic Diseases. 2014 Jan;73(1):48-55
	Certolizumab 400 mg SC at week 0, 2, and 4 then 400 mg SC every 4 weeks	135				
	Placebo	136				
SPIRIT-P2 (NCT02349295) (21) Phase III RCT, double blind study 109 centres across ten countries in Asia, Australia, Europe, and	Ixekizumab 80 mg every 4 weeks following 160 mg initial dose	122	24 weeks	Patients with an inadequate response at week 16 were required to add or modify concomitant drugs. Inadequate responders continued taking their originally assigned dose of ixekizumab or, if receiving placebo, were re-randomized to ixekizumab every 2 weeks or every 4 weeks in a 1:1 ratio	24 weeks	Nash P, Kirkham B, Okada M, Rahman P, Combe B, Burmester GR, et al. Ixekizumab for the treatment of patients with active psoriatic arthritis and an inadequate response to tumour necrosis factor inhibitors: results from the 24-week randomized, double-blind, placebo-controlled period of the SPIRIT-
	Ixekizumab 80 mg every 2 weeks following 160 mg initial dose	123				

Trial	Treatment arms	Number of patients randomized	Duration of randomized treatment	Rescue therapy/details of cross-over/treatment details post placebo controlled phase	Duration of follow up	Reference
North America						P2 phase 3 trial. Lancet (London, England). 2017;389(10086):2317-27
	Placebo	118				
OPAL BEYOND Double-blind, Phase III RCT 103 sites from 14 countries	Tofacitinib 5 mg BID	130	3 months	After 3 months patients in the placebo arms were advanced to tofacitinib 5 mg or 10 mg BID (determined by group at randomization)	6 months for the double blind extension period (3 month double blind placebo controlled)	Gladman D, Rigby W, Azevedo VF, Behrens F, Blanco R, Kaszuba A, et al. Tofacitinib for Psoriatic Arthritis in Patients with an Inadequate Response to TNF Inhibitors. N Engl J Med. 2017;377(16):1525-36
	Tofacitinib 10 mg BID	130				
	Placebo (two groups of 65 patients at randomization)	130				

1.6 Literature search for clinical Question 1 and 3 (TNFi naïve patients)

Original search performed 29.06.2018.

Updated search performed 25.04.2019 did not identify additional clinical studies of relevance for this application.

Pubmed search (all fields):

((((("tofacitinib"[Supplementary Concept] OR "tofacitinib"[All Fields]) OR ("tofacitinib"[Supplementary Concept] OR "tofacitinib"[All Fields] OR "xeljanz"[All Fields])) OR ("tofacitinib"[Supplementary Concept] OR "tofacitinib"[All Fields] OR "cp 690550"[All Fields])) AND (("adalimumab"[MeSH Terms] OR "adalimumab"[All Fields]) OR ("adalimumab"[MeSH Terms] OR "adalimumab"[All Fields] OR "humira"[All Fields]))) AND ((("arthritis, psoriatic"[MeSH Terms] OR ("arthritis"[All Fields] AND "psoriatic"[All Fields]) OR "psoriatic arthritis"[All Fields] OR ("psoriatic"[All Fields] AND "arthritis"[All Fields])) OR (("psoriasis"[MeSH Terms] OR "psoriasis"[All Fields]) AND ("arthritis"[MeSH Terms] OR "arthritis"[All Fields]))) OR PsA[All Fields])

A total of 20 publications were identified using above search string.

Search string Cochrane central:

#1: Tofacitinib or Xeljanz:

#2: Adalimumab or Humira

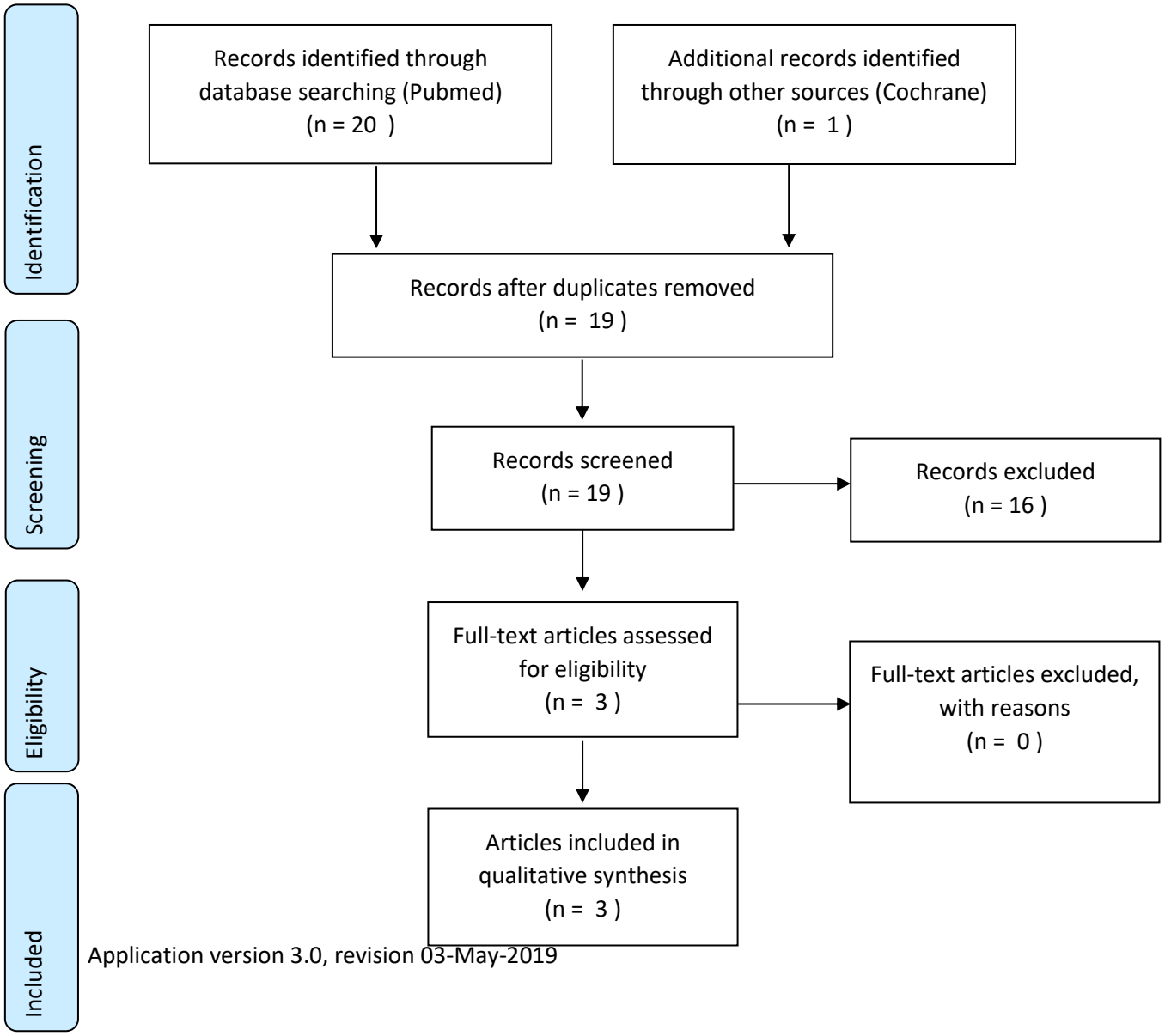
#3: Psoriatic arthritis

#4: #1 AND #3

#5: #2 AND #3

#6: #4 AND #5

PRISMA Flow Diagram



1.7 Literature search for clinical Question 2 and 4

Search performed 29-06-2018 (biological experienced PsA patients)

Updated search on 25.04.2019 did not identify additional clinical studies of relevance for this application.

PubMed Search string: All field search, no time restriction:

((((("tofacitinib"[Supplementary Concept] OR "tofacitinib"[All Fields]) OR ("tofacitinib"[Supplementary Concept] OR "tofacitinib"[All Fields] OR "xeljanz"[All Fields])) OR ("tofacitinib"[Supplementary Concept] OR "tofacitinib"[All Fields] OR "cp 690550"[All Fields])) AND ((("arthritis, psoriatic"[MeSH Terms] OR ("arthritis"[All Fields] AND "psoriatic"[All Fields]) OR "psoriatic arthritis"[All Fields] OR ("psoriatic"[All Fields] AND "arthritis"[All Fields])) OR (("psoriasis"[MeSH Terms] OR "psoriasis"[All Fields]) AND ("arthritis"[MeSH Terms] OR "arthritis"[All Fields]))) OR PsA[All Fields])) OR ((("secukinumab"[Supplementary Concept] OR "secukinumab"[All Fields]) OR ("secukinumab"[Supplementary Concept] OR "secukinumab"[All Fields] OR "cosentyx"[All Fields])) AND ((("arthritis, psoriatic"[MeSH Terms] OR ("arthritis"[All Fields] AND "psoriatic"[All Fields]) OR "psoriatic arthritis"[All Fields] OR ("psoriatic"[All Fields] AND "arthritis"[All Fields])) OR (("psoriasis"[MeSH Terms] OR "psoriasis"[All Fields]) AND ("arthritis"[MeSH Terms] OR "arthritis"[All Fields]))) OR PsA[All Fields])

A total of 276 publications where identified using above search string.

Using the alternative MeSH string: ("tofacitinib"[Supplementary Concept] AND "arthritis, psoriatic"[MeSH Terms]) OR ("secukinumab"[Supplementary Concept] AND "arthritis, psoriatic"[MeSH Terms]) 58 publications where identified, all of which were included in above search results

Cochrane search string, no time restriction

#1: Tofacitinib OR Xeljanz

#2: Secukinumab OR Cosentyx

#3: Psoriatic arthritis

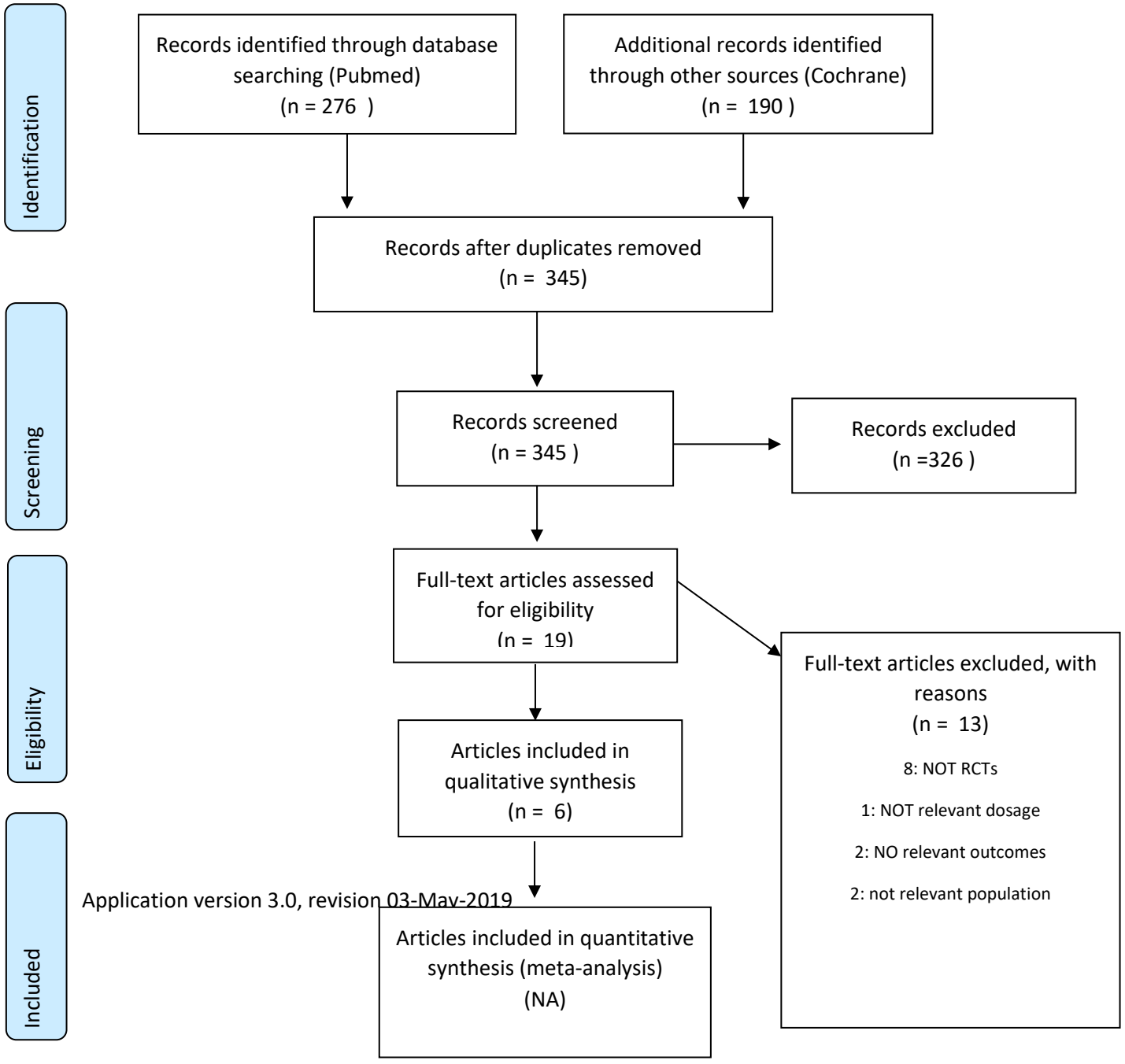
#4: #1 AND #3

#5: #2 AND #3

#6: #4 OR #5

There were a total of 190 results: 181 results from 1282920 records for #6 in Trials, 7 cochrane reviews and 2 technology assessments

PRISMA Flow Diagram



Exclusion list from literature search:

1. McInnes IB, Mease PJ, Schett G, Kirkham B, Strand V, Williams N, Fox T, Pricop L, Jugl SM, Gandhi KK; FUTURE 2 Study Group. Secukinumab provides rapid and sustained pain relief in psoriatic arthritis over 2 years: results from the FUTURE 2 study. Arthritis Res Ther. 2018 Jun 7;20(1):113. doi: 10.1186/s13075-018-1610-3. PubMed PMID: 29880010; PubMed Central PMCID: PMC5992664. Full text as relevant dose and RCT.

2. Matos da Cunha B. Are the loading dose treatment groups superior to the 150 mg without loading dose group in the secukinumab FUTURE 5 study? Ann Rheum Dis. 2018 May 31. pii: annrheumdis-2018-213770. doi: 10.1136/annrheumdis-2018-213770. [Epub ahead of print] PubMed PMID: 29853450.

3. Aletaha D, Kerschbaumer A, Smolen JS. Tofacitinib for Psoriatic Arthritis. N Engl J Med. 2018 Feb 22;378(8):775. doi: 10.1056/NEJMc1715189. PubMed PMID: 29469555.

4. Mease P, Gladman D. Tofacitinib for Psoriatic Arthritis. N Engl J Med. 2018 Feb 22;378(8):775-776. doi: 10.1056/NEJMc1715189. PubMed PMID: 29466165.

5. Coates LC, Mease PJ, Gossec L, Kirkham B, Sherif B, Gaillez C, Mpofu S, Jugl SM, Karyekar C, Gandhi KK. Minimal Disease Activity among Active Psoriatic Arthritis Patients Treated with Secukinumab: 2-year Results from the FUTURE 2 Study. Arthritis Care Res (Hoboken). 2018 Feb 6. Doi: 10.1002/acr.23537. [Epub ahead of print] PubMed PMID: 29409133

6. Onuora S. Spondyloarthropathies: Tofacitinib shows promise in PsA trials. Nat Rev Rheumatol. 2017 Dec 19;14(1):4. doi: 10.1038/nrrheum.2017.183. PubMed PMID: 29255210

7. Mease P, Hall S, FitzGerald O, van der Heijde D, Merola JF, Avila-Zapata F, Cieślak D, Graham D, Wang C, Menon S, Hendrikx T, Kanik KS. Tofacitinib or Adalimumab versus Placebo for Psoriatic Arthritis. N Engl J Med. 2017 Oct 19;377(16):1537-1550. doi: 10.1056/NEJMoa1615975. PubMed PMID: 29045212

8. McInnes IB, Mease PJ, Ritchlin CT, Rahman P, Gottlieb AB, Kirkham B, Kajekar R, Delicha EM, Pricop

L, Mpofu S. Secukinumab sustains improvement in signs and symptoms of psoriatic arthritis: 2 year results from the phase 3 FUTURE 2 study. Rheumatology (Oxford). 2017 Nov 1;56(11):1993-2003. doi: 10.1093/rheumatology/kex301. PubMed PMID: 28968735; PubMed Central PMCID: PMC5850284. Selected.

9. Kammüller M, Tsai TF, Griffiths CE, Kapoor N, Kolattukudy PE, Brees D, Chibout SD, Safi J Jr, Fox T. Inhibition of IL-17A by secukinumab shows no evidence of increased Mycobacterium tuberculosis infections. Clin Transl Immunology. 2017 Aug 25;6(8):e152. doi: 10.1038/cti.2017.34. eCollection 2017 Aug. PubMed PMID: 28868144; PubMed Central PMCID: PMC5579471

10. Mease PJ, McInnes IB, Kirkham B, Kavanaugh A, Rahman P, van der Heijde D, Landewé R, Nash P, Pricop L, Yuan J, Richards HB, Mpofu S; FUTURE 1 Study Group. Secukinumab Inhibition of Interleukin-17A in Patients with Psoriatic Arthritis. N Engl J Med. 2015 Oct;373(14):1329-39. doi: 10.1056/NEJMoa1412679. PubMed PMID: 26422723

11. Duarte JH. Therapy: Secukinumab improves symptoms of psoriatic arthritis. Nat Rev Rheumatol. 2015 Sep;11(9):503. doi: 10.1038/nrrheum.2015.99. Epub 2015 Jul 14. PubMed PMID: 26168911.

12. Helliwell P, Coates L. Interleukin-17 inhibition in psoriatic arthritis. Lancet. 2015 Sep 19;386(9999):1114-6. doi: 10.1016/S0140-6736(15)61170-9. Epub 2015 Jun 28. PubMed PMID: 26135705.

13. Rahman P , Strand V , McInnes IB , Marzo-Ortega H , Dokoupilova E , Churchill M , Kandala S , Pricop L and Mpofu S, Secukinumab improves physical function, quality of life, fatigue and work productivity in patients with active psoriatic arthritis in future 2, a phase 3 trialAnnals of the rheumatic diseases., 2015, 74, 356

Protokol for vurdering af den kliniske merværdi af tofacitinib til behandling af psoriasisartrit

Handelsnavn	Xeljanz
Generisk navn	Tofacitinib
Firma	Pfizer
ATC kode	L04AA29
Virkningsmekanisme	Janus Kinase inhibitor
Administration/dosis	Tabletter 5 mg 2 gange dagligt.
EMA Indikation	*Xeljanz in combination with MTX is indicated for the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy.*
Godkendelsesdato Offentliggørelsesdato Dokumentnummer Versionsnummer	28/5-18 28/5-18 19683 1.0
Fagudvalget og sekretariatets arbejdsgruppe	Sammensætningen findes i bilag 1

Indhold

Forkortelser

ACR	*American College of Rheumatology*
ARR	Absolut Risiko Reduktion
CI	*Confidence Interval* eller Konfidensinterval
CRP	C-reaktivt protein
csDMARD	*Conventional Synthetic Disease Modifying Antirheumatic Drug*
DMARD	*Disease Modifying Antirheumatic Drug*
DRS	Dansk Reumatologisk Selskab
EMA	*European Medicines Agency*
EPAR	*EMAs Public Assessment Report*
GRADE	System til vurdering af evidens (*Grading of Recommendations Assessment, Development and Education)*
HAQ-DI	*Health Assessment Questionnaire Disability Index*
HR	Hazard Ratio
ITT	*Intention To Treat*
JAK	Janus kinase
mTSS	*modified Total Sharp Score*
MTX	Methotrexat
OR	*Odds Ratio*
PASI	*Psoriasis Area Severity Index*
PsA	Psoriasisartrit
RR	Relativ Risiko
TNF	*Tumor Necrosis Factor*
VAS	*Visual Analogue Scale*

1 Formål

Protokollen har til formål at definere de kliniske spørgsmål, der ønskes belyst i vurderingen af tofacitinib som mulig standardbehandling til psoriasisartrit (PsA). I protokollen angives en definition af populationer, komparator og effektmål, der skal præsenteres i den endelige ansøgning, samt de metoder der ønskes anvendt i den komparative analyse. Arbejdet med protokollen er igangsat på baggrund af den foreløbige ansøgning vedrørende tofacitinib modtaget den 18. april 2018.

Protokollen danner grundlaget for den endelige ansøgning for vurderingen af den kliniske merværdi af tofacitinib sammenlignet med dansk standardbehandling. Alle effektmål, der er opgivet i denne protokol, skal besvares med en sammenlignende analyse mellem tofacitinib og komparator 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.

2 Baggrund

PsA er en kronisk inflammatorisk ledsygdom, der ofte (men ikke nødvendigvis) optræder sammen med den kroniske hudsygdom psoriasis [1]. Patogenesen er en T-celle medieret inflammation af leddenes synovialmembraner, som også kan være rettet mod rygsøjlen og senernes vedhæftning til knoglerne. Sygdommen betragtes som multifaktoriel og er betinget af både genetiske og miljømæssige faktorer [2].

PsA kan således både manifestere sig ved inflammation i perifere led og i rygsøjlen, og der kan desuden optræde ekstra-artikulære symptomer som inflammation i senetilhæftninger (entesit), hævede fingre eller tæer (daktylit) og negledystrofi [3]. Patienterne kan også have betændelse i øjets regnbue- og årehinde (uveitis) eller kronisk inflammatorisk tarmsygdom. Det kan være vanskeligt at skelne diagnostisk mellem PsA og spondylartrit af anden art.

I den nationale behandlingsvejledning for PsA fra Dansk Reumatologisk Selskab beskrives, at der mangler validerede kliniske diagnosekriterier for PsA, men at der er udviklet klassifikationskriterier, som kan benyttes som støtte. Diagnosen stilles på baggrund af objektiv undersøgelse af bevægeapparat og hud, sammen med serologi og biokemi [3].

Prævalensen er svær at estimere grundet manglen på klare diagnostiske kriterier, men den estimeres at være på 0,1 %. Det skønnes, at op til ca. 15 % af patienter med psoriasis udvikler PsA [3]. Sygdommen debuterer oftest i alderen 40-50 år, og prævalensen er ens for mænd og kvinder.

2.1 Nuværende behandling

Den nuværende behandling af patienter med artrit er dels smertelindrende, dels sygdomsmodificerende. Sygdomsmodificerende behandling (*disease modifying antirheumatic drugs* (DMARDs)) gives ved betydelig affektion af led. Til patienter med lav sygdomsaktivitet og lav risiko for progressiv ledsygdom (under 5 led) anvendes monoterapi med lægemidler af typen konventionelle DMARDs (csDMARDs), hvor methotrexat (MTX) sædvanligvis er førstevalg i dansk klinisk praksis [3].

Ved patienter med betydelig ledaffektion (mere end fire led) eller ved utilstrækkelig effekt af csDMARDs, eventuelt i kombination med lokale steroidinjektioner [1], kan biologisk behandling indledes. Kriterierne for at indlede biologisk behandling omfatter sygdomsaktivitet, fravær af kontraindikationer, og at beslutningen træffes på konference med speciallæger i reumatologi [3].

Af biologisk behandling benyttes på nuværende tidspunkt TNF-alfa hæmmerne infliximab, adalimumab, etanercept, certolizumab og golimumab. Desuden benyttes ustekinumab, som er et monoklonalt antistof mod interleukin 12 og interleukin 23, samt secukinumab, der er et monoklonalt antistof mod interleukin 17A.

2.2 Tofacitinib

Tofacitinib virker ved at binde sig til og hæmme Janus kinase-familiens enzymer. Den anbefalede dosis forventes at være 5 mg 2 gange dagligt. Tofacitinib gives som tablet, og patienten kan selv administrere behandlingen.

3 Kliniske spørgsmål

De kliniske spørgsmål skal indeholde specifikation af patientgruppen, interventionen, alternativet/erne til interventionen og effektmål. Følgende opdeling af patientpopulationer og komparatorer benyttes i denne vurdering:

	Bionaive (patienter der ikke har modtaget biologisk behandling tidligere)	**Bioerfarne (patienter der tidligere har modtaget biologisk behandling)**
Patienter med PsA	Klinisk spørgsmål 1 Komparator er adalimumab	Klinisk spørgsmål 2 Komparator er secukinumab
Patienter med PsA og moderat til svær plaque-psoriasis	Klinisk spørgsmål 3 Komparator er adalimumab	Klinisk spørgsmål 4 Komparator er secukinumab

Tabel 1 Oversigt over patientpopulationer og komparatorer ved de kliniske spørgsmål

3.1 Klinisk spørgsmål 1: Hvilken klinisk merværdi tilbyder tofacitinib til bionaive patienter med PsA uden samtidig moderat til svær plaque psoriasis, sammenlignet med adalimumab?

Population

Patienter med PsA **uden** moderat til svær plaque psoriasis, som opfylder kriterierne for biologisk behandling, og som endnu ikke har modtaget biologisk behandling.

Intervention

Tofacitinib 5 mg 2 gange dagligt.

Komparator

Adalimumab i den anbefalede dosis (subkutan injektion á 40 mg hver 14. dag).

Den valgte komparator beror på det foreliggende dokumentationsgrundlag og den gældende behandlingsvejledning [4], hvor adalimumab er fundet ligestillet med infliximab, etanercept, certolizumab, golimumab og secukinumab (150 mg), der alle anbefales som førstelinjebehandlinger.

Effektmål

Kritiske og vigtige effektmål kan ses i tabel 2.

3.2 Klinisk spørgsmål 2: Hvilken klinisk merværdi tilbyder tofacitinib til bioerfarne patienter med PsA uden samtidig moderat til svær plaque psoriasis, sammenlignet med secukinumab?

Population

Patienter med PsA **uden** moderat til svær plaque psoriasis, som opfylder kriterierne for biologisk behandling, og som tidligere har modtaget biologisk behandling.

Intervention

Tofacitinib 5 mg 2 gange dagligt.

Komparator

Secukinumab i den anbefalede dosis til bioerfarne patienter (subkutan injektion á 300 mg uge 0,1,2,3,4 og herefter månedligt) er valgt som komparator, da dette lægemiddel har en anden virkningsmekanisme end TNF-hæmmerne og er anbefalet i 2. linje efter bl.a. en række TNF-hæmmere.

Effektmål

Kritiske og vigtige effektmål kan ses i tabel 2.

3.3 Klinisk spørgsmål 3: Hvilken klinisk merværdi tilbyder tofacitinib til bionaive patienter med PsA og samtidig moderat til svær plaque psoriasis, sammenlignet med adalimumab?

Population

Patienter med PsA **med** moderat til svær plaque psoriasis, som opfylder kriterierne for biologisk behandling, og som endnu ikke har modtaget biologisk behandling.

Intervention

Tofacitinib 5 mg 2 gange dagligt.

Komparator

Adalimumab i den anbefalede dosis (subkutan injektion á 40 mg hver 14. dag).

Den valgte komparator beror på det foreliggende dokumentationsgrundlag og den gældende behandlingsvejledning [4], hvor adalimumab er fundet ligestillet med infliximab og secukinumab, der begge anbefales som 1. linjebehandlinger [1].

Effektmål

Kritiske og vigtige effektmål kan ses i tabel 2.

3.4 Klinisk spørgsmål 4: Hvilken klinisk merværdi tilbyder tofacitinib til bioerfarne patienter med PsA og samtidig moderat til svær plaque psoriasis, sammenlignet med secukinumab?

Population

Patienter med PsA **med** moderat til svær psoriasis, som opfylder kriterierne for biologisk behandling, og som tidligere har modtaget biologisk behandling.

Intervention

Tofacitinib 5 mg 2 gange dagligt.

Komparator

Secukinumab i den anbefalede dosis til bioerfarne patienter (subkutan injektion á 300 mg uge 0,1,2,3,4 og herefter månedligt) er valgt som komparator, da dette lægemiddel har en anden virkningsmekanisme end TNF-hæmmerne, og er anbefalet som 1. linje 2. valg efter infliximab (TNF-hæmmer) [1].

Effektmål

Kritiske og vigtige effektmål kan ses i tabel 2.

3.5 Valg af effektmål

Tabel 2 summerer de valgte effektmål, deres vigtighed, mindste kliniske 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.

Fagudvalget har i sit valg af effektmål tilstræbt konsistens med de relevante effektmål, måleenheder og mindste klinisk relevante forskelle for vurderinger af lægemidler til reumatoid artrit (jf. protokollen for sarilumab til reumatoid artrit). Dette er suppleret med et effektmål for hudaffektion, hvor PASI75 er valgt. Her er valgt samme mindste klinisk relevante forskel som for vurdering af lægemidler til psoriasis (jf. protokoller for guselkumab og brodalumab til psoriasis).

Effektmål	**Vigtighed**	**Kategori**	**Måleenhed**	**Mindste klinisk relevante forskelle (absolutte værdier)**
American College of Rheumatology respons (ACR50)	Kritisk	Alvorlige symptomer og bivirkninger	Andel patienter	Forskel på 15 procentpoint mellem grupperne
Behandlingsophør grundet uønskede hændelser	Vigtig	Alvorlige symptomer og bivirkninger	Andel patienter	Forskel på 5 procentpoint mellem grupperne
Behandlingsophør grundet manglende effekt	Vigtig	Behandlingsophør grundet manglende effekt	Andel Patienter	Forskel på 10 procentpoint mellem grupperne
Health Assessment Questionnaire Disability Index (HAQ-DI)	Vigtig	Alvorlige symptomer og bivirkninger	Andel patienter der opnår en ændring på 0,22 point på scoren	Forskel på 15 procentpoint mellem grupperne
Modified Total Sharp Score (mTSS)	Vigtig	Alvorlige symptomer og bivirkninger	Andel patienter uden progression	Forskel på 10 procentpoint mellem grupperne.
Psoriatic Area and Severity Index (PASI75)*	Vigtig	Alvorlige symptomer og bivirkninger	Andel patienter	Forskel på 15 procentpoint mellem grupperne
SF-36	Vigtig	Helbredsrelateret livskvalitet	Gennemsnitlig ændring	Forskel på 0.5 SD mellem grupperne
Alvorlige infektioner	Vigtig	Alvorlige symptomer og bivirkninger	Andel patienter	Forskel på 5 procentpoint mellem grupperne

Tabel 2 Oversigt over valgte effektmål. For hver effektmål er angivet deres vigtighed. For kritiske og vigtige effektmål er desuden angivet den mindste kliniske relevante forskel samt indplacering i de fire kategorier (overlevelse, alvorlige symptomer og bivirkninger, livskvalitet og ikke-alvorlige symptomer og bivirkninger).
* Kun for klinisk spørgsmål 3 og 4, hvor patienterne har PsA og moderat til svær plaque psoriasis

Den samlede kliniske merværdi af tofacitinib baseres på en tidshorisont på 12 måneder.

3.5.1 Kritiske effektmål

American College of Rheumatology respons (ACR50)

Det primære mål for effekt er ACR50. Dette er defineret som en 50 % forbedring i både ømme og hævede led, samt 50 % forbedring inden for mindst tre ud af følgende fem kategorier: patientens overordnede vurdering (Visual Assessment Scale (VAS) global), patientens vurdering af smerte, lægens overordnede vurdering (VAS doctor), HAQ-DI score og C-Reaktivt Protein (CRP). Fagudvalget vurderer, at en 50 % 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 (tofacitinib vs. komparator) på 15 procentpoint.

3.5.2 Vigtige effektmål

Behandlingsophør grundet uønskede hændelser

Det er fagudvalgets vurdering, at uønskede hændelser, der fører til ophør af behandlingen, er et brugbart surrogatmål for den samlede tyngde af bivirkninger. Den mindste klinisk relevante forskel defineres som en forskel på 5 procentpoint mellem grupperne.

Behandlingsopgør grundet manglende effekt

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. Fagudvalget vurderer, at en forskel på 10 procentpoint mellem grupperne er klinisk relevant.

*Health Assessment Questionnaire DIsability Index (*HAQ-DI)

Dette er inkluderet som et mål for patienternes invaliditet/funktionstab. Det er et domænespecifikt instrument, der er pålideligt, velundersøgt og valideret [5]. HAQ-DI er valgt grundet stor relevans for gigtpatienter, 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 [6].

SF-36

Fagudvalget vurderer, at kun få sygdomsspecifikke livskvalitetsmål er valideret for populationen af patienter med PsA. Derfor ønsker fagudvalget livskvalitet rapporteret for det generiske instrument SF-36. Såfremt der ikke findes data fra SF-36, kan andre instrumenter anvendes, eksempelvis global VAS. I så fald bedes ansøger redegøre for valg og validitet af instrument. For helbredsrelateret livskvalitet anvendes ofte en mindste klinisk relevant forskel på 0,5 standarddeviationer (SD) [7], og fagudvalget har derfor angivet en ændring på 0,5 SD som mindste klinisk relevant forskel.

Modified Total Sharp Score (mTTS)

Fagudvalget ønsker at benytte et radiografisk effektmål, der kan tolkes som udtryk for leddestruktion og dermed sygdomsprogression. Fagudvalget ønsker at benytte en modificeret udgave af Total Sharp Score (mTSS) som er udviklet til scoring af patienter med PsA [8]. Den mindste klinisk relevante forskel er defineret som andel af patienter uden progression, hvor 10 procentpoint betragtes som en relevant forskel mellem grupperne.

Psoriatic Area and Severity Index PASI75

Fagudvalget ønsker at benytte et effektmål for hudaffektion på de populationer, hvor dette er relevant (klinisk spørgsmål 3 og 4). Her har fagudvalget valgt Psoriasis Area and Severity Index (PASI), som kombinerer størrelsen på det areal af huden, som er ramt, med alvorligheden heraf på en score fra 0 til 72, hvor 72 udtrykker maksimal sygdom. PASI75 afspejler det antal patienter, som opnår en 75 % reduktion i PASI score. Fagudvalget betragter en forskel på 15 procentpoint mellem grupperne som den mindste klinisk relevante forskel.

Alvorlige infektioner

Fagudvalget finder, det er vigtigt for patienterne at undgå infektioner, hvorfor alvorlige infektioner indgår som et selvstændigt effektmål. Den mindste klinisk relevante forskel defineres som 5 procentpoint mellem grupperne.

3.5.3 Mindre vigtige effektmål

Fagudvalget har ikke defineret mindre vigtige effektmål

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 (fx Medical Subject Headings, MeSH) og fritekstsøgning skal anvendes. Søgningen skal indeholde, men ikke være begrænset til, søgetermerne i tabellerne nedenfor.

[tofacitinib, Xeljanz] *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, fx ved coformuleringer.*	*Blokkene til venstre og højre kombineres med* **AND**	[psoriatic 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 **AND** (der forventes at være direkte sammenlignende studier, og derfor benyttes AND)		
[adalimumab, Humira] *Udover 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, fx ved coformuleringer*		

Tabel 3 Litteratursøgningsstrategi for klinisk spørgsmål 1 og 3 (bionaive populationer)

[tofacitinib, Xeljanz] *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, fx ved coformuleringer.*	*Blokkene til venstre og højre kombineres med* **AND**	[psoriatic 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** (der forventes **IKKE** at være direkte sammenlignende studier, og derfor benyttes OR)		
[secukinumab, Cosentyx] *Udover 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, fx ved coformuleringer*		

Tabel 4 Litteratursøgningsstrategi for klinisk spørgsmål 2 og 4 (bioerfarne populationer)

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 eksklusions-kriterierne, skal der anvendes et forsigtighedsprincip til fordel for artiklen, hvorved fuldtekstartiklen vurderes.

Inklusions- og eksklusionskriterier: Andre studiedesign end randomiserede kontrollerede studier ekskluderes, fase I og fase IIa studier ekskluderes, studier med andre populationer end de her beskrevne ekskluderes, 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 Scientific Discussion. Data skal derudover stemme overens med protokollens beskrivelser. Upublicerede data, og data fra fx 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, hoved-

publikationerne 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 baseline-karakteristikken af studiepopulationerne beskrives i Medicinrådets ansøgningsskema. Det skal angives hvilke studier, der benyttes til at besvare hvilke kliniske spørgsmål.

Alt 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 kliniske spørgsmål specielt ift. præspecificeret population og effektmål, begrundes dette.

Hvis data for et effektmål ikke er tilgængelige 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 (eksempelvis SAE, behandlingsstop pga. bivirkninger og ikke-alvorlige 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*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 per 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 (meta-analyse eller narrativ beskrivelse) begrundes, og specifikke analysevalg truffet i forhold til metoden skal fremgå tydeligt.

6 Andre overvejelser

7 Referencer

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8 Bilag 1: Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende gigtsygdomme

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