Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende filgotinib til behandling af kronisk leddegigt

Vers. 1.0

Bilagsoversigt

1. Høringssvar samt fortrolig rapport med data fra de igangværende MANTA-studier fra ansøger
2. Svarbrev til ansøger på baggrund af høringssvar
3. Medicinrådets vurdering vedr. filgotinib til behandling af kronisk leddegigt, version 2.0
4. Ansøgers endelige ansøgning
5. Ansøgers tekniske dokument til den sundhedsøkonomiske ansøgning
6. Medicinrådets protokol for vurdering vedr. filgotinib til behandling af kronisk leddegigt, version 1.0

Response letter to the Danish Medicines Councils evaluation of filgotinib for the treatment of rheumatoid arthritis

9 April 2021

CONTACT INFORMATION

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To the DMC,

Thank you for the evaluation report regarding the use of filgotinib for treatment of moderate to severe RA. Following our review of the report we have a few comments and clarifications that we would like to be considered in the final decision by the DMC. These are listed below:

1. Page 12: We note that the scientific committee has the following concern regarding the baseline characteristics for the FINCH 1 population:

   > "Fagudvalget bemærker dog, at hhv. 3,6 % og 2,5 % af patienterne i de to arme tidligere har modtaget biologisk behandling"

   We would like to clarify that the allowed previous biological treatment was limited to 1 biologic with exposure for less than 3 months and no use of adalimumab or rituximab (or other selective B-lymphocyte depleting agents). Patients could not have prior non-response or intolerance to any bDMARD.

2. Page 13, first bullet point. Please note that the FINCH 1 results were published during the review process and can now be found in peer review: Combe B, et al. Ann Rheum Dis 2021;**0**:1–11

3. Page 13, Second bullet point, the scientific committee note the following concerning study design and standard of care:

   > "Ansøger har ikke opgjort, hvilken standardbehandling patienterne skiftede til"

   We would like to clarify that "standard of care" was as determined by the investigator. Accordingly, standard treatment could vary.

4. Page 13, second bullet point. We note that the scientific committee has the following concern about the study design for FINCH 1:

   > "betyder, at der er en vis usikkerhed forbundet med størrelsesordenen af den rapporterede effektforskel, da patienterne ikke nødvendigvis under hele opfølgningstiden modtog den intervention, de blev randomiseret til ved studiestart."

   We would like to clarify that patients requiring rescue therapy (standard of care) and thus no longer received the randomized intervention they were assigned at study start were recorded as non-responder, and non-responder imputation (NRI) was employed for primary and key secondary binary endpoint analyses. Multiple imputation was conducted to determine the impact of NRI on the robustness of results.

5. Page 20, concerns regarding cardiovascular risk. We note that the scientific committee has the following concern:

   > "hvorfor filgotinibs bivirkningsprofil med øget risiko for forhøjede lipider, kardiovaskulær risiko og VTE er bekymrende."

   We would like it to be clarified in the report that although a change in lipids have been observed, no increased risk of cardiovascular events or VTEs has been observed in the clinical trial program for filgotinib in RA. As stated in the EPAR it is noted for MACE events that:

"The exposure-adjusted incidence rate of MACE was higher for the filgotinib 200 mg group than for the adalimumab group, but lower than for the MTX monotherapy group". (EPAR, Section 2.6.1. Discussion on clinical safety, p 140)

Specifically, the exposure-adjusted incidence rate (EAIR) of MACE was 0.5 for the filgotinib 200 mg group, 0.3 for the adalimumab group, and 0.6 for the MTX monotherapy group (EPAR, table 24). The EAIR was slightly higher for filgotinib 100 mg than for filgotinib 200 mg and thus, no dose-relation was seen.

"…a majority of the subjects had cardiovascular risk factor such as obesity, hypertension, hyperlipidaemia, or advanced age. (EPAR, Section 2.6.1. Discussion on clinical safety, p 140)

At the CHMP's request, a warning on the cardiovascular risk was included in the SmPC Section 4.4.

For VTE´s the EPAR states that:

"It is noted that the EAIR for venous thromboembolism is not higher for filgotinib than for adalimumab or MTX." (EPAR, Section 2.6.1. Discussion on clinical safety, p 141).

At the CHMP's request, a warning on the VTE risk was included in the Section 4.4 SmPC.

Regarding the lipid changes, the SmPC text states that:

Treatment with filgotinib was associated with dose-dependent increases in lipid parameters, including total cholesterol, and high-density lipoprotein (HDL) levels, while low-density lipoprotein (LDL) levels were slightly increased (see section 4.8). LDL cholesterol returned to pre-treatment levels in the majority of patients who started statin therapy while taking filgotinib. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined. (SmPC, Section 4.4)

Treatment with filgotinib was associated with dose-dependent increases in total cholesterol and HDL levels, while LDL levels were slightly increased. LDL/HDL ratios were generally unchanged. Lipid changes were observed within the first 12 weeks of filgotinib treatment and remained stable thereafter. (SmPC, Section 4.8)

6. Page 20, concerns regarding death. We note that the scientific committee has the following concern:

> "filgotinibs EPAR er det desuden fremhævet, at det kliniske studieprogram har vist, at der er højere incidensrate for død ved behandling med 200 mg filgotinib sammenlignet med adalimumab, men at der er tale om få tilfælde"

For full clarity we would like to add the full text from the EPAR stating that:

"With regards to the observed mortality difference between filgotinib (0.5 E per 100 PYE) and adalimumab (0.3 E per 100 PYE), the CHMP agreed with the applicant that the exposure to adalimumab in filgotinib clinical studies is low and that this influences the ability to achieve an accurate estimate of mortality rates. (EPAR, Section 2.6.1. Discussion on clinical safety, p 142)

When compared to other RA clinical trial programs, the EAIR for death for filgotinib is comparable to the other approved JAK inhibitors, although limitations of inter-study comparisons are acknowledged". (EPAR, Section 2.6.1. Discussion on clinical safety, p 142)

7. Page 20, we note that the scientific committee has the following observation:

> ”Derudover kan filgotinib forårsage fosterskader, baseret på fund hos dyr, og derfor er filgotinib kontraindiceret under graviditet, og kvinder i den fertile alder bør benytte sikker kontraception”

Since this observation has been taken into consideration by the DMC as a negative observation compared to other treatments, we would like to clarify the following:

a) For the drug recommended as first choice for RA in DK, Methotrexate, use in pregnancy is contraindicated and the SmPC highlight that:

”Methotrexat har udvist reproduktionstoksicitet i dyreforsøg, navnlig i første tredjedel af drægtighedsperioden (se pkt. 5.3). Det er påvist, at methotrexat er teratogent for mennesker, idet der er rapporteret om fosterdød, aborter og/eller medfødte anomaliteter (f.eks. i kraniet/ansigtet, hjertet/blodkarrene, centralnervesystemet og ekstremiteterne).

Methotrexat er et kraftigt humant teratogen, der medfører øget risiko for spontan abort, intrauterin vækstbegrænsning og medfødte misdannelser i tilfælde af eksponering under graviditet.” (Methotrexate (Sandoz) SmPC, Dec 2020, downloaded from produktresume.dk)

b) For the chosen comparators, adalimumab and etanercept, the SmPC text include that:

“Should only be used during pregnancy if clearly needed” (Humira SmPC Jan 29, 2021 update and Enbrel SmPC March 25, 2021 update)

The treatment recommendations from the DMC itself likewise state that:

”Som udgangspunkt bør behandlingen – uanset den specifikke TNF-hæmmer – seponeres ved konstateret graviditet.” (Medicinrådets lægemiddelrekommandation og behandlingsvejledning vedrørende lægemidler til kronisk leddegigt, Juli 2020)

c) Use during pregnancy is contraindicated for all approved JAK inhibitors. Also for baricitinib and upadacitinib which has been included in the DMC recommendations/have been evaluated by the DMC without a negative observation. Accordingly, similar to filgotinib it is stated in the SmPC section 4.6; fertility, pregnancy and lactation for upadacitinib and baricitinib:

<u>Upadacitinib</u>
“There are no or limited data on the use of upadacitinib in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Upadacitinib was teratogenic in rats and rabbits with effects in bones in rat foetuses and in the heart in rabbit foetuses when exposed in utero.

Upadacitinib is contraindicated during pregnancy (see section 4.3).” (Rinvoq SmPC Feb 3, 2021 update)

<u>Baricitinib:</u>
“There are no adequate data from the use of baricitinib in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Baricitinib wa steratogenic in rats and rabbits. Animal studies indicate that baricitinib may have an adverse effect on bone development in utero at higher dosages.

Olumiant is contraindicated during pregnancy (see section 4.3). (Olumiant SmPC Dec 15, 2020 update)

In summary, the wording on fetal toxicity is comparable to drugs recommended as first choice treatment by the DMC and comparable to other advanced products approved for standard use without a negative observation/remark for this outcome and accordingly this should also be the case for filgotinib.

8. Page 20, Concerns regarding male fertility. The scientific committee notes that:

> ”To igangværende studier, MANTA og MANTA-RAY, undersøger toksiciteten af behandling med 200 mg filgotinib på mænds fertilitet nærmere. Fagudvalget er bekendt med, at FDA ikke har godkendt filgotinib, bl.a. på baggrund af den potentielle påvirkning af mandlig fertilitet, og finder, at en mulig irreversibel påvirkning af mandlig fertilitet giver anledning til bekymring.”

We would like to get a clarification if the data from the MANTA and MANTA-Ray study sent during the evaluation (March 5, 2021) was taken into consideration? The data forwarded to the DMC included information on the primary endpoint and showed that 10/120 (8.3%) patients on placebo and 8/120 (6.7%) patients on filgotinib had a 50% decline or more in sperm concentration.

In total, 248 patients were randomized 1:1 to receive filgotinib 200 mg once daily or placebo for an initial 13-week, double-blind treatment period. The primary endpoint in both trials was the proportion of patients who had a reduction of 50% or more in sperm concentration at Week 13. Patients who met this endpoint discontinued study treatment at Week 13, were switched to standard of care treatment and were monitored for reversibility every 13 weeks for up to 52 weeks.

Out of the 248 randomized patients, 240 reached Week 13 with two evaluable semen samples at baseline and Week 13. Of those, 18 patients showed a ≥50% decline in sperm concentration, with 10/120 (8.3%) patients on placebo and 8/120 (6.7%) patients on filgotinib.

Beyond the double-blind, placebo-controlled, 13-week period, for which MANTA and MANTA-RAy results are pooled, patients who did not meet the primary endpoint of 50% or more decline in sperm motility or morphology could continue under their respective trial protocol on blinded treatment, receive open-label filgotinib or receive standard of care therapy based on disease response, for another 13 weeks before entering a long-term extension period. At any point, patients exhibiting a predetermined sperm decline enter a monitoring phase in which they are assessed every 13 weeks for reversibility for up to 52 weeks.

If this information was taken into consideration and more information was deemed needed by the expert committee, please see the attached confidential report. This report has been submitted to EMA as part of their ongoing assessment of the indication extension for filgotinib in ulcerative colitis.

We further note that the scientific committee state that:

> ”Fagudvalget anerkender imidlertid EMAs afgørelse og håndtering af denne potentielle bivirkning som beskrevet i produktresuméet.”

However, in the conclusion on page 25 the scientific committee notes that:

> ”Derfor finder fagudvalget, at den samlede konklusion ikke omfatter mænd med ønske om børn”

This is in contrast to the SmPC where filgotinib for males wanting to have children is not contraindicated.

The CHMP has made an assessment based upon the totality of the available data, taking into consideration the benefits and the risks of filgotinib for both male and female patients. Based on these analyses CHMP approved filgotinib for the treatment of male and female adult patients with moderate to severe RA who have responded inadequately to, or who are intolerant to one or more DMARDs.

The CHMP requested to include a precautionary statement in the SmPC section 4.4, the package leaflet (PL) and the educational materials regarding the potential risk of reduced fertility or infertility in male patients treated with filgotinib. This was considered acceptable to the CHMP until the interim data from the MANTA and MANTA-RAy studies will be submitted (1H21). The current SmPC text states that:

“The potential risk of reduced fertility or infertility should be discussed with male patients before initiating treatment” (SmPC, Section 4.4)

In summary; with the clinical data provided and the current SmPC text, we would like the scientific committee to re-evaluate the listed limitations regarding male fertility and filgotinib.

9. Page 49, the DMC notes that:

> ”Medicinrådet har tidligere udtrykt en bekymring for den øgede risiko for lungeemboli og VTE hos patienter med risikofaktorer for VTE samt øget risiko for alvorlige infektioner hos patienter over 65 år ved behandling med en anden JAK-hæmmer; tofacitinib [24]. Medicinrådet har i den forbindelse fundet, at det ikke kan udelukkes, at der er tale om en klasseeffekt for JAK-hæmmere, men med det tilgængelige datagrundlag foreligger der ikke evidens til at konkludere dette.”

For VTEs, please see previous comment (point 5) on data from the filgotinib clinical trial program. For serious infections we would like to clarify that the EPAR states that:

“In pooled safety data from the final CSRs presented in response to day 120 LoQ, the exposure-adjusted incidence rate for serious infections was not higher for any filgotinib group than for adalimumab. The risk was numerically lower for filgotinib 200 mg than for filgotinib 100 mg.” (EPAR, Section 2.6.1. Discussion on clinical safety, p 139)

When specifically considering the elderly population the reported EAIRs for SIEs in patients under the age of 65 is 1.5 (CI 1.1;1.9) for filgotinib 200 mg, 1.7 (CI 0.4;4.2) for placebo and 2.6 (CI 0.9;5.6) for adalimumab (EPAR, table 38). For those above 65 years of age the EAIRS are 2.6 (CI 1.5;4.1) for filgotinib 200 mg, 5.0 (CI 1.0;14.6) for placebo and 6.9 (CI 1.9;17.6) for adalimumab and thus no specific SIE signal is seen with this age cut off for filgotinib. The EPAR notes the following for filgotinib for those patients of 75 years of age and above:

"For patients treated with MTX monotherapy group, the EAIR of TEAE, TE serious AE, Infectious AE, Serious Infectious AE were not higher for subjects ≥ 75 years of age as compared to subjects <75 years of age. For the filgotinib 200 mg +/-csDMARD all these EAIRs were higher for subjects≥ 75 years compared to subjects<75 years while the pattern was less distinct for the lower filgotinib dose group. For adalimumab, most of these EAIRs were higher in the oldest group. Thus, the effect of age on safety appears more prominent for the higher filgotinib dose as compared to MTX monotherapy and also, to some extent, compared to the lower filgotinib dose." (EPAR, Section 2.6.1. Discussion on clinical safety, p 144)

"...Therefore, a starting dose of 100 mg is recommended for patients aged 75 or above." (EPAR, Section 2.6.1. Discussion on clinical safety, p 144)

In accordance with this, the filgotinib SmPC text address the concerns of elderly by recommending a starting dose of 100 mg to patients aged 75 or older.

Comments to the Economic evaluation

Please see previous comments regarding male fertility and fetal toxicity made for the clinical evaluation.

Page 14: We note the following statement:

> ”Derudover påpeger fagudvalget, at der er mistanke om, at der er en generel klasseeffekt på JAK-inhibitorer i forhold til venøs tromboembolisk sygdom (VTE) hos ældre patienter over 65 år.”

Which we believe refers to page 49 in the clinical evaluation:

> ”Medicinrådet har tidligere udtrykt en bekymring for den øgede risiko for lungeemboli og VTE hos patienter med risikofaktorer for VTE samt øget risiko for alvorlige infektioner hos patienter over 65 år ved behandling med en anden JAK-hæmmer; tofacitinib [24]. Medicinrådet har i den forbindelse fundet, at det ikke kan udelukkes, at der er tale om en klasseeffekt for JAK-hæmmere, men med det tilgængelige datagrundlag foreligger der ikke evidens til at konkludere dette.”

For the concerns regarding both VTEs and serious infections therefore please see the response for the clinical evaluation. Specifically, please note that the distinction is made at age of 75 (not 65) in the EPAR for SIEs and for this patient population a starting dose of 100 mg is suggested.

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26. maj 2021

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Tilbagemelding på jeres høringssvar vedr. filgotinib til kronisk leddegigt

Kære Viktor Hedlöf Kanje,

Tak for jeres høringssvar vedr. filgotinib til kronisk leddegigt, hvor Gilead både har kommenteret på indholdet i vurderingsrapporten, den samlede vurdering samt præsenteret nye fortrolige data.

Medicinrådet og fagudvalget vedr. gigtsygdomme har forholdt sig til de nye fortrolige data. De vurderer, at [redacted] hvorfor Rådet ikke har fundet anledning til at ændre på konklusionen på baggrund af jeres høringssvar. Ud fra et forsigtighedsprincip fastholder Medicinrådet således sin konklusion i vurderingsrapporten. Medicinrådet vil tage stilling til, om beslutningen skal revurderes, når EMA har behandlet de nye data.

Medicinrådet er enigt i jeres ønske om, at bemærkningen om potentiel øget risiko for fosterskader ved behandling med filgotinib bør fjernes fra konklusionen. Kontraindikationen af filgotinib under graviditet gælder også for øvrige JAK-hæmmere, hvor Medicinrådet tidligere ikke har fremhævet dette specifikt i sin konklusion. Bemærkningen er derfor fjernet fra konklusionen.

Medicinrådet og fagudvalget har noteret sig jeres øvrige kommentarer til vurderingsrapporten, men finder ikke, at de giver anledning til ændringer i den samlede vurdering.

Med venlig hilsen,

Steen Werner Hansen og Jørgen Schøler Kristensen
Formænd for Medicinrådet

Medicinrådet

Medicinrådets vurdering vedrørende filgotinib til behandling af kronisk leddegigt

Version 2.0

Om Medicinrådet

Medicinrådet er et uafhængigt råd etableret af Danske Regioner.

Medicinrådet vurderer, om nye lægemidler og indikationsudvidelser skal anbefales som mulig standardbehandling. Medicinrådet udarbejder også behandlingsvejledninger og rekommandationer for anvendelse af medicin på sygehusene. Derudover kan Medicinrådet tage andre typer sager op, der handler om medicinanvendelse.

Om vurderingsrapporten

Vurderingsrapporten indeholder Medicinrådets vurdering af, hvilken værdi lægemidlet har for patienten i forhold til nuværende standardbehandling.

Værdien for patienten og omkostningerne for samfundet danner grundlaget for Medicinrådets beslutning om, hvorvidt lægemidlet anbefales som mulig standardbehandling. Dette bliver sammenfattet i Medicinrådets anbefaling vedr. lægemidlet.

Lægemidlet er vurderet efter *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*, som du kan finde på Medicinrådets hjemmeside under siden Metoder.

Dokumentoplysninger	
Godkendelsesdato	26. maj 2021
Dokumentnummer	116355
Versionsnummer	2.0

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Bilag 2: GRADE 59

Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 26. maj 2021

1. Medicinrådets konklusion

Filgotinib er blevet vurderet til fire patientpopulationer med moderat til svær kronisk leddegigt, hvor konventionel syntetisk behandling (csDMARD) enten har haft utilstrækkelig effekt eller ikke er tolereret. Det gælder for:

- Filgotinib i kombination med methotrexat (MTX) til patienter i MTX-behandling:
    - som ikke tidligere har modtaget biologisk/targeteret syntetisk behandling (b/tsDMARDs)
    - som tidligere har modtaget b/tsDMARDs-behandling.
- Filgotinib som monoterapi til patienter, hvor csDMARD-behandling ikke er en mulighed, og:
    - hvor patienterne ikke tidligere har modtaget b/tsDMARDs-behandling
    - hvor patienterne tidligere har modtaget b/tsDMARDs-behandling.

Til alle patientpopulationer vurderer Medicinrådet, at der ikke er forskel mellem behandlingseffekten af filgotinib og den behandling, patienterne i den relevante population modtager i dag. Imidlertid er der rejst bekymring vedrørende påvirkning af mandlig fertilitet ved behandling med filgotinib. Derfor vurderer Medicinrådet samlet, at filgotinib har en **negativ værdi** for patienter med moderat til svær kronisk leddegigt.

MEDICINRÅDET KATEGORISERER LÆGEMIDLERS VÆRDI I EN AF FØLGENDE KATEGORIER:

- **Stor merværdi:** Der er påvist en stor forbedring i effektforhold i forhold til gældende standardbehandling, eksempelvis markant forbedret overlevelse, markant reduktion i forekomsten af alvorlige symptomer og/eller alvorlige bivirkninger.
- **Moderat merværdi:** Der er påvist en moderat forbedring i forhold til gældende standardbehandling, eksempelvis moderat forbedret overlevelse, moderat reduktion i forekomsten af symptomer og/eller bivirkninger.
- **Lille merværdi:** Der er påvist en lille forbedring i forhold til gældende standardbehandling, eksempelvis en dokumenteret forbedret overlevelse, en reduktion i forekomsten af symptomer og/eller bivirkninger.
- **Merværdi af ukendt størrelse:** Der er påvist en forbedring i forhold til gældende standardbehandling, men størrelsen af forbedring kan ikke bestemmes. Lægemidlets merværdi er som minimum lille, men kunne også være moderat eller stor.
- **Ingen dokumenteret merværdi:** Der er ikke påvist en merværdi i forhold til gældende standardbehandling. Omvendt tyder den tilgængelige evidens heller ikke på, at der er en negativ værdi.
- **Negativ værdi:** Der er påvist en negativ værdi i forhold til gældende standardbehandling.

I nogle situationer er det ikke muligt at kategorisere lægemidlets samlede værdi. De situationer opstår, når evidensgrundlaget for vurderingen er for usikkert til at kategorisere værdien jf. Medicinrådets metoder (fx på grund af usikkerheder omkring effektforhold og spinkelt datagrundlag). Medicinrådet konkluderer da, at samlet værdi ikke kan kategoriseres. Medicinrådet vil i disse tilfælde argumentere for, om der er grund til at formode, at det nye lægemiddel er dårligere eller evt. bedre end gældende standardbehandling, eller der ikke er grund til at skelne mellem behandlingerne. Det sker på baggrund af det foreliggende datagrundlag og fagudvalgets kliniske erfaring. Vurderingen er forbundet med større usikkerhed end vurderinger, hvor lægemidlets værdi kan kategoriseres.

MEDICINRÅDET VURDERER KVALITETEN AF DE DATA, DER LIGGER TIL GRUND FOR VURDERINGEN AF LÆGEMIDLET (EVIDENSENS KVALITET) I EN AF FØLGENDE GRADE-KATEGORIER:

- **Høj:** Nye studier vil med meget lav sandsynlighed ændre konklusionen.
- **Moderat:** Nye studier vil med lav sandsynlighed ændre konklusionen.
- **Lav:** Nye studier vil med moderat sandsynlighed ændre konklusionen.
- **Meget lav:** Nye studier vil med høj sandsynlighed ændre konklusionen.

2. Begreber og forkortelser

ACR50: *American College of Rheumatology 50 % response*

bDMARD: Biologisk *Disease Modifying Anti-Rheumatic Drug*

CCP: *Citric Citrullinated Peptide*

CI: Konfidensinterval

CRP: C-reaktivt protein

csDMARD: Konventionelt syntetisk *Disease Modifiying Anti-Rheumatic Drug*

DANBIO: Dansk Reumatologisk Database

DMARD: *Disease Modifying Anti-Rheumatic Drug*

EMA: Det Europæiske Lægemiddelagentur (*European Medicines Agency)*

EPAR: *European Public Assessment Report*

EULAR: *European League Against Rheumatism*

FAS: *Full analysis set*

GRADE: System til at vurdere evidens (*Grading of Recommendations, Assessment, Development and Evaluation*)

HAQ-DI: *Health Assessment Questionnaire Disability Index*

HR: *Hazard ratio*

ITT: *Intention-to-treat*

JAK: Janus kinase

mTSS: *Modified Total Sharp Score*

MTX: Methotrexat

NA: Ikke tilgængeligt (*not available)*

NSAID: Non-steroide antiinflammatoriske lægemidler

OR: *Odds ratio*

PICO: Population, intervention, komparator og effektmål (*Population, Intervention, Comparator and Outcome)*

PP: *Per Protocol*

RCT: Randomiseret kontrolleret studie *(Randomised Controlled Trial)*

RF: *Rheumatoid Factor*

RR: Relativ risiko

SAE: Alvorlig uønsket hændelse (*Serious Adverse Event)*

SJC66: *Swollen Joint Count in 66 joints*

SMD: *Standardized Mean Difference*

TJC68: *Tender Joint Count in 68 joints*

TNF: Tumor nekrosis faktor

tsDMARD: Targeteret syntetisk *Disease Modifying Anti-Rheumatic Drug*

TSS: *Total Sharp Score*

3. Introduktion

Formålet med Medicinrådets vurdering af filgotinib til moderat til svær kronisk leddegigt er at vurdere den værdi, lægemidlet har sammenlignet med dansk standardbehandling.

Vurderingen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra Gilead Sciences. Medicinrådet modtog ansøgningen den 21. december 2020.

De kliniske spørgsmål er:

1. Hvilken værdi har filgotinib i kombination med MTX sammenlignet med adalimumab i kombination med MTX for behandlingsnaive patienter med moderat til svær kronisk leddegigt?
2. Hvilken værdi har filgotinib i kombination med MTX sammenlignet med adalimumab i kombination med MTX for behandlingserfarne patienter med moderat til svær kronisk leddegigt?
3. Hvilken værdi har filgotinib som monoterapi sammenlignet med etanercept som monoterapi for behandlingsnaive patienter med moderat til svær kronisk leddegigt?
4. Hvilken værdi har filgotinib som monoterapi sammenlignet med etanercept som monoterapi for behandlingserfarne patienter med moderat til svær kronisk leddegigt?

3.1 Kronisk leddegigt

Kronisk leddegigt er en systemisk og fremadskridende sygdom [1], der er karakteriseret ved betændelse i led og lednære strukturer, hvilket kan medføre leddestruktion. De vigtigste symptomer er ledhævelser og ledsmerter, der medfører nedsat funktionsevne. For en betydelig del af patienterne er funktionsevnen nedsat i en sådan grad, at de bliver helt eller delvist uarbejdsdygtige. Udover leddestruktion kan sygdommen medføre symptomer fra andet end led, bl.a. hjertekarsygdomme. Kronisk leddegigt er forbundet med øget dødelighed, især pga. hjertekarsygdomme, åreforsnævring og lungeinvolvering. Der er mange forskellige årsager, som spiller sammen ved udvikling af kronisk leddegigt, hvor genetik (visse vævstyper) og miljøfaktorer (f.eks. tobaksrygning) spiller en rolle.

Sygdommen klassificeres efter 2010 ACR/EULAR, hvilket er kriterier, som er defineret af American College of Rheumatology (ACR) og European League Against Rheumatism (EULAR) [2]. Klassifikationen er baseret på antal involverede led, blodprøver (autoimmun serologi og akutfase respons), og hvor længe symptomerne har varet.

Kronisk leddegigt forekommer globalt, men med geografisk og etnisk variation. I DANBIO (Dansk Reumatologisk Database) var der ved udgangen af 2019 registreret ca. 24.800 patienter i behandling for kronisk leddegigt, og i 2018 var der ca. 1.300 nye patienter i behandling [3,4]. Sygdommen kan debutere i alle aldre, men typisk mellem 50 og 70 år [5].

3.2 Filgotinib

Filgotinib (Jyseleca®) er en selektiv Janus kinase (JAK)-inhibitor, der primært hæmmer JAK1. JAK spiller en vigtig rolle i betændelsesprocessen og i den beskadigelse af leddene, som finder sted ved kronisk leddegigt.

Filgotinib administreres oralt 200 mg én gang dagligt.

Det Europæiske Lægemiddelagentur (EMA) har givet filgotinib følgende indikation: *Jyseleca er indiceret til behandling af moderat til svært aktiv reumatoid artritis hos voksne patienter, som har opnået utilstrækkelig respons på, eller som er intolerante for et eller flere disease-modifying anti-rheumatic drugs (DMARD'er). Jyseleca kan anvendes som monoterapi eller i kombination med methotrexat (MTX).*

Filgotinib har ikke andre indikationer.

3.3 Nuværende behandling

Der findes ingen behandling, som kan kurere kronisk leddegigt, men tidlig behandling kan bremse sygdommen og bedre prognosen. Tidlig og målrettet behandling er vigtig for at forebygge leddestruktion. Behandlingen er principielt livslang og består af immunhæmmende medicin, der er delt op i symptomlindrende behandling (smertestillende (non-steroide antiinflammatoriske lægemidler (NSAID))) og sygdomsmodificerende behandling (Disease Modifying Anti Rheumatic Drugs (DMARDs)). Behandlingen er en specialistopgave, som varetages af reumatologer.

Methotrexat (MTX), en konventionel syntetisk DMARD (csDMARD), er førstevalg ved opstart af behandling med DMARDs. Hvis MTX ikke har tilfredsstillende effekt, bliver det kombineret med andre csDMARDs, typisk Salazopyrin og hydroxychloroquin (triplebehandling). Hvis patienten heller ikke her opnår lav sygdomsaktivitet/remission, er næste behandlingsmulighed biologisk behandling med antistoffer (bDMARDs) eller targeteret syntetisk behandling med små molekyler (tsDMARDs), enten i kombination med MTX (kombinationsbehandling) eller som monoterapi. De biologiske DMARDs kan opdeles i tumor nekrosis faktor (TNF)-hæmmere (adalimumab, certolizumab, etanercept, golimumab og infliximab) og biologiske lægemidler med andre virkningsmekanismer (rituximab, tocilizumab, sarilumab, abatacept og anakinra). Dertil kommer de targeterede syntetiske DMARDs (tsDMARDs) (baricitinib og tofacitinib).

I DANBIO var der ved udgangen af 2019 registreret ca. 24.800 patienter i behandling for kronisk leddegigt, hvoraf ca. 6.100 var i behandling med bDMARDs/tsDMARDs [4]. De fleste patienter vil blive behandlet med csDMARDs alene eller i kombination med bDMARDs/tsDMARDs. For nogle patienter er behandling med csDMARDs ikke en mulighed pga. toksicitet og intolerans. Her vil bDMARDs/tsDMARDs monoterapi være eneste mulige behandling. Et studie fra 2015 baseret på data fra DANBIO [6] viser, at 19 % af patienterne med kronisk leddegigt var i bDMARDS/tsDMARDS monoterapi (ca. 1.100 patienter). Af disse var 70 % (ca. 770 patienter) initieret på monoterapi med

bDMARDs, og ca. 30 % (ca. 330 patienter) havde tidligere været i kombinationsterapi med MTX.

Antallet af patienter med kronisk leddegigt i behandling med bDMARDs/tsDMARDs er således stigende med en gennemsnitlig stigning på ca. 250 patienter pr. år siden 2010 [7–10]. Der er før 2010 beskrevet en stigning på ca. 500 behandlingsnaive patienter pr. år [11], og det skønnes, at det egentlige tal ligger et sted imellem 250 og 500. Fagudvalget anslår, at 10-15 % af patienter i behandling med bDMARDs/tsDMARDs vil skifte præparat i løbet af et år, hvilket hovedsageligt skyldes mangel på effekt eller uacceptable bivirkninger. Det vil sige, at omkring 700 patienter i behandling med bDMARDs/tsDMARDs i 2018 vil have skiftet lægemiddel i løbet af et år.

4. Metode

Medicinrådets protokol for vurdering af filgotinib til behandling af kronisk leddegigt beskriver sammen med *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*, hvordan Medicinrådet vil vurdere lægemidlets værdi for patienterne.

5. Resultater

5.1 Klinisk spørgsmål 1

5.1.1 Litteratur

Nedenfor beskriver og vurderer Medicinrådet den litteratur, som ansøger har anvendt i sin endelige ansøgning til at besvare klinisk spørgsmål 1. Det kliniske spørgsmål er:

Hvilken værdi har filgotinib i kombination med MTX sammenlignet med adalimumab i kombination med MTX for behandlingsnaive patienter med moderat til svær kronisk leddegigt?

Ansøgningen baserer sig på det ene studie, FINCH 1, der er angivet i protokollen (tabel 1). Studiet er endnu ikke publiceret, men studiets design, metoder og primære resultater er beskrevet i filgotinibs EPAR (European Public Assessment Report) [12] og i den endelige ansøgning for filgotinib. Desuden indgår EMAs EPAR og produktresumé for filgotinib [12,13] og adalimumab [14] som datagrundlag i ansøgningen.

FINCH 1

Dette er et randomiseret, dobbeltblindet fase III-studie, der undersøgte effekten og sikkerheden af filgotinib i kombination med MTX sammenlignet med placebo eller adalimumab i kombination med MTX hos patienter med kronisk leddegigt og fortsat moderat til svær sygdomsaktivitet trods MTX-behandling. Næsten alle patienterne er biologisk behandlingsnaive.

Patienterne blev randomiseret 3:3:2:3 til filgotinib 200 mg dagligt (n = 475), filgotinib 100 mg dagligt (n = 480), adalimumab 40 mg/ml subkutant hver 2. uge (n = 325) eller placebo (n = 475), mens de fortsatte på MTX. Randomiseringen var bl.a. stratificeret efter geografi og tidligere behandling med bDMARDs. Studiet kørte over 52 uger med en planlagt ublindet analyse ved uge 24 efterfulgt af en ekstensionsperiode til uge 52. Patienter, der ikke var stoppet med behandlingen undervejs, kunne efter de 52 uger fortsætte i behandling i FINCH 4-studiet, som er et langtidsekstensionsstudie. Ved manglende effekt ved uge 14 stoppede patienterne behandlingen og skiftede til standardbehandling, som blev bestemt af investigator. Ved uge 24 blev alle patienter i placeboarmen randomiseret på ny 1:1 til filgotinib 200 mg eller 100 mg i kombination med MTX. Patienter, der herefter ikke opnåede effekt, stoppede med behandlingen og skiftede til standardbehandling.

Primære effekt- og sikkerhedsanalyser blev foretaget på data fra alle randomiserede patienter, der modtog mindst én studiedosis. Studiets primære effektmål var American College of Rheumatology 20 % response (ACR20) ved uge 12. Sekundære effektmål af relevans er ACR50 (50 % respons), livskvalitet målt ved HAQ-DI (*Health Assessment Questionnaire Disability Index)*, *modified Total Sharp Score* (mTSS), ophør af behandling pga. manglende effekt og sikkerhed.

Tabel 1. Oversigt over studier

Publikationer	Klinisk forsøg	NCT-nummer	Population	Intervention vs. komparator
Fuldtekstartikel er endnu ikke publiceret EPAR	FINCH 1	NCT02889796	Biologisk behandlingsnaive patienter med moderat til svær kronisk leddegigt	Filgotinib + MTX vs. adalimumab + MTX

Tabel 2 lister baselinekarakteristika for patientpopulationen i FINCH 1-studiet for patienter i de relevante behandlingsarme.

Tabel 2. Baselinekarakteristika*

	Filgotinib 200 mg + MTX	Adalimumab + MTX
Kvinder, antal (%)	379 (79,8 %)	266 (81,8 %)
Sygdomsvarighed, år	7,3 (7,4)	8,0 (7,4)
Alder, år	52 (12,8)	53 (12,9)
Tidligere behandling med bDMARDs, antal (%)	17 (3,6 %)	8 (2,5 %)
SJC66	15 (8,5)	16 (8,4)
TJC68	25 (13,5)	24 (13,2)
RF- + anti-CCP-positive, antal (%)	331 (69,7)	219 (67,4)
DAS28-CRP	5,8 (8,9)	5,7 (0,9)
HAQ-DI	1,59 (0,61)	1,59 (0,60)
TSS	NA	NA

*Alle værdier er opgjort som gennemsnit ± SD, medmindre andet er specificeret.
SJC66 = *Swollen joint count in 66 joints* (antal hævede led ud af 66 led), TJC68 = *Tender joint count in 68 joints*, RF = *Rheumatoid factor*, CCP = *Citric citrullinated peptide*, DAS28-ESR = *Disease Activity Score 28 – C-reactive protein value*, TSS = *Total Sharp Score/van der Heijde score*, HAQ-DI = *Health Assessment Questionnaire Disability Index*, NA = ikke tilgængelig.

Fagudvalget finder, at der ikke er nogen betydende forskelle i baselinekarakteristika mellem de to studiearme, og at patientkarakteristika i studierne ikke afviger væsentligt fra den danske patientpopulation. Fagudvalget bemærker dog, at hhv. 3,6 % og 2,5 % af patienterne i de to arme tidligere har modtaget biologisk behandling, mens det kliniske spørgsmål omfatter biologisk behandlingsnaive patienter, dvs. patienter, der ikke tidligere har modtaget behandling med bDMARDs eller tsDMARDs. Fagudvalget vurderer, at denne forskel kan underestimere behandlingseffekten en smule. Da det imidlertid gælder for begge studiearme, finder fagudvalget, at det ikke er af betydning for vurderingen af den kliniske værdi.

5.1.2 Databehandling og analyse

I dette afsnit er ansøgers datagrundlag, databehandling og analyse for hvert effektmål beskrevet.

For samtlige effektmål har ansøger foretaget en direkte sammenligning af filgotinib i kombination med MTX og adalimumab i kombination med MTX med data fra FINCH 1-studiet. Ansøger har indsendt data for alle effektmål efter 52 ugers opfølgningstid.

Den direkte sammenligning er i henhold til Medicinrådets metoder. Medicinrådet har ikke fundet anledning til at foretage ændringer af beregninger foretaget af ansøger eller supplere med yderligere beregninger.

Fagudvalget og sekretariatet ønsker at fremhæve følgende vedrørende den direkte sammenligning:

- Resultater for samtlige effektmål er data-on-file og stammer fra studiets fortrolige *Clinical Study Report* (CSR) (dog fremgår resultatet for effektmålet ACR50 også af filgotinibs produktresumé [13]). Medicinrådet har vurderet, at beskrivelsen af studiets design i hhv. filgotinibs EPAR og den endelige ansøgning er fyldestgørende. På den baggrund accepterer Medicinrådet, jf. Medicinrådets kriteriepapir om anvendelsen af upublicerede data, at resultaterne stammer fra data-on-file.
- Data stammer fra alle randomiserede patienter i filgotinib- og adalimumab-armen (*Full Analysis Set* (FAS)). Under studiet kunne patienter stoppe behandling ved manglende effekt og skifte over til standardbehandling (se beskrivelse af studiet i afsnit 5.1.1). I studieperioden skiftede 29 patienter ud af 475 (6,1 %) fra filgotinib til standardbehandling pga. manglende effekt, hvilket var tilfældet for 14 patienter ud af 325 (4,3 %) behandlet med adalimumab. Ansøger har ikke opgjort, hvilken standardbehandling patienterne skiftede til. Det betyder, at der er en vis usikkerhed forbundet med størrelsesordenen af den rapporterede effektforskel, da patienterne ikke nødvendigvis under hele opfølgningstiden modtog den intervention, de blev randomiseret til ved studiestart. Da relativt få patienter i de to arme skiftede behandling pga. manglende effekt, vurderer fagudvalget, at denne usikkerhed påvirker effektforskellen i mindre grad.
- Ansøger har leveret data på *modified Total Sharp Score* (mTSS) fremfor TSS, hvilket fagudvalget vurderer er acceptabelt. Der blev ikke foretaget *missing data imputation*, hvilket betyder, at kun observerede værdier (dvs. kun fra patienter, hvor der foreligger data) indgik i analyserne. Dette medfører, at der indgår færre patienter i analyserne, end der blev randomiseret til de to behandlingsarme.
- Ansøger har leveret data på HAQ-DI fra *Full Analysis Set* (FAS)-populationen. Dog blev patienter med HAQ-DI < 0,22 ekskluderet fra analyserne, hvilket medfører, at der indgår færre patienter i analyserne, end der blev randomiseret til de to behandlingsarme. Fagudvalget vurderer, at dette er acceptabelt, da det drejer sig om relativt få patienter (16 patienter i filgotinib-armen og 9 patienter i adalimumab-armen).

5.1.3 Evidensens kvalitet

Medicinrådet har anvendt GRADE til at foretage en systematisk og transparent vurdering af kvaliteten af evidensen. Nedenfor følger en beskrivelse af vurderingen af de væsentligste domæner for hvert klinisk spørgsmål. Vurdering af risikoen for bias fremgår af bilag 1. Den fuldstændige GRADE-vurdering og begrundelserne er samlet i en GRADE-profil (bilag 2).

Der er udarbejdet én GRADE-profil for det kliniske spørgsmål. Hvor evidensen er nedgraderet, er dette foretaget på baggrund af inkonsistens (kun ét studie) og unøjagtighed (konfidensintervallet for effektmålene *behandlingsophør grundet uønskede hændelser*, *alvorlige infektioner* og *ophør grundet manglende effekt* indeholder mulighed for både positive og negative konklusioner).

Evidensens kvalitet er lav, hvilket betyder, at nye studier med moderat sandsynlighed kan ændre konklusionen.

5.1.4 Effektestimater og kategorier

I tabellen herunder fremgår de absolutte og relative effektforskelle, de foreløbige og aggregerede kategorier, den samlede kategori og den samlede kvalitet af evidensen for klinisk spørgsmål 1.

Tabel 3. Resultater for klinisk spørgsmål 1 – filgotinib i kombination med MTX sammenlignet med adalimumab i kombination med MTX til behandlingsnaive patienter

Effektmål	Målenhed (MKRF)	Vigtighed	Forskel i absolutte tal		Forskel i relative tal		Aggregeret værdi for effektmålet
			Forskel [95 % CI]	Foreløbig værdi	Forskel [95 % CI]	Foreløbig værdi	
American College of Rheumatology 50 % response (ACR50)	Andel patienter, der oplever respons (15 %-point)	Kritisk	3,5 %-point [-3,2; 11,1]	Ingen dokumenteret merværdi	RR: 1,06 [0,95; 1,19]	Ingen dokumenteret merværdi	Ingen dokumenteret merværdi
Bivirkninger	Andel patienter, der ophører behandling grundet uønskede hændelser (5 %-point)	Kritisk	-0,1 %-point [-3,6; 3,1]	Kan ikke kategoriseres	RR: 0,99 [0,55; 1,77]	Kan ikke kategoriseres	Kan ikke kategoriseres
	Andel patienter, der oplever alvorlige infektioner (5 %-point)		-0,3 %-point [-3,0; 2,3]	Ingen dokumenteret merværdi	RR: 0,89 [0,36; 2,00]	Kan ikke kategoriseres	
	Gennemgang af bivirkningsprofil		Se nedenfor				
Behandlingsophør grundet manglende effekt	Andel patienter, der ophører behandling (10 %-point)	Vigtig	1,8 %-point [-1,5; 4,9]	Ingen dokumenteret merværdi	RR: 1,42 [0,76; 2,64]	Kan ikke kategoriseres	Ingen dokumenteret merværdi
Total Sharp Score (TSS) efter minimum 12 måneder	Andel patienter uden progression (10 %-point)	Vigtig	5,2 %-point [-0,3; 11,1]	Ingen dokumenteret merværdi	RR: 1,06 [1,00; 1,14]	Ingen dokumenteret merværdi	Ingen dokumenteret merværdi

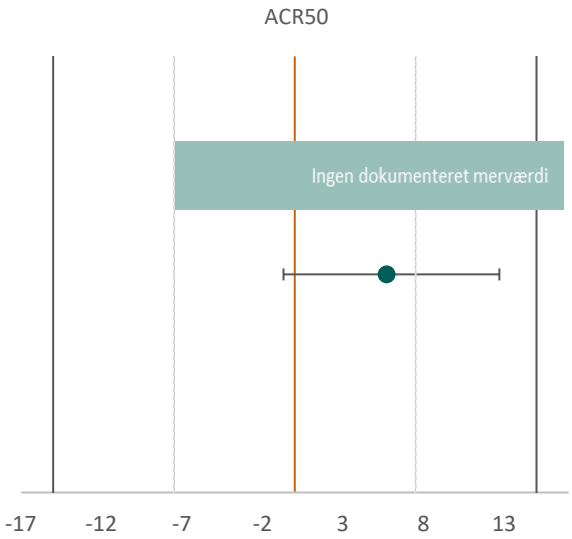
Health Assessment Questionnaire Disability Index (HAQ-DI)	Andel patienter, der oplever respons (15 %-point)	Vigtig	5,7 %-point [-0,7; 12,7]	Ingen dokumenteret merværdi	RR: 1,08 [0,99; 1,18]	Ingen dokumenteret merværdi	Ingen dokumenteret merværdi
Konklusion							
Samlet kategori for lægemidlets værdi	Ingen dokumenteret merværdi						
Kvalitet af den samlede evidens	Lav						

CI = Konfidensinterval, RR = Relativ risiko

ACR50

Effektmålet ACR50 er kritisk for vurderingen af lægemidlets værdi for patienterne, da det er det primære mål for effekt på sygdomsaktivitet. ACR50 er defineret som 50 %'s forbedring i både ømme og hævede led samt 50 %'s forbedring inden for mindst tre ud af følgende fem domæner: patientens overordnede vurdering af, hvor meget gigten som helhed påvirker hverdagen (*Visual Assessment Scale* (VAS) global), patientens vurdering af smerte, lægens overordnede vurdering af patientens samlede sygdomsaktivitet (VAS doctor), HAQ-DI-score, som måler patientens funktionsniveau, og C-Reaktivt Protein (CRP). Fagudvalget finder, at en 50 %'s forbedring hos den enkelte patient er tilstrækkelig for at definere respons, hvorimod en 20 %'s forbedring (ACR20) i fagudvalgets optik ikke er et tilstrækkeligt klinisk respons.

296 ud af 475 patienter (62,3 %) opnåede ACR50 ved uge 52 i filgotinib-armen, hvilket var tilfældet for 192 ud af 325 patienter (59,1 %) i adalimumab-armen.



Figur 1. Punktestimat og 95 % konfidensinterval for den absolutte forskel for ACR50. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Den absolutte forskel er vist i figur 1 ovenfor. Punktestimatet på 3,5 %-point for den absolutte effektforskel afspejler ikke en klinisk relevant effektforskel, da den ligger under den mindste klinisk relevante forskel på 15 %-point. Den nedre grænse for konfidensintervallet er tættere på 0 (ingen effekt) end på en negativ klinisk relevant forskel. Derfor har filgotinib foreløbigt ingen dokumenteret merværdi vedr. effektmålet ACR50.

Baseret på den relative effektforskel, som fremgår af tabel 3, har filgotinib foreløbigt ingen dokumenteret merværdi vedr. effektmålet ACR50.

Fagudvalget vurderer, at filgotinib aggregeret har **ingen dokumenteret merværdi** vedr. effektmålet ACR50, baseret på ovenstående gennemgang af de absolutte og relative effektforskelle.

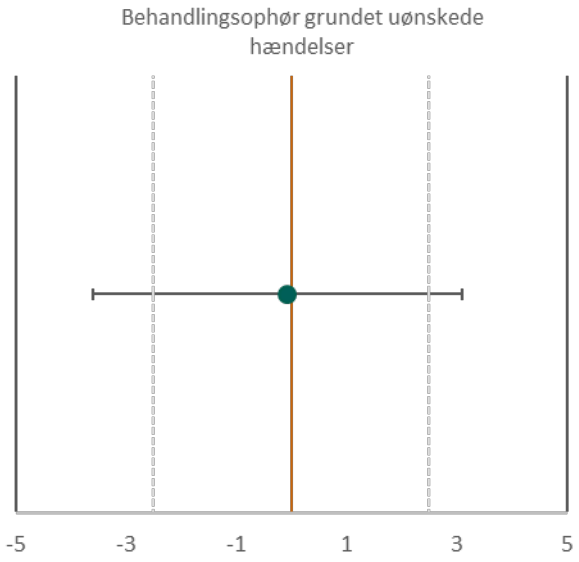
Bivirkninger

Effektmålet bivirkninger er kritisk for vurderingen af lægemidlets værdi, fordi de både er generende for patienterne og kan forårsage pauser i behandlingen, hvilket kan forværre sygdommen. Effektmålet er delt op på tre delmål: behandlingsophør grundet uønskede hændelser, alvorlige infektioner og en kvalitativ gennemgang af de to lægemidlers bivirkningsprofiler.

Behandlingsophør grundet uønskede hændelser

Det er fagudvalgets vurdering, at uønskede hændelser, der fører til ophør af behandlingen, er et brugbart mål for bivirkninger.

26 ud af 475 patienter (5,5 %) havde ved uge 52 ophørt behandlingen grundet uønskede hændelser i filgotinib-armen, hvilket var tilfældet for 18 ud af 325 patienter (5,5 %) i adalimumab-armen.



Figur 2. Punktestimat og 95 % konfidensinterval for den absolutte forskel for behandlingsophør grundet uønskede hændelser. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

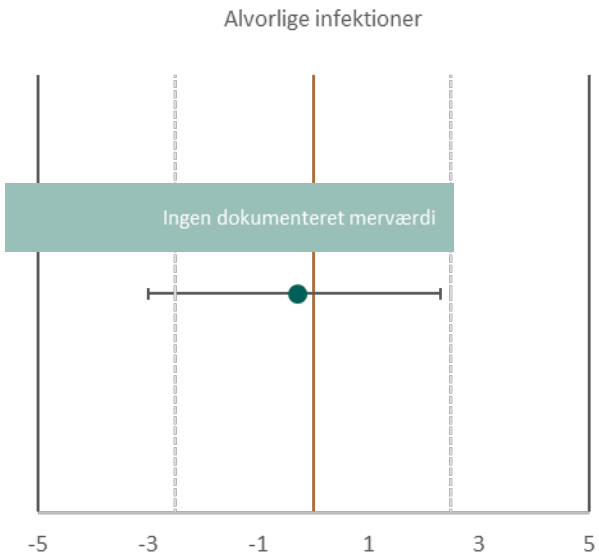
Den absolutte forskel er vist i figur 2 ovenfor. Punktestimatet på -0,1 %-point for den absolutte effektforskel afspejler ikke en klinisk relevant effektforskel, da den ligger under den mindste klinisk relevante forskel på 5 %-point. Den øvre grænse for konfidensintervallet ligger tættere på en negativ klinisk relevant forskel end på 0 (ingen effektforskel). Usikkerheden ved resultaterne er dermed for stor, hvilket medfører, at den foreløbige værdi af filgotinib vedr. deleffektmålet behandlingsophør grundet uønskede hændelser ikke kan kategoriseres efter Medicinrådets metoder.

Baseret på den relative effektforskel, som fremgår af tabel 3, har filgotinib foreløbigt en værdi, der ikke kan kategoriseres vedr. deleffektmålet behandlingsophør grundet uønskede hændelser.

Alvorlige infektioner

Alvorlige infektioner er et relevant delmål, da disse særligt frygtes af patienter og klinikere, idet de kan forårsage pauser i behandlingen med risiko for forværring af symptomer/sygdomsprogression.

13 ud af 475 patienter (2,7 %) havde ved uge 52 haft en alvorlig infektion i filgotinib-armen, hvilket var tilfældet for 10 ud af 325 patienter (3,1 %) i adalimumab-armen.



Figur 3. Punktestimat og 95 % konfidensinterval for den absolutte forskel for alvorlige infektioner. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Den absolutte forskel er vist i figur 3 ovenfor. Punktestimatet på 0,3 %-point for den absolutte effektforskel afspejler ikke en klinisk relevant effektforskel, da det ligger under den mindste klinisk relevante forskel på 5 %-point. Den øvre grænse for konfidensintervallet er tættere på 0 (ingen effekt) end på en negativ klinisk relevant forskel. Derfor har filgotinib foreløbigt ingen dokumenteret merværdi vedr. deleffektmålet alvorlige infektioner.

Baseret på den relative effektforskel, som fremgår af tabel 3, har filgotinib foreløbigt en værdi, der ikke kan kategoriseres vedr. deleffektmålet alvorlige infektioner.

Gennemgang af bivirkningsprofil

Gennemgangen af bivirkningsprofilerne for filgotinib og adalimumab tager udgangspunkt i lægemidlernes produktresuméer [13,14], hvor bivirkningsprofilerne er sammenlagt fra de underliggende kliniske studier.

Filgotinib

De hyppigst indberettede bivirkninger er kvalme (3,5 %), øvre luftvejsinfektioner (3,3 %), urinvejsinfektioner (1,7 %) og svimmelhed (1,2 %). Den hyppigste alvorlige bivirkning er lungebetændelse. Der er også rapporteret om infektioner, som kan opstå, når immunforsvaret er svækket (opportunistiske infektioner), herunder tuberkulose, svampeinfektion i mund/spiserør (øsofageal candidiasis), gærsvampeinfektion (cryptokokkose) og herpes zoster. Øvrige bivirkninger af særlig interesse, som fremhæves i produktresuméet og risikostyringsplanen, inkluderer malignitet, hæmatologiske anomalier, forhøjede lipider, kardiovaskulær risiko og venøs tromboemboli (VTE) [13]. Fagudvalget bemærker, at patienter med kronisk leddegigt har en risiko for hjertekarsygdom på niveau med type 2-diabetes-patienter, hvorfor filgotinibs bivirkningsprofil med øget risiko for forhøjede lipider, kardiovaskulær risiko og VTE er bekymrende. I filgotinibs EPAR er det desuden fremhævet, at det kliniske studieprogram har vist, at der er højere incidensrate for død ved behandling med 200 mg filgotinib sammenlignet med adalimumab, men at der er tale om få tilfælde. EMA konkluderer, at det er svært at vurdere relevansen af denne observation, da forskellen mellem de forskellige behandlingsgrupper er lille og ikke statistisk signifikant [12].

Der er i dyreforsøg blevet observeret nedsat fertilitet samt irreversibel nedsat spermatogenese og histopatologiske virkninger på hanlige kønsorganer. Filgotinibs potentielle virkning på sædproduktion og mandlig fertilitet hos mennesker kendes ikke på nuværende tidspunkt. I filgotinibs produktresumé fremhæves denne potentielle bivirkning i risikostyringsplanen, som bør drøftes med mandlige patienter inden initiering af behandling [13]. Derudover kan filgotinib forårsage fosterskader, baseret på fund hos dyr, og derfor er filgotinib kontraindiceret under graviditet, og kvinder i den fertile alder bør benytte sikker kontraception [13]. To igangværende studier, MANTA og MANTA-RAY, undersøger toksiciteten af behandling med 200 mg filgotinib på mænds fertilitet nærmere. Fagudvalget er bekendt med, at FDA ikke har godkendt filgotinib, bl.a. på baggrund af den potentielle påvirkning af mandlig fertilitet, og finder, at en mulig irreversibel påvirkning af mandlig fertilitet giver anledning til bekymring. Fagudvalget anerkender imidlertid EMAs afgørelse og håndtering af denne potentielle bivirkning som beskrevet i produktresuméet.

Adalimumab

De hyppigst rapporterede bivirkninger er øvre luftvejsinfektioner, reaktioner på injektionsstedet (udslæt (erytem), kløe, blødning, smerter eller hævelse), hovedpine og muskuloskeletal smerte. Ved brug af adalimumab er der rapporteret om dødelige og livstruende infektioner (inkl. blodforgiftning, opportunistiske infektioner og tuberkulose), hepatitis B-reaktivering og leverenzymforhøjelse. Dertil kan en øget risiko for malignt melanom og non-melanom hudkræft ikke udelukkes. Der er også rapporteret om alvorlige hæmatologiske (blodmangel, leukopeni, pancytopeni), neurologiske (Guillain-Barrés syndrom) og autoimmune reaktioner. Sjældne bivirkninger er bl.a. tarmperforation, lungefibrose, Stevens-Johnsons syndrom og dissemineret sklerose [14].

Samlet vurdering af bivirkningsprofiler
Fagudvalget fremhæver, at der ved behandling med filgotinib er rejst bekymring om irreversibel påvirkning af mandlig fertilitet og potentiel risiko for fosterskader, baseret på fund i dyr. Derfor finder fagudvalget, at mænd med ønske om børn ikke bør tilbydes behandling med filgotinib, og at kvinder i den fertile alder bør anvende sikker kontraception.

Fagudvalget bemærker, at der for JAK-hæmmeren tofacitinib er en øget risiko for VTE og risiko for alvorlige infektioner hos patienter > 65 år, hvilket giver anledning til bekymring hos ældre patienter med komorbiditet [15]. Det er imidlertid usikkert, om der er tale om en klasseeffekt for JAK-hæmmere, og dermed om samme risiko vil gøre sig gældende for filgotinib.

Udover ovenstående fremhævede forskelle finder fagudvalget, at filgotinib og adalimumab har sammenlignelige bivirkningsprofiler hvad angår sværhedsgrad og håndtering.

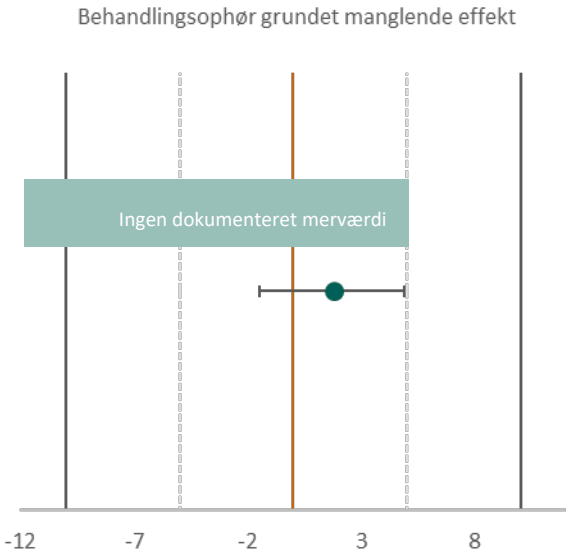
Samlet for effektmålet bivirkninger

Baseret på ovenstående gennemgang af effektmålets tre delmål vurderer fagudvalget, at filgotinib aggregeret har en merværdi, som **ikke kan kategoriseres** vedr. effektmålet bivirkninger. Både den absolutte og relative effektforskel for delmålet *andel patienter, der oplever uønskede hændelser* samt den absolutte forskel for delmålet *andel patienter, der oplever alvorlige infektioner* kan ikke kategoriseres efter Medicinrådets metoder pga. usikkerhed ved resultaterne. Fagudvalget understreger, at de absolutte forskelle ikke er af klinisk betydning, da de ligger under de mindste klinisk relevante forskelle.

Imidlertid udtrykker fagudvalget bekymring om påvirkning af mandlig fertilitet og potentielt øget risiko for fosterskader ved behandling med filgotinib. Derfor finder fagudvalget, at mænd med ønske om børn ikke bør tilbydes behandling med filgotinib, og at kvinder i den fertile alder bør anvende sikker kontraception.

Behandlingsophør grundet manglende effekt
Dette er et vigtigt effektmål, da det er relevant at afdække forskelle i manglende effekt af lægemidler med potentielle bivirkninger. En belysning af dette effektmål vil bidrage til at muliggøre valg af den bedste behandling først og dermed reducere unødvendig behandling.

29 ud af 475 patienter (6,1 %) havde ophørt behandlingen grundet manglende effekt ved uge 52 i filgotinib-armen, hvilket var tilfældet for 14 ud af 325 patienter (4,3 %) i adalimumab-armen.



Figur 4. Punktestimat og 95 % konfidensinterval for den absolutte forskel for behandlingsophør grundet manglende effekt. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

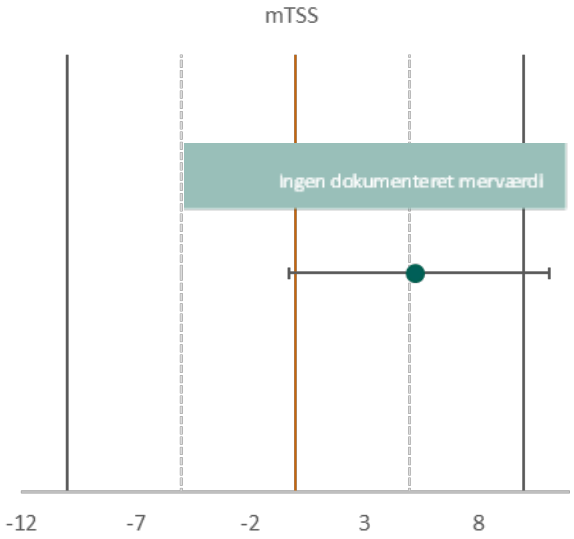
Den absolutte forskel er vist i figur 4 ovenfor. Punktestimatet på 1,8 %-point for den absolutte effektforskel afspejler ikke en klinisk relevant effektforskel, da den ligger under den mindste klinisk relevante forskel på 10 %-point. Den nedre grænse for konfidensintervallet er tættere på 0 (ingen effekt) end på en negativ klinisk relevant forskel. Derfor har filgotinib foreløbigt ingen dokumenteret merværdi vedr. effektmålet behandlingsophør grundet manglende effekt.

Baseret på den relative effektforskel, som fremgår af tabel 3, har filgotinib foreløbigt en værdi, der ikke kan kategoriseres vedr. effektmålet behandlingsophør grundet manglende effekt.

Fagudvalget vurderer, at filgotinib aggregeret har **ingen dokumenteret merværdi** vedr. effektmålet behandlingsophør grundet manglende effekt, baseret på ovenstående gennemgang af de absolutte og relative effektforskelle.

Total Sharp Score (TSS)
Fagudvalget mener, at dette er et relevant radiologisk effektmål efter minimum 12 måneders opfølgning, da det kan tolkes som et udtryk for sygdomsprogression.

365 ud af 417 patienter (87,5 %) havde ikke haft radiologisk progression målt ved mTSS ved uge 52 i filgotinib-armen, hvilket var tilfældet for 225 ud af 273 patienter (82,4 %) i adalimumab-armen.



Figur 5. Punktestimat og 95 % konfidensinterval for den absolutte forskel for mTSS. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Den absolutte forskel er vist i figur 5 ovenfor. Punktestimatet på 5,2 %-point for den absolutte effektforskel afspejler ikke en klinisk relevant effektforskel, da den ligger under den mindste klinisk relevante forskel på 10 %-point. Den nedre grænse for konfidensintervallet er tættere på 0 (ingen effekt) end på en negativ klinisk relevant forskel. Derfor har filgotinib foreløbigt ingen dokumenteret merværdi vedr. effektmålet TSS.

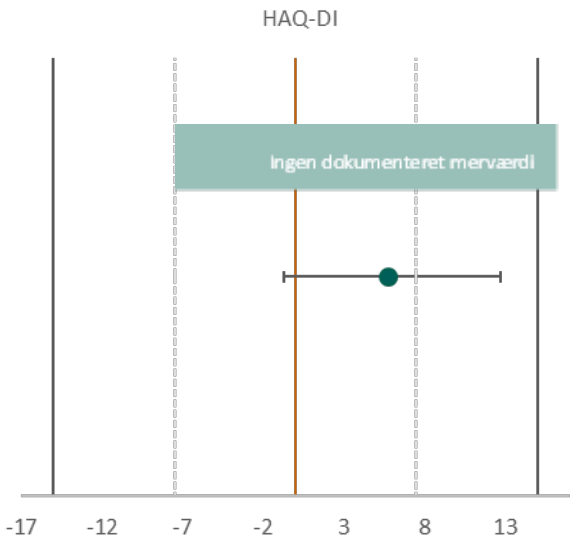
Baseret på den relative effektforskel, som fremgår af tabel 3, har filgotinib foreløbigt ingen dokumenteret merværdi vedr. effektmålet TSS.

Fagudvalget vurderer, at filgotinib aggregeret har **ingen dokumenteret merværdi** vedr. effektmålet TSS, baseret på ovenstående gennemgang af de absolutte og relative effektforskelle.

HAQ-DI

HAQ-DI er et mål for patienternes funktionsniveau. Da kronisk leddegigt kan medføre betydeligt funktionstab, kan HAQ-DI i denne sammenhæng afspejle livskvalitet. Det er et domænespecifikt instrument, der er pålideligt, velundersøgt og valideret til leddegigt [16]. HAQ-DI er valgt fremfor et generisk instrument, idet fagudvalget vurderer, at det er af større relevans for patienter med kronisk leddegigt, og fordi det anvendes i dansk klinisk praksis og bl.a. registreres ved ambulante besøg. HAQ-DI scorer på en skala fra 0 til 3, hvor 0 angiver ”uden besvær”, og 3 angiver ”kan ikke udføre”. En klinisk signifikant ændring er defineret som et fald eller en forbedring i HAQ-DI-score på ≥ 0,22 fra baseline [17].

348 ud af 459 patienter (75,8 %) havde opnået en klinisk signifikant forbedring målt ved HAQ-DI ved uge 52 i filgotinib-armen, hvilket var tilfældet for 222 ud af 316 patienter (70,3 %) i adalimumab-armen.



Figur 6. Punktestimat og 95 % konfidensinterval for den absolutte forskel for HAQ-DI. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Den absolutte forskel er vist i figur 6 ovenfor. Punktestimatet på 5,7 %-point for den absolutte effektforskel afspejler ikke en klinisk relevant effektforskel, da den ligger under den mindste klinisk relevante forskel på 15 %-point. Den nedre grænse for konfidensintervallet er tættere på 0 (ingen effekt) end på en negativ klinisk relevant forskel. Derfor har filgotinib foreløbigt ingen dokumenteret merværdi vedr. effektmålet HAQ-DI.

Baseret på den relative effektforskel, som fremgår af tabel 3, har filgotinib foreløbigt ingen dokumenteret merværdi vedr. effektmålet HAQ-DI.

Fagudvalget vurderer, at filgotinib aggregeret har **ingen dokumenteret merværdi** vedr. effektmålet HAQ-DI, baseret på ovenstående gennemgang af de absolutte og relative effektforskelle.

5.1.5 Fagudvalgets konklusion

Fagudvalget vurderer, at filgotinib i kombination med MTX til biologisk behandlingsnaive patienter med moderat til svær kronisk leddegigt giver **ingen dokumenteret merværdi** sammenlignet med adalimumab i kombination med MTX.

Fagudvalgets konklusion er foretaget på baggrund af de aggregerede merværdier for de enkelte effektmål. Her ses det, at samtlige effektmål indikerer, at der ikke kan påvises en klinisk effektforskel mellem de to behandlinger.

Imidlertid udtrykker fagudvalget bekymring vedr. påvirkning af mandlig fertilitet og potentielt øget risiko for fosterskader. Derfor finder fagudvalget, at den samlede konklusion ikke omfatter mænd med ønske om børn og kvinder med aktuelt graviditetsønske.

5.2 Klinisk spørgsmål 2

5.2.1 Litteratur

Nedenfor beskriver og vurderer Medicinrådet den litteratur, som ansøger har anvendt i sin endelige ansøgning til at besvare klinisk spørgsmål 2. Det kliniske spørgsmål er:

Hvilken værdi har filgotinib i kombination med MTX sammenlignet med adalimumab i kombination med MTX for behandlingserfarne patienter med moderat til svær kronisk leddegigt?

Ansøger har søgt litteratur med søgestrengen fra protokollen og fundet én fuldtekstartikel (med data fra FINCH 2-studiet), der stemmer overens med in- og eksklusionskriterierne fra Medicinrådets protokol. Artiklen omhandler et klinisk studie for filgotinib (FINCH 2) [18]. Ansøger har ikke fundet litteratur vedrørende komparatoren adalimumab, der kan bruges til sammenligning med FINCH 2-studiet.

Desuden indgår EMAs EPAR og produktresumé for filgotinib [12,13] og adalimumab [14].

FINCH 2

Dette er et randomiseret, dobbeltblindet fase III-studie, der undersøgte effekten og sikkerheden af filgotinib i kombination med csDMARD(s) sammenlignet med placebo i kombination med csDMARD(s) hos patienter med moderat til svær kronisk leddegigt, der havde oplevet manglende respons eller intolerance af mindst én bDMARD. Patienterne er således biologisk behandlingserfarne.

Patienterne blev randomiseret 1:1:1 til filgotinib 200 mg dagligt (n = 147), filgotinib 100 mg dagligt (n = 153) eller placebo (n = 148), mens de fortsatte behandling med csDMARDs. Randomiseringen var bl.a. stratificeret efter geografi og antallet af bDMARDS, som patienten tidligere havde modtaget (< 3 eller ≥ 3). Studiet kørte over 24 uger. Patienter, der ikke var stoppet med behandlingen undervejs, kunne efter de 24 uger fortsætte i behandling i FINCH 4-studiet, som er et langtidsekstensionsstudie. Ved manglende effekt ved uge 14 stoppede patienterne behandlingen og skiftede til standardbehandling.

Primære effekt- og sikkerhedsanalyser blev foretaget på data fra alle randomiserede patienter, der modtog mindst én studiedosis. Studiets primære effektmål var American

College of Rheumatology 20 % response (ACR20) ved uge 12. Sekundære effektmål af relevans er ACR50, livskvalitet målt ved HAQ-DI, ophør af behandling pga. manglende effekt og sikkerhed.

Tabel 4. Oversigt over studier

Publikationer	Klinisk forsøg	NCT-nummer	Population	Intervention vs. komparator
Genovese et al. 2019 [18] EPAR [12]	FINCH 2	NCT02873936	Biologisk behandlingserfarne patienter med moderat til svær kronisk leddegigt	Filgotinib + csDMARDs vs. placebo + csDMARDS

Tabel 5 lister baselinekarakteristika for patientpopulationen i FINCH 2-studiet.

Tabel 5. Baselinekarakteristika*

	Filgotinib 200 mg + csDMARDs	Placebo + csDMARDs
Kvinder, antal (%)	120 (81,6 %)	121 (81,8 %)
Sygdomsvarighed, år	12,6 (9,5)	12,6 (10,3)
Alder, år	56 (12,5)	56 (12,1)
Antal tidligere behandlinger med bDMARDs, antal (%)		
< 3	110 (74,8 %)	114 (77 %)
≥ 3	37 (25,2 %)	32 (23 %)
Samtidig brug af MTX, antal (%)	124 (84,4 %)	116 (78,4 %)
SJC66	18 (12,5)	17 (9,7)
TJC68	28 (16,1)	27 (15,5)
RF- + anti-CCP-positive, antal (%)	91 (61,9)	84 (56,8)
DAS28-CRP	5,9 (1,0)	5,9 (0,9)
HAQ-DI	1,70 (0,66)	1,65 (0,63)
TSS	NA	NA

*Alle værdier er opgjort som gennemsnit ± SD, medmindre andet er specificeret.
SJC66 = *Swollen joint count in 66 joints* (antal hævede led ud af 66 led), TJC68 = *Tender joint count in 68 joints*, RF = *Rheumatoid factor*, CCP = *Citric citrullinated peptide*, DAS28-CRP = *Disease Activity Score 28 - C-reactive protein value*, mTSS = *modificeret Total Sharp Score/van der Heijde score*, HAQ-DI = *Health Assessment Questionnaire Disability Index*, NA = ikke tilgængeligt.

Da der ikke foreligger noget data på komparatoren adalimumab, er der ikke grundlag for at sammenligne studiepopulationer.

Fagudvalget finder, at patientkarakteristika i FINCH 2-studiet ikke afviger væsentligt fra den danske patientpopulation.

5.2.2 Databehandling og analyse

I dette afsnit er ansøgers datagrundlag, databehandling og analyse for hvert effektmål beskrevet.

Da ansøger ikke har fundet litteratur vedrørende komparatoren adalimumab til at besvare klinisk spørgsmål 2, er der ikke indsendt komparative analyser. Derfor kan fagudvalget ikke vurdere værdien af filgotinib efter Medicinrådets metoder.

Ansøger har i stedet lavet en narrativ beskrivelse af filgotinib 200 mg baseret på FINCH 2-studiet og har indsendt resultater for samtlige effektmål, undtagen TSS, ved uge 24.

Ved besvarelsen af det kliniske spørgsmål tager fagudvalget udgangspunkt i ansøgers narrative beskrivelse af data. Dertil har fagudvalget forholdt sig til, om det er muligt at ekstrapolere konklusionerne fra klinisk spørgsmål 1, der dog omhandler biologisk behandlingsnaive patienter. Dermed er vurderingen af den samlede værdi af filgotinib i kombination med MTX til biologisk behandlingserfarne patienter baseret på den narrative beskrivelse af FINCH 2-studiedata, på ekstrapolering fra klinisk spørgsmål 1 og på fagudvalgets kliniske ekspertise og erfaring.

Fagudvalget og sekretariatet ønsker at fremhæve følgende vedrørende den narrative beskrivelse og sammenligning:

- Filgotinib kan kun gives i kombination med MTX i henhold til EMA-indikationen og ikke i kombination med andre csDMARDs, som FINCH 2-studiet ellers har inddraget. I studiet modtager 15,6 % af patienterne i filgotinib-armen en anden csDMARD end MTX. Fagudvalget finder, at dette ikke er af betydning for vurderingen af den kliniske merværdi.
- Data fra FINCH 2 stammer fra alle randomiserede patienter i filgotinib-armen (*Full Analysis Set* (FAS)). Under studiet kunne patienterne stoppe behandling ved manglende effekt og skifte over til standardbehandling (se beskrivelse af studiet i afsnit 5.2.1). I studieperioden stoppede 12 patienter (8,2 %) behandling med filgotinib pga. manglende effekt. Det betyder, at der er en vis usikkerhed forbundet med størrelsesordenen af den rapporterede effekt, da patienterne ikke nødvendigvis under hele opfølgningstiden modtog den intervention, de blev randomiseret til ved studiestart. Da primære effekt- og sikkerhedsanalyser blev foretaget på data fra alle randomiserede patienter, der modtog mindst én studiedosis, vurderer fagudvalget dog, at usikkerheden vedr. skiftepatienter påvirker effektforskellen minimalt.

5.2.3 Evidensens kvalitet

Da der ikke foreligger nogen komparative analyser, har fagudvalget ikke anvendt GRADE til at foretage en formel vurdering af kvaliteten af evidensen. Vurdering af risikoen for bias i FINCH 2 fremgår af bilag 1.

Da der er tale om en narrativ beskrivelse og sammenligning, er evidensens kvalitet meget lav, hvilket betyder, at nye studier med høj sandsynlighed kan ændre konklusionen.

5.2.4 Effektestimater og kategorier

I tabellen herunder fremgår kun data for filgotinib- og placeboarmen fra FINCH 2-studiet og dermed ingen absolutte effektforskelle. Dertil fremgår den samlede kvalitet af evidensen for klinisk spørgsmål 2. Da der ikke kan foretages komparative analyser, er det ikke muligt at kategorisere de enkelte effektmål og dermed heller ikke den samlede værdi af filgotinib.

Tabel 6. Resultater for klinisk spørgsmål 2 – filgotinib i kombination med MTX til behandlingserfarne patienter

Effektmål	Målenhed (MKRF)	Vigtighed	Forskel i absolutte tal	Aggregeret værdi for effektmålet
			FINCH 2 filgotinib 200 mg vs. placebo Uge 24	
American College of Rheumatology 50 % response (ACR50)	Andel patienter, der oplever respons (15 %-point)	Kritisk	45,6 % FIL vs. 18,2 % PBO	Kan ikke kategoriseres***
Bivirkninger	Andel patienter, der ophører behandling grundet uønskede hændelser (5 %-point)	Kritisk	2,0 % FIL vs. 2,0 % PBO	Kan ikke kategoriseres***
	Andel patienter, der oplever alvorlige infektioner (5 %-point)		0,7 % FIL vs. 1,4 % PBO	
	Gennemgang af bivirkningsprofil		Se beskrivelse nedenfor	
Behandlingsophør grundet manglende effekt	Andel patienter, der ophører behandling (10 %-point)	Vigtig	8,2 % FIL vs. 21,6 % PBO	Kan ikke kategoriseres***
Total Sharp Score (TSS) efter minimum 12 måneder	Andel patienter uden progression (10 %-point)	Vigtig	Ikke tilgængelig	Kan ikke kategoriseres***
Health Assessment Questionnaire Disability Index (HAQ-DI)	Andel patienter, der oplever respons (15 %-point)	Vigtig	68,8 % FIL vs. 35,4 % PBO	Kan ikke kategoriseres***

Konklusion	
Samlet kategori for lægemidlets værdi	Kan ikke kategoriseres. Fagudvalget vurderer imidlertid, at der ikke er evidens for, at der er forskel på behandlingseffekten mellem filgotinib i kombination med MTX og adalimumab i kombination med MTX til behandlingserfarne patienter.
Kvalitet af den samlede evidens	Meget lav

FIL = filgotinib, PBO = placebo, ADA = adalimumab
* Data for uge 24.
** Data for placebo er ikke tilgængelig.
*** Kategorisering er ikke mulig pga. manglende komparative analyser.

ACR50
Effektmålet ACR50 er kritisk for vurderingen af lægemidlets værdi for patienterne, da det er det primære mål for effekt på sygdomsaktivitet, se afsnit 5.1.4 for definition af ACR50. Fagudvalget finder, at en 50 %'s forbedring hos den enkelte patient er tilstrækkelig for at definere respons, hvorimod en 20 %'s forbedring (ACR20) i fagudvalgets optik ikke er et tilstrækkeligt klinisk respons.

I FINCH 2 havde 67 ud af 147 patienter (45,6 %) opnået ACR50 ved uge 24 i filgotinib-armen, hvilket var tilfældet for 27 ud af 148 patienter (18,2 %) i placeboarmen.

Da der ikke foreligger nogen komparative analyser mellem filgotinib og adalimumab, kan den foreløbige værdi af filgotinib vedr. effektmålet ACR50 **ikke kategoriseres** efter Medicinrådets metoder.

Baseret på ovenstående gennemgang, klinisk erfaring og ekstrapolering fra klinisk spørgsmål 1 omhandlende behandlingsnaive patienter vurderer fagudvalget imidlertid, at der ikke er evidens for, at der er forskel mellem filgotinib i kombination med MTX og adalimumab i kombination med MTX hvad angår effektmålet ACR50.

Bivirkninger
Effektmålet bivirkninger er kritisk for vurderingen af lægemidlets værdi, fordi bivirkninger både er generende for patienterne og kan forårsage pauser i behandlingen, hvilket kan forværre sygdommen. Effektmålet er delt op på tre delmål: behandlingsophør grundet uønskede hændelser, alvorlige infektioner og en kvalitativ gennemgang af de to lægemidlers bivirkningsprofiler.

Behandlingsophør grundet uønskede hændelser
Det er fagudvalgets vurdering, at uønskede hændelser, der fører til ophør af behandlingen, er et brugbart mål for bivirkninger.

I FINCH 2 havde 3 ud af 147 patienter (2,0 %) ophørt behandlingen grundet uønskede hændelser ved uge 24 i filgotinib-armen, hvilket var tilfældet for 3 ud af 148 patienter (2,0 %) i placeboarmen.

Alvorlige infektioner
Alvorlige infektioner er et relevant delmål, da disse særligt frygtes af patienter og klinikere, idet de kan forårsage pauser i behandlingen med risiko for forværring af symptomer/sygdomsprogression.

I FINCH 2 havde 1 ud af 147 patienter (0,7 %) haft en alvorlig infektion ved uge 24 i filgotinib-armen, hvilket var tilfældet for 2 ud af 148 patienter (1,4 %) i placeboarmen.

Gennemgang af bivirkningsprofil
Se gennemgangen af bivirkningsprofiler ved klinisk spørgsmål 1, afsnit 5.1.4. Ifølge fagudvalget forventes der ikke at være forskel i bivirkninger mellem behandlingsnaive og behandlingserfarne patienter. Dermed gælder de nævnte forbehold ved behandling med

filgotinib, som er fremhævet ved gennemgangen af resultaterne for klinisk spørgsmål 1, også her.

Samlet for effektmålet bivirkninger

Da der ikke foreligger nogen komparative analyser mellem filgotinib og adalimumab, kan den foreløbige værdi af filgotinib vedr. effektmålet bivirkninger **ikke kategoriseres** efter Medicinrådets metoder.

Imidlertid udtrykker fagudvalget bekymring om påvirkning af mandlig fertilitet og potentielt øget risiko for fosterskader ved behandling med filgotinib. Derfor finder fagudvalget, at mænd med ønske om børn ikke bør tilbydes behandling med filgotinib, og at kvinder i den fertile alder bør anvende sikker kontraception.

Behandlingsophør grundet manglende effekt

Dette er et vigtigt effektmål, da det er relevant at afdække forskelle i manglende effekt af lægemidler med potentielle bivirkninger. En belysning af dette effektmål vil bidrage til at muliggøre valg af den bedste behandling først og dermed reducere unødvendig behandling.

I FINCH 2 havde 12 ud af 147 patienter (8,2 %) ophørt behandlingen pga. manglende effekt ved uge 24 i filgotinib-armen, hvilket var tilfældet for 32 ud af 148 patienter (21,6 %) i placeboarmen.

Da der ikke foreligger nogen komparative analyser mellem filgotinib og adalimumab, kan den foreløbige værdi af filgotinib vedr. effektmålet behandlingsophør grundet manglende effekt **ikke kategoriseres** efter Medicinrådets metoder.

Baseret på ovenstående gennemgang, klinisk erfaring og ekstrapolering fra klinisk spørgsmål 1 omhandlende behandlingsnaive patienter vurderer fagudvalget imidlertid, at der ikke er evidens for, at der er forskel mellem filgotinib i kombination med MTX og adalimumab i kombination med MTX hvad angår effektmålet behandlingsophør grundet manglende effekt.

Total Sharp Score (TSS)

Fagudvalget mener, at dette er et relevant radiologisk effektmål efter minimum 12 måneders opfølgning, da det kan tolkes som et udtryk for sygdomsprogression.

Ansøger har ikke indsendt data for TSS, da effektmålet ikke var undersøgt i FINCH 2-studiet. Den foreløbige merværdi af filgotinib vedr. effektmålet TSS kan dermed **ikke kategoriseres** efter Medicinrådets metoder.

HAQ-DI

HAQ-DI er et mål for patienternes funktionsniveau. Da kronisk leddegigt kan medføre betydeligt funktionstab, kan HAQ-DI i denne sammenhæng afspejle livskvalitet. Det er et domænespecifikt instrument, der er pålideligt, velundersøgt og valideret til leddegigt [16]. HAQ-DI er valgt fremfor et generisk instrument, idet fagudvalget vurderer, at det er af større relevans for patienter med kronisk leddegigt, og fordi det anvendes i dansk

klinisk praksis og bl.a. registreres ved ambulante besøg. HAQ-DI scorer på en skala fra 0 til 3, hvor 0 angiver ”uden besvær”, og 3 angiver ”kan ikke udføre”. En klinisk signifikant ændring er defineret som et fald eller forbedring i HAQ-DI-score på ≥ 0,22 fra baseline [17].

I FINCH 2 havde 99 ud af 144 patienter (68,8 %) opnået en klinisk signifikant ændring målt ved HAQ-DI ved uge 24 i filgotinib-armen, hvilket var tilfældet for 51 ud af 144 patienter (35,4 %) i placeboarmen.

Da der ikke foreligger nogen komparative analyser mellem filgotinib og adalimumab, kan den foreløbige værdi af filgotinib vedr. effektmålet HAQ-DI **ikke kategoriseres** efter Medicinrådets metoder.

Baseret på ovenstående gennemgang, klinisk erfaring og ekstrapolering fra klinisk spørgsmål 1 omhandlende behandlingsnaive patienter vurderer fagudvalget imidlertid, at der ikke er evidens for, at der er forskel mellem filgotinib i kombination med MTX og adalimumab i kombination med MTX hvad angår effektmålet HAQ-DI.

5.2.5 Fagudvalgets konklusion

Fagudvalget vurderer, at den samlede værdi af filgotinib i kombination med MTX til biologisk behandlingserfarne patienter med moderat til svær kronisk leddegigt **ikke kan kategoriseres** sammenlignet med adalimumab i kombination med MTX.

Årsagen hertil er, at der ikke foreligger data vedrørende komparator. Fagudvalget har narrativt gennemgået FINCH 2-data for filgotinib i kombination med MTX til behandlingserfarne patienter. Vurderingen af den samlede værdi er dermed baseret på denne narrative gennemgang, på ekstrapolering fra klinisk spørgsmål 1 omhandlende behandlingsnaive patienter og på fagudvalgets kliniske ekspertise og erfaring.

Fagudvalget vurderer, at der ikke er evidens for, at der er forskel på behandlingseffekten mellem filgotinib i kombination med MTX og adalimumab i kombination med MTX.

Dog udtrykker fagudvalget bekymring vedr. påvirkning af mandlig fertilitet og potentielt øget risiko for fosterskader. Derfor finder fagudvalget, at den samlede konklusion ikke omfatter mænd med ønske om børn og kvinder med aktuelt graviditetsønske.

5.3 Klinisk spørgsmål 3

5.3.1 Litteratur

Nedenfor beskriver og vurderer Medicinrådet den litteratur, som ansøger har anvendt i sin endelige ansøgning til at besvare klinisk spørgsmål 3. Det kliniske spørgsmål er:

Hvilken værdi har filgotinib som monoterapi sammenlignet med etanercept som monoterapi for behandlingsnaive patienter med moderat til svær kronisk leddegigt?

Ansøger har søgt litteratur med søgestrengen fra protokollen og fundet fire fuldtekstartikler fra tre kliniske studier, der stemmer overens med in- og eksklusionskriterierne fra Medicinrådets protokol. Artiklerne omhandler et klinisk studie for filgotinib (DARWIN 2) [19,20] og to kliniske studier for etanercept (Moreland et al. og JERA) [21,22].

Desuden indgår EMAs EPAR og produktresumé for filgotinib [12,13] og etanercept [23].

DARWIN 2

Dette er et randomiseret, dobbeltblindet placebo-kontrolleret fase IIb-studie, der undersøgte effekten og sikkerheden af filgotinib monoterapi sammenlignet med placebo hos patienter med kronisk leddegigt og fortsat moderat til svær sygdomsaktivitet trods MTX-behandling. Næsten alle patienter var biologisk behandlingsnaive.

Patienterne blev randomiseret 1:1:1:1 til filgotinib 50 mg dagligt (n = 72), filgotinib 100 mg dagligt (n = 70), filgotinib 200 mg dagligt (n = 69) eller placebo (n = 72). Randomiseringen var stratificeret efter geografi og tidligere behandling med bDMARDs. Studiet kørte over 24 uger. Ved uge 12 skiftede alle patienter i placeboarmen og patienter på 50 mg i filgotinib-armen, som havde utilstrækkelig effekt (< 20 % forbedring i SJC66 (*swollen joint count in 66 joints*) og TJC66 (*tender joint count in 68 joints*)), over til 100 mg filgotinib.

Primære effekt- og sikkerhedsanalyser blev foretaget på data fra alle randomiserede patienter, der modtog mindst én studiedosis (ITT-population). Studiets primære effektmål var ACR20 ved uge 12. Sekundære effektmål af relevans er ACR50, livskvalitet målt ved HAQ-DI, ophør af behandling pga. manglende effekt og sikkerhed.

Moreland et al.

Dette er et randomiseret, dobbeltblindet placebo-kontrolleret fase II-studie, der undersøgte effekten og sikkerheden af etanercept monoterapi sammenlignet med placebo hos patienter med kronisk leddegigt og fortsat moderat til svær sygdomsaktivitet trods behandling med 1-4 DMARDs. Patienterne var således biologisk behandlingsnaive.

Patienterne blev randomiseret 1:1:1 til etanercept 10 mg to gange om ugen (n = 76), etanercept 25 mg to gange om ugen (n = 78) eller placebo (n = 80). Randomiseringen var stratificeret efter geografi og ensartet allokering til behandling. Studiet kørte over 26 uger.

En ITT-analyse blev foretaget på alle randomiserede patienter, der modtog studiebehandling. Studiets primære effektmål var ACR20 og ACR50 ved 3 og 6 måneder. Sekundære effektmål af relevans er livskvalitet målt ved HAQ-DI, ophør af behandling pga. manglende effekt og sikkerhed.

JERA

Dette er et randomiseret, dobbeltblindet placebo-kontrolleret fase III-studie, der undersøgte effekten og sikkerheden af etanercept monoterapi sammenlignet med MTX hos japanske patienter med moderat til svær kronisk leddegigt. I studiet indgik der både

patienter, som var MTX-naive, og patienter, der havde haft utilstrækkelig effekt/var intolerante over for MTX. Alle patienter i studiet havde dog tidligere været behandlet med DMARD. Patienterne var således biologisk behandlingsnaive.

Patienterne blev randomiseret 1:1:1 til etanercept 10 mg to gange om ugen (n = 192), etanercept 25 mg to gange om ugen (n = 182) eller MTX oralt (6 mg om ugen, der blev øget til 8 mg ved uge 8, hvis effekten var utilstrækkelig) (n = 176). Studiet bestod af en 4-ugers screeningperiode efterfulgt af 52 ugers behandlingsperiode og 4 ugers opfølgningsperiode.

Primære effekt- og sikkerhedsanalyser blev foretaget på data fra alle randomiserede patienter, der modtog mindst én studiedosis. Studiets primære effektmål var ændring fra baseline i mTSS ved 52 uger. Sekundære effektmål af relevans er ACR50, livskvalitet målt ved HAQ-DI, ophør af behandling pga. manglende effekt og sikkerhed.

I de komparative analyser indgår der subgruppedata fra JERA-studiet for de patienter, der er relevante for det kliniske spørgsmål, dvs. patienter, der ikke har haft tilstrækkelig effekt/var intolerante over for MTX (MTX-IR). Disse er publiceret i en post-hoc-analyse fra JERA-studiet [22].

Tabel 7. Oversigt over studier

Publikationer	Klinisk forsøg	NCT-nummer	Population	Intervention vs. komparator
Kavanaugh et al. 2017 [19] Genovese et al. 2018 [20] EPAR [12]	DARWIN 2	NCT01894516	Biologisk behandlingsnaive patienter med moderat til svær kronisk leddegigt	Filgotinib monoterapi vs. placebo monoterapi
Moreland et al. 1999 [21] EPAR	-	-	Biologisk behandlingsnaive patienter med moderat til svær kronisk leddegigt	Etanercept monoterapi vs. placebo monoterapi
Takeuchi et al. – post-hoc-analyse [22] EPAR	JERA	NCT00445770	Biologisk behandlingsnaive patienter med moderat til svær kronisk leddegigt	Etanercept monoterapi vs. MTX

Tabel 8 lister baselinekarakteristika for patientpopulationen i hhv. DARWIN 2, Moreland et al. og JERA.

Tabel 8. Baselinekarakteristika*

	DARWIN 2 Filgotinib 200 mg (n = 69)	Moreland et al. Etanercept 2 x 25 mg (n = 78)	JERA**, MTX-IR Etanercept 2 x 25 mg (n = 122)
Kvinder, antal (%)	60 (87)	58 (74)	100 (82)
Etnicitet	NA		
Asiatiske (%)			122 (100)
Kaukasier (%)		73 (94)	
Sygdomsvarighed, år	9 (1)	11	3,4 (2,7)
Median alder, år	52 (1,4)	53	51 (10,6)
Tidligere behandling med bDMARDs, antal (%)	5 (7,2)	0	0
Tidligere brug af csDMARDs, antal (%)			
MTX	58 (84,1)	68 (87)	122 (100)
Andet	NA	NA[§]	NA
Brug af kortikosteroider, antal (%)	47 (68,1)[¶]	63 (81)	NA
Gennemsnitlig daglig dosis af kortikosteroider i mg	NA	7,3	NA
SJC66	15,7 (1,0)	NA	14,8 (9,7)[†]
TJC68	26,2 (1,5)	NA	19,0 (12,4)[†]
RF-positive, antal (%)	50 (72,5)	62 (79)	99 (81,2)
Anti-CCP-positive, antal (%)	57, (82,6)	NA	NA
DAS28-CRP	6,1 (0,1)	NA	5,9 (1,0)[‡]
HAQ-DI	1,8 (0,06)	NA	1,08 (0,68)
mTSS	NA	NA	NA

*Alle værdier er opgjort som gennemsnit ± SD, medmindre andet er specificeret.
**Baselinekarakteristika for subpopulation af patienter i JERA-studiet, der ikke har haft tilstrækkelig effekt/været intolerante over for MTX (MTX-IR). Data stammer fra post-hoc-analyse [22].
SJC66 = *Swollen joint count in 66 joints* (antal hævede led ud af 66 led), TJC = *Tender joint count in 68 joints*, RF = *Rheumatoid factor*, CCP = *Citric citrullinated peptide*, DAS28-CRP = *Disease Activity Score 28 - C-reactive protein value*, mTSS = *modificeret Total Sharp Score/van der Heijde score*, HAQ-DI = *Health Assessment Questionnaire Disability Index*, NA = ikke tilgængeligt.
[§]Mange patienter havde tidligere været behandlet med andre DMARDs såsom salazopyrin og hydroxychloroquin.
[†]Data for SJC68 = *Swollen joint count in 68 joints* og TJC71 = *Tender joint count in 71 joints*.
[‡]Data for DAS28-4ESR = *DAS28-erythrocyte sedimentation rate*.
[¶] ≤ 10 mg/dag.

JERA-studiet adskiller sig væsentligt fra de andre to studier. Der indgår kun japanske patienter i studiet, som ikke er sammenlignelige med kaukasier, bl.a. hvad angår bivirkninger og godkendt dosis i forbindelse med medicinsk behandling. Derudover var sygdomsvarigheden markant lavere i JERA-studiet sammenlignet med de andre to studier, hvilket er af betydning for behandlingsresponsen. Fagudvalget inddrager derfor ikke data fra JERA-studiet i den indirekte komparative analyse.

Overordnet er baselinekarakteristika mellem interventionsarmene i DARWIN 2- og Moreland et al.-studierne sammenlignelige og afviger ikke væsentligt fra den danske patientpopulation. DARWIN 2-studiet adskiller sig fra Moreland et al.-studiet ved, at en mindre andel af patienterne (7,2 %) tidligere har modtaget biologisk behandling, mens det kliniske spørgsmål omfatter biologisk behandlingsnaive patienter, dvs. patienter, der ikke tidligere har modtaget behandling med bDMARDs eller tsDMARDs. Fagudvalget vurderer, at denne forskel ikke har større klinisk betydning. Fagudvalget bemærker desuden, at i DARWIN 2 modtager patienterne samtidig kortikosteroidbehandling med doser op til 10 mg/dag. Den gennemsnitlige daglige dosis er dog ikke opgjort, og det vides dermed ikke, om den er sammenlignelig med den gennemsnitlige daglige dosis på 7,3 mg i Moreland et al. Det bidrager med en vis usikkerhed vedr. den reelle behandlingseffekt, da høj daglig dosis på f.eks. prednisolon (10 mg) kan holde sygdommen i ro hos nogle patienter. Derudover blev alle patienter i placeboarmen skiftet over til 100 mg filgotinib i DARWIN 2-studiet ved 12 uger, mens skift fra kontrolarmen til interventionsarmen ikke var tilladt i Moreland et al.-studiet.

5.3.2 Databehandling og analyse

I dette afsnit er ansøgers datagrundlag, databehandling og analyse for hvert effektmål beskrevet.

Ansøger har lavet to indirekte komparative analyser af filgotinib og etanercept, hvor den relative og absolutte forskel er estimeret ved brug af Buchers metode:

- I den ene indirekte analyse indgår der data for filgotinib fra DARWIN 2 og etanercept fra Moreland et al. Der er data for samtlige effektmål undtagen alvorlige infektioner, TSS og HAQ-DI.
- I den anden indirekte analyse indgår der data for filgotinib fra DARWIN 2 og fra en metaanalyse af etanercept-data fra Moreland et al. og subgruppen fra JERA. Der er data for samtlige effektmål undtagen TSS og HAQ-DI.

Fagudvalget vurderer, jf. afsnit 5.3.1, at det ikke er meningsfuldt at inkludere JERA i den indirekte komparative analyse. Fagudvalgets vurdering af filgotinibs kliniske merværdi til behandlingsnaive patienter i monoterapi vil dermed være baseret på den indirekte komparative analyse på baggrund af DARWIN 2 og Moreland et al.

Den indirekte sammenligning er i henhold til Medicinrådets metoder. Medicinrådet har ikke fundet anledning til at foretage ændringer af beregninger foretaget af ansøger eller supplere med yderligere beregninger.

Følgende fremhæves vedr. de indirekte sammenligninger:

- Pga. forskellige opfølgningstider i de to kliniske studier er der forskel på nogle effektmål, ift. hvilket tidspunkt de er blevet opgjort. Dette bliver fremhævet under de relevante effektmål.
- Fagudvalget bemærker, at der er stor forskel i effektestimaterne, både i interventions- og placeboarmen, for effektmålet *behandlingsophør grundet manglende effekt* mellem DARWIN 2 og Moreland et al. 2,8 % af patienterne i placeboarmen ophørte behandling pga. manglende effekt i DARWIN 2 sammenlignet med 52,5 % i placeboarmen i Moreland et al. Det er uklart, hvad forklaringen på denne forskel mellem studierne er, men det kan skyldes forskel i definitionen af effektmålet. Resultaterne fra den indirekte sammenligning er dermed forbundet med stor usikkerhed hvad angår dette effektmål.
- Ansøger har ikke indsendt komparative analyser for alvorlige infektioner, TSS og HAQ-DI, da data i DARWIN 2 (TSS) og Moreland et al. (TSS og HAQ-DI) ikke blev opgjort på samme måde som defineret i protokollen, og da data for alvorlige infektioner ikke blev opgjort i Moreland et al. I vurderingen af disse effektmål inddrager fagudvalget derfor viden fra gennemgangen af resultater for klinisk spørgsmål 1 samt klinisk erfaring.

5.3.3 Evidensens kvalitet

Medicinrådet har anvendt GRADE til at foretage en systematisk og transparent vurdering af kvaliteten af evidensen. Nedenfor følger en beskrivelse af vurderingen af de væsentligste domæner for hvert klinisk spørgsmål. Vurdering af risikoen for bias ved de enkelte studier fremgår af bilag 1. Den fuldstændige GRADE-vurdering og begrundelserne er samlet i en GRADE-profil (bilag 2).
Indledningsvist blev lægemidlernes direkte sammenligninger med placebo vurderet.

- Overordnet var evidensen baseret på DARWIN 2 af filgotinib sammenlignet med placebo af lav kvalitet. Evidensen er nedgraderet på baggrund af inkonsistens (kun ét studie) og unøjagtighed (konfidensintervallet for effektmålene *ophør grundet uønskede hændelser*, *alvorlige infektioner* og *ophør grundet manglende effekt* indeholder mulighed for både positive og negative konklusioner).
- Overordnet var evidensen baseret på Moreland et al. af etanercept sammenlignet med placebo af lav kvalitet. Evidensen er nedgraderet på baggrund af inkonsistens (kun ét studie) og unøjagtighed (konfidensintervallet for effektmålet *behandlingsophør grundet uønskede hændelser* indeholder mulighed for både positive og negative konklusioner).

Da merværdien af filgotinib sammenlignet med etanercept er vurderet via indirekte sammenligninger, er der for alle effektmål efterfølgende nedjusteret for indirekte evidens. Den samlede evidenskvalitet for klinisk spørgsmål 3 er efterfølgende vurderet ud fra det lavest vurderede kritiske effektmål (*behandlingsophør grundet uønskede hændelser* og *alvorlige infektioner* ved DARWIN 2 og *ophør grundet uønskede hændelser* ved Moreland et al.).

Evidensens kvalitet er meget lav, hvilket betyder, at nye studier med høj sandsynlighed kan ændre konklusionen.

5.3.4 Effektestimater og kategorier

I tabellen herunder fremgår de absolutte og relative effektforskelle, de foreløbige og aggregerede kategorier, den samlede kategori og den samlede kvalitet af evidensen for klinisk spørgsmål 3.

Tabel 9. Resultater for klinisk spørgsmål 3 – filgotinib monoterapi sammenlignet med etanercept monoterapi til behandlingsnaive patienter

Effektmål	Målenhed (MKRF)	Vigtighed	Forskel i absolutte tal		Forskel i relative tal		Aggregeret værdi for effektmålet
			Forskel [95 % CI]	Foreløbig værdi	Forskel [95 % CI]	Foreløbig værdi	
American College of Rheumatology 50 % response (ACR50)	Andel patienter, der oplever respons (15 %-point)	Kritisk	-11,7 %-point [-31,0; 45,2]	Kan ikke kategoriseres	RR: 0,72 [0,24; 2,10]	Kan ikke kategoriseres	Kan ikke kategoriseres
Bivirkninger	Andel patienter, der ophører behandling grundet uønskede hændelser (5 %-point)	Kritisk	-0,61 %-point [-2,5; 35,2]	Kan ikke kategoriseres	RR: 0,76 [0,04; 14,7]	Kan ikke kategoriseres	Kan ikke kategoriseres
	Andel patienter, der oplever alvorlige infektioner (5 %-point)		NA	Kan ikke kategoriseres	NA	Kan ikke kategoriseres	
	Gennemgang af bivirkningsprofil		Se nedenfor				
Behandlingsophør grundet manglende effekt	Andel patienter, der ophører behandling (10 %-point)	Vigtig	-4,4 %-point [-14,9; 84,6]	Kan ikke kategoriseres	RR: 0,71 [0,03; 15,3]	Kan ikke kategoriseres	Kan ikke kategoriseres
Total Sharp Score (TSS) efter minimum 12 måneder	Andel patienter uden progression (10 %-point)	Vigtig	NA	Kan ikke kategoriseres	NA	Kan ikke kategoriseres	Kan ikke kategoriseres

Health Assessment Questionnaire Disability Index (HAQ-DI)	Andel patienter, der oplever respons (15 %-point)	Vigtig	NA	Kan ikke kategoriseres	NA	Kan ikke kategoriseres	Kan ikke kategoriseres

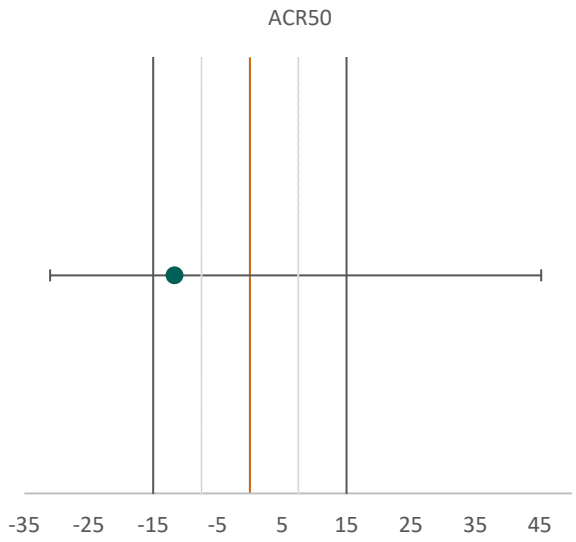
Konklusion	
Samlet kategori for lægemidlets værdi	Kan ikke kategoriseres. Fagudvalget vurderer imidlertid, at der ikke er evidens for, at der er forskel på behandlingseffekten mellem filgotinib og etanercept til behandlingsnaive patienter.
Kvalitet af den samlede evidens	Meget lav

CI = konfidensinterval, RR = relativ risiko, NA = ikke tilgængeligt.

ACR50

Effektmålet ACR50 er kritisk for vurderingen af lægemidlets værdi for patienterne, da det er det primære mål for effekt på sygdomsaktivitet. Se afsnit 5.1.4 for definition af ACR50. Fagudvalget finder, at en 50 %'s forbedring hos den enkelte patient er tilstrækkelig for at definere respons, hvorimod en 20 %'s forbedring (ACR20) i fagudvalgets optik ikke er et tilstrækkeligt klinisk respons.

43,5 % af patienterne opnåede ACR50 ved uge 12 i filgotinib-armen i DARWIN 2 [19], hvilket var tilfældet for 41 % af patienterne ved 3 måneder i etanercept-armen i Moreland et al. [21].



Figur 7. Punktestimat og 95 % konfidensinterval for den absolutte forskel for ACR50. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Den absolutte forskel udregnet vha. Buchers metode til indirekte sammenligning er vist i figur 7 ovenfor. Punktestimatet på -11,7 %-point for den absolutte effektforskel afspejler ikke en klinisk relevant effektforskel, da den ligger under den mindste klinisk relevante forskel på 15 %-point. Den nedre grænse for konfidensintervallet ligger tættere på en negativ klinisk relevant forskel end på 0 (ingen effektforskel). Usikkerheden ved resultaterne er dermed for stor, hvilket medfører, at den foreløbige værdi af filgotinib vedr. effektmålet ACR50 ikke kan kategoriseres efter Medicinrådets metoder.

Baseret på den relative effektforskel, som fremgår af tabel 9, kan filgotinibs merværdi vedr. ACR50 foreløbigt ikke kategoriseres efter Medicinrådets metoder.

Fagudvalget vurderer, at filgotinib aggregeret har en merværdi, som **ikke kan kategoriseres** vedr. ACR50, baseret på ovenstående gennemgang af de absolutte og relative effektforskelle.

Baseret på ovenstående gennemgang vurderer fagudvalget imidlertid, at der ikke er evidens for, at der er forskel mellem filgotinib og etanercept hvad angår effektmålet ACR50.

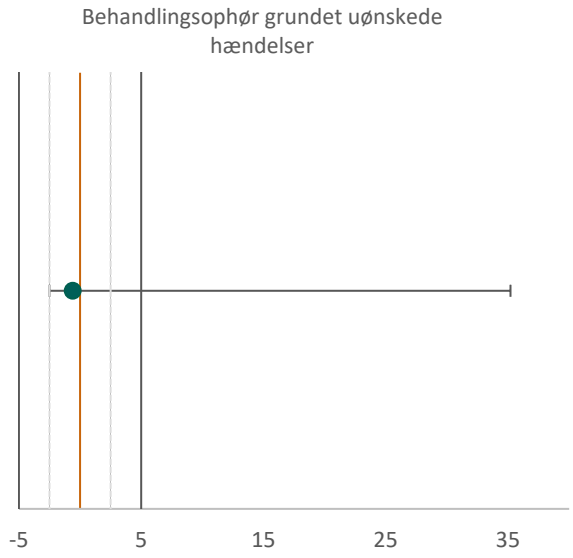
Bivirkninger

Effektmålet bivirkninger er kritisk for vurderingen af lægemidlets værdi, fordi bivirkninger både er generende for patienterne og kan forårsage pauser i behandlingen, hvilket kan forværre sygdommen. Effektmålet er delt op på tre delmål: behandlingsophør grundet uønskede hændelser, alvorlige infektioner og en kvalitativ gennemgang af de to lægemidlers bivirkningsprofiler.

Behandlingsophør grundet uønskede hændelser

Det er fagudvalgets vurdering, at uønskede hændelser, der fører til ophør af behandlingen, er et brugbart mål for bivirkninger.

1,4 % af patienterne havde ved uge 12 ophørt behandlingen grundet uønskede hændelser i filgotinib-armen i DARWIN 2-studiet [19], hvilket var tilfældet for 2,6 % af patienterne ved 6 måneder i etanercept-armen i Moreland et al. [21].



Figur 8. Punktestimat og 95 % konfidensinterval for den absolutte forskel for behandlingsophør grundet uønskede hændelser. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Den absolutte forskel udregnet vha. Buchers metode til indirekte sammenligning er vist i figur 8 ovenfor. Punktestimatet på -0,61 %-point for den absolutte effektforskel afspejler ikke en klinisk relevant effektforskel, da den ligger under den mindste klinisk relevante forskel på 5 %-point. Den øvre grænse for konfidensintervallet ligger tættere på en negativ klinisk relevant forskel end på 0 (ingen effektforskel). Usikkerheden ved resultaterne er dermed for stor, hvilket medfører, at den foreløbige værdi af filgotinib

vedr. deleffektmålet behandlingsophør grundet uønskede hændelser ikke kan kategoriseres efter Medicinrådets metoder.

Baseret på den relative effektforskel, som fremgår af tabel 9, har filgotinib foreløbigt en værdi, der ikke kan kategoriseres vedr. deleffektmålet behandlingsophør grundet uønskede hændelser. Fagudvalget bemærker, at der er relativt kort opfølgningstid i DARWIN 2, hvilket medfører, at der potentielt vil opstå flere tilfælde af behandlingsophør grundet uønskede hændelser efter længere opfølgningstid.

Alvorlige infektioner

Alvorlige infektioner er et relevant delmål, da disse særligt frygtes af patienter og klinikere, idet de kan forårsage pauser i behandlingen med risiko for forværring af symptomer/sygdomsprogression.

Alvorlig infektion blev ikke rapporteret i Moreland et al.-studiet. Dermed foreligger der ikke data, der kan indgå i en indirekte komparativ analyse. Den foreløbige og aggregerede merværdi af filgotinib vedr. alvorlige infektioner kan dermed **ikke kategoriseres** efter Medicinrådets metoder.

Ingen patienter i placeboarmen havde haft en alvorlig infektion, mens det var tilfældet for 1,4 % af patienterne ved uge 12 i filgotinib-armen i DARWIN 2-studiet [19].

Gennemgang af bivirkningsprofil

Gennemgangen af bivirkningsprofilerne for filgotinib og etanercept tager udgangspunkt i lægemidlernes produktresuméer, hvor bivirkningsprofilerne er sammenlagt fra de underliggende studier.

Filgotinib

Se gennemgangen af filgotinibs bivirkningsprofil ved klinisk spørgsmål 1 (afsnit 5.1.4).

Etanercept

De hyppigst rapporterede bivirkninger er reaktioner på injektionsstedet, infektioner (f.eks. i de øvre luftveje, bronkitis, blærebetændelse og hudinfektioner), allergiske reaktioner, udvikling af autoantistoffer, kløe og feber. Der er også rapporteret om alvorlige bivirkninger, f.eks. dødelige og livstruende infektioner og sepsis, tuberkulose og opportunistiske infektioner (herunder invasive svampeinfektioner, listeriose og legionærsygdom) i forbindelse med brugen af etanercept. Dertil kan en øget risiko for malignt melanom og non-melanom hudcancer ikke udelukkes. Der er desuden rapporteret om alvorlige hæmatologiske (f.eks. blodmangel, leukopeni og trombocytopeni), neurologiske (f.eks. demyelinisering, neuropati og Guillain-Barré syndrom) og autoimmune reaktioner (f.eks. anafylaksi). Øvrige sjældne bivirkninger er bl.a. pancytopeni, autoimmun hepatitis, Stevens-Johnsons syndrom, interstitiel lungesygdom, erythema multiforme og lichenoide reaktioner i huden [23].

Samlet vurdering af bivirkningsprofiler

Fagudvalget fremhæver, at ved behandling med filgotinib, er der rejst bekymring om irreversibel påvirkning af mandlig fertilitet og potentiel risiko for fosterskader, baseret på

fund i dyr. Derfor finder fagudvalget, at mænd med ønske om børn ikke bør tilbydes behandling med filgotinib, og at kvinder i den fertile alder bør anvende sikker kontraception.

Fagudvalget bemærker, at der for JAK-hæmmeren tofacitinib er en øget risiko for VTE og risiko for alvorlige infektioner hos patienter > 65 år, som giver anledning til bekymring hos ældre patienter med komorbiditet [15]. Det er imidlertid usikkert, om der er tale om en klasseeffekt for JAK-hæmmere, og dermed om samme risiko vil gøre sig gældende for filgotinib.

Med ovenstående fremhævede forskelle finder fagudvalget derudover, at filgotinib og etanercept har sammenlignelige bivirkningsprofiler hvad angår sværhedsgrad og håndtering.

Samlet for effektmålet bivirkninger

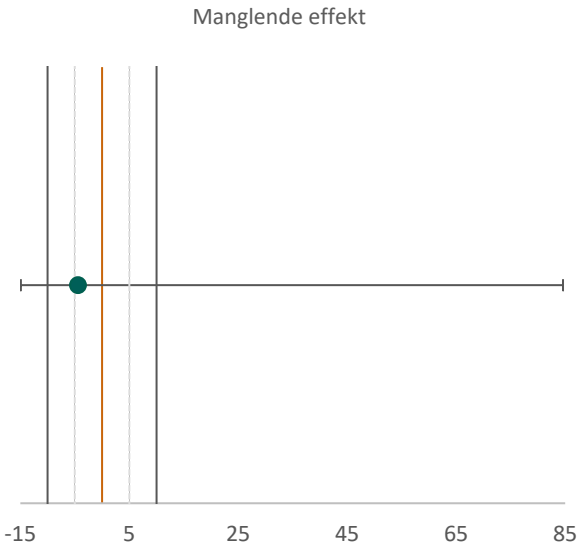
Baseret på ovenstående gennemgang af effektmålets tre delmål vurderer fagudvalget, at filgotinib aggregeret har en merværdi, som **ikke kan kategoriseres** vedr. effektmålet bivirkninger. For både *andel patienter, der oplever uønskede hændelser* og *andel patienter, der oplever alvorlige infektioner,* kan hverken den absolutte eller relative effektforskel kategoriseres efter Medicinrådets metoder. Fagudvalget understreger, at de absolutte forskelle ikke er af klinisk betydning, da de ligger under de mindste klinisk relevante forskelle. Derudover bemærker fagudvalget, at opfølgningstiden i DARWIN 2 er relativt kort, hvorfor flere bivirkninger vil kunne opstå ved længere opfølgningstid.

Imidlertid udtrykker fagudvalget bekymring om påvirkning af mandlig fertilitet og potentielt øget risiko for fosterskader ved behandling med filgotinib. Derfor finder fagudvalget, at mænd med ønske om børn ikke bør tilbydes behandling med filgotinib, og at kvinder i den fertile alder bør anvende sikker kontraception.

Behandlingsophør grundet manglende effekt

Dette er et vigtigt effektmål, da det er relevant at afdække forskelle i manglende effekt af lægemidler med potentielle bivirkninger. En belysning af dette effektmål vil bidrage til at muliggøre valg af den bedste behandling først og dermed reducere unødvendig behandling.

Ingen af patienterne havde ophørt behandlingen grundet manglende effekt ved uge 12 i filgotinib-armen i DARWIN 2-studiet [19], hvilket var tilfældet for 15,4 % af patienterne ved 6 måneder i etanercept-armen i Moreland et al. [21].



Figur 9. Punktestimat og 95 % konfidensinterval for den absolutte forskel for behandlingsophør grundet manglende effekt. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Den absolutte forskel udregnet vha. Buchers metode til indirekte sammenligning er vist i figur 9 ovenfor. Punktestimatet på -4,4 %-point for den absolutte effektforskel afspejler ikke en klinisk relevant effektforskel, da den ligger under den mindste klinisk relevante forskel på 10 %-point. Den øvre grænse for konfidensintervallet ligger tættere på en negativ klinisk relevant forskel end på 0 (ingen effektforskel). Usikkerheden ved resultaterne er dermed for stor, hvilket medfører, at den foreløbige værdi af filgotinib vedr. effektmålet behandlingsophør grundet manglende effekt ikke kan kategoriseres efter Medicinrådets metoder.

Baseret på den relative effektforskel, som fremgår af tabel 9, har filgotinib foreløbigt en værdi, der ikke kan kategoriseres vedr. effektmålet behandlingsophør grundet manglende effekt.

Fagudvalget vurderer, at filgotinib aggregeret har en merværdi, som **ikke kan kategoriseres** vedr. effektmålet behandlingsophør grundet manglende effekt, baseret på ovenstående gennemgang af de absolutte og relative effektforskelle. Fagudvalget understreger, at resultaterne skal tages med forbehold, da der er stor usikkerhed forbundet med den indirekte komparative analyse pga. væsentlige forskelle i effektestimaterne fra de to respektive studier.

Baseret på ovenstående gennemgang vurderer fagudvalget imidlertid, at der ikke er evidens for, at der er forskel mellem filgotinib og etanercept hvad angår effektmålet behandlingsophør grundet manglende effekt.

Total Sharp Score (TSS)
Fagudvalget mener, at dette er et relevant radiologisk effektmål efter minimum 12 måneders opfølgning, da det kan tolkes som et udtryk for sygdomsprogression.

TSS blev ikke rapporteret i DARWIN 2- og Moreland et al.-studierne. Dermed foreligger der ikke data, der kan indgå i en indirekte komparativ analyse. De foreløbige og den aggregerede merværdi af filgotinib vedr. TSS kan dermed **ikke kategoriseres** efter Medicinrådets metoder.

Baseret på ovenstående gennemgang, klinisk erfaring og ekstrapolering fra klinisk spørgsmål 1 omhandlende behandlingsnaive patienter i kombinationsbehandling vurderer fagudvalget imidlertid, at der ikke er evidens for, at der er forskel mellem filgotinib og etanercept hvad angår effektmålet TSS.

HAQ-DI
HAQ-DI er et mål for patienternes funktionsniveau. Da kronisk leddegigt kan medføre betydeligt funktionstab, kan HAQ-DI i denne sammenhæng afspejle livskvalitet. Det er et domænespecifikt instrument, der er pålideligt, velundersøgt og valideret til leddegigt [16]. Se yderlige i afsnit 5.1.4.

HAQ-DI blev ikke rapporteret i Moreland et al.-studiet i henhold til Medicinrådets protokol for filgotinib. Dermed foreligger der ikke data, der kan indgå i en indirekte komparativ analyse. Den foreløbige og aggregerede merværdi af filgotinib vedr. HAQ-DI kan dermed **ikke kategoriseres** efter Medicinrådets metoder.

Der foreligger data fra DARWIN 2-studiet på andel patienter, der har oplevet klinisk signifikant ændring (≥ 0,22 ændring fra baseline) i HAQ-DI [19]. 55 ud af 69 patienter (79,7 %) havde opnået en klinisk signifikant ændring målt ved HAQ-DI ved uge 12 i filgotinib-armen, hvilket var tilfældet for 37 ud af 72 patienter (51,4 %) i placeboarmen.

Baseret på ovenstående gennemgang, klinisk erfaring og ekstrapolering fra klinisk spørgsmål 1 omhandlende behandlingsnaive patienter i kombinationsbehandling vurderer fagudvalget imidlertid, at der ikke er evidens for, at der er forskel mellem filgotinib og etanercept hvad angår effektmålet HAQ-DI.

5.3.5 Fagudvalgets konklusion

Fagudvalget vurderer, at den samlede merværdi af filgotinib sammenlignet med etanercept til biologisk behandlingsnaive patienter med moderat til svær kronisk leddegigt **ikke kan kategoriseres** efter Medicinrådets metoder.

Fagudvalgets konklusion er foretaget på baggrund af de aggregerede merværdier for de enkelte effektmål. For samtlige effektmål kan merværdien ikke kategoriseres efter Medicinrådets metoder på baggrund af den indirekte sammenligning. Fagudvalget vurderer imidlertid, at der ikke er evidens for, at der er forskel på behandlingseffekten mellem filgotinib sammenlignet med etanercept.

Dog udtrykker fagudvalget bekymring vedr. påvirkning af mandlig fertilitet og potentielt øget risiko for fosterskader. Derfor finder fagudvalget, at den samlede konklusion ikke omfatter mænd med ønske om børn og kvinder med aktuelt graviditetsønske.

5.4 Klinisk spørgsmål 4

5.4.1 Litteratur

Det kliniske spørgsmål er:

Hvilken værdi har filgotinib som monoterapi sammenlignet med etanercept som monoterapi for behandlingserfarne patienter med moderat til svær kronisk leddegigt?

Ansøger har søgt litteratur med søgestrengen fra protokollen. Der blev ikke fundet litteratur for hverken filgotinib eller etanercept, der kunne bruges til at besvare det kliniske spørgsmål. Derfor er det ikke muligt at vurdere værdien efter Medicinrådets metoder. Besvarelsen af det kliniske spørgsmål er baseret på ekstrapolering fra klinisk spørgsmål 3 (behandlingsnaive patienter i monoterapi) og fagudvalgets kliniske ekspertise og erfaring.

5.4.2 Evidensens kvalitet

Fagudvalget har ikke anvendt GRADE til at foretage en formel vurdering af kvaliteten af evidensen, da der ikke er en sammenligning.

Risiko for bias er ikke vurderet, da der ikke er et randomiseret studie af filgotinib eller etanercept til besvarelsen af det kliniske spørgsmål.

5.4.3 Effektestimater og kategorier

Der er ingen data og derfor ingen tabel over effektforskelle eller gennemgang af effektmål.

5.4.4 Fagudvalgets konklusion

Fagudvalget vurderer, at den samlede værdi af filgotinib sammenlignet med etanercept til behandlingserfarne patienter med moderat til svær kronisk leddegigt **ikke kan kategoriseres** efter Medicinrådets metoder.

Fagudvalget fremhæver, at der ikke er noget, der taler for, at balancen mellem effekt og sikkerhed af filgotinib sammenlignet med etanercept til behandlingserfarne patienter adskiller sig fra behandlingsnaive patienter (klinisk spørgsmål 3). Her vurderede fagudvalget, at der ikke er evidens for, at der er forskel på behandlingseffekten mellem filgotinib og etanercept.

Dog udtrykker fagudvalget bekymring vedr. påvirkning af mandlig fertilitet og potentielt øget risiko for fosterskader. Derfor finder fagudvalget, at den samlede konklusion ikke omfatter mænd med ønske om børn og kvinder med aktuelt graviditetsønske.

6. Andre overvejelser

Som det fremgår i vurderingen, udtrykker fagudvalget en bekymring vedr. påvirkning af mandlig fertilitet og øget risiko for fosterskader ved behandling med filgotinib. To igangværende studier, MANTA (ved inflammatoriske tarmsygdomme) og MANTARAY (hos voksne mænd med kronisk leddegigt), undersøger påvirkning af behandling med 200 mg filgotinib på mandlig fertilitet, men data fra studierne foreligger ikke endnu. Fagudvalget kan ikke udelukke, at data fra disse studier kan ændre på fagudvalgets beslutning om, at konklusionen ikke omfatter mænd med ønske om børn og kvinder med aktuelt graviditetsønske.

Medicinrådet har tidligere udtrykt en bekymring for den øgede risiko for lungeemboli og VTE hos patienter med risikofaktorer for VTE samt øget risiko for alvorlige infektioner hos patienter over 65 år ved behandling med en anden JAK-hæmmer; tofacitinib [24]. Medicinrådet har i den forbindelse fundet, at det ikke kan udelukkes, at der er tale om en klasseeffekt for JAK-hæmmere, men med det tilgængelige datagrundlag foreligger der ikke evidens til at konkludere dette.

7. Relation til behandlingsvejledning

Medicinrådet har i 2018 udarbejdet en behandlingsvejledning for kronisk leddegigt, som Medicinrådet har besluttet at opdatere. Medicinrådet vil først tage stilling til filgotinibs indplacering i behandlingsvejledningen i forbindelse med denne opdatering. Årsagen hertil er fagudvalgets bekymring vedr. mulig påvirkning af mandlig fertilitet, mulig øget risiko for fosterskader samt den mulige klasseeffekt for JAK-hæmmere ift. øget risiko for lungeemboli, VTE og alvorlige infektioner som beskrevet i kapitel 6.

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9. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende gigtsygdomme

Sammensætning af fagudvalg	
Formand	**Indstillet af**
Annemarie Lyng Svensson *Overlæge*	Lægevidenskabelige Selskaber
Medlemmer	**Udpeget af**
Salome Kristensen *Overlæge*	Region Nordjylland
Lars Erik Bartels *Afdelingslæge*	Region Midtjylland
Hanne M. Lindegaard *Overlæge, klinisk lektor*	Region Syddanmark
Thomas Adelsten *Uddannelsesansvarlig overlæge*	Region Sjælland
Maria Krogstrup *Afdelingslæge*	Region Hovedstaden
Per Damkier *Professor, overlæge*	Dansk Selskab for Klinisk Farmakologi
Thomas Loof Hedegård *Farmaceut*	Dansk Selskab for Sygehusapotekledelse
Dorte Vendelbo Jensen *Overlæge, sekretariatsleder*	DANBIO
Udpegning i gang	Dansk Reumatologisk Selskab
Connie Ziegler *Patient/patientrepræsentant*	Danske Patienter
Lene Mandrup Thomsen *Patient/patientrepræsentant*	Danske Patienter

Tidligere medlemmer, som har bidraget til arbejdet	Udpeget af
Ulrik Tarp *Ledende overlæge*	Lægevidenskabelige Selskaber og Dansk Reumatologisk Selskab

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10. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
2.0	26. maj 2021	Konklusionen er blevet tilrettet, så der ikke længere står, at der er rejst bekymring vedr. potentielt øget risiko for fosterskade ved behandling med filgotinib. Dette skyldes, at alle JAK-hæmmere er kontraindiceret under graviditet, hvilket i tidligere vurderinger af andre JAK-hæmmere ikke har været fremhævet specifikt i Medicinrådets konklusion.
1.0	24. marts 2021	Godkendt af Medicinrådet

11. Bilag

Bilag 1: Cochrane – risiko for bias

Vurdering af risiko for bias ved Cochrane risk of bias tool 2.0.

Tabel 10. Vurdering af risiko for bias i FINCH-1, NCT02889796

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiserings-processen	**Lav**	Randomisering foretaget ved brug af et interaktivt webrespons-system. Maskering lavet med filgotinib- og adalimumab-matchende placeboer og en double-dummy teknik.
Effekt af tildeling til intervention	**Lav**	Dobbeltblindet studie, hvor både investigator og deltagere var blindede til den allokerede behandling. Maskering lavet med filgotinib- og adalimumab-matchende placeboer og en double-dummy teknik. Patienter fra placeboarmen blev randomiseret på ny til 100/200 mg filgotinib på en blindet måde ved uge 24.
Manglende data for effektmål	**Lav**	Data er opgjort på FAS-populationen, og der foreligger data på de effektmål, der er beskrevet i studieprotokollen. Data er dog data-on-file.
Risiko for bias ved indsamlingen af data	**Forbehold**	Dobbeltblindet studie, men blinding blev afbrudt ved uge 24 pga. en planlagt ublindet analyse. Der mangler information om, hvem der indsamler og analyserer data og dermed ikke længere er blindede. Der er dog ingen indikation om forskel ved indsamling af data mellem behandlingsarme.
Risiko for bias ved udvælgelse af resultater, der rapporteres	**Lav**	Der foreligger data på de effektmål, der er beskrevet i studieprotokollen, og der er ingen indikation om selektiv rapportering.
Overordnet risiko for bias	**Forbehold**	Den overordnede risiko for bias er med forbehold pga. risiko for bias ved indsamling af data.

Tabel 11. Vurdering af risiko for bias i FINCH-2, NCT02873936

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiserings-processen	**Lav**	Randomisering er foretaget ved brug af et interaktivt webrespons-system. Placebotabletter matchede filgotinib i udseende. Randomiseringssekvens er udført af en uafhængig statistiker.
Effekt af tildeling til intervention	**Lav**	Dobbeltblindet studie, hvor både investigator og deltagere var blindede til den allokerede behandling. Placebotabletter matchede filgotinib i udseende. Allokering til behandling udført via et interaktivt webrespons-system.
Manglende data for effektmål	**Lav**	Data er opgjort på FAS-population, og der foreligger data på de effektmål, der er beskrevet i studieprotokollen.
Risiko for bias ved indsamlingen af data	**Lav**	Dobbeltblindet, placebo-kontrolleret studie.
Risiko for bias ved udvælgelse af resultater, der rapporteres	**Lav**	Der foreligger data på de effektmål, der er beskrevet i studieprotokollen, og der er ingen indikation om selektiv rapportering.
Overordnet risiko for bias	**Lav**	Den overordnede risiko for bias er lav, da alle domæner har lav risiko for bias.

Tabel 12. Vurdering af risiko for bias i DARWIN 2, NCT01894516

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiserings-processen	**Lav**	Randomisering er foretaget ved brug af et interaktivt voice- og webrespons-system.
Effekt af tildeling til intervention	**Lav**	Dobbeltblindet studie hvor deltagere, investigator, studiekoordinatorer, sponsor og studieteam var blindet vedr. allokering af behandling.
Manglende data for effektmål	**Lav**	Data er opgjort på ITT-populationen, og der foreligger data på de effektmål, der er beskrevet i studieprotokollen.
Risiko for bias ved indsamlingen af data	**Lav**	Dobbeltblindet, placebo-kontrolleret studie. Effektanalyser er lavet med non-responder imputering på ITT-populationen.
Risiko for bias ved udvælgelse af resultater, der rapporteres	**Lav**	Der foreligger data på de effektmål, der er beskrevet i studieprotokollen, og der er ingen indikation om selektiv rapportering.
Overordnet risiko for bias	**Lav**	Den overordnede risiko for bias er lav, da alle domæner har lav risiko for bias.

Tabel 13. Vurdering af risiko for bias i Moreland et al. 1999

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiserings-processen	**Lav**	Block-randomisering stratificeret efter geografi og ensartet allokering til behandling. Randomiseringskoden er bevaret hos studiesponsor. Etanercept og placebo er begge givet som subkutane injektioner. Baselinekarakteristika er sammenlignelige mellem studiearme, hvilket indikerer, at der ikke var bias i randomiseringen.
Effekt af tildeling til intervention	**Lav**	Dobbeltblindet studie. Blinding er bevaret, indtil alle patienter havde afsluttet 6 måneders behandling, hvorefter databasen blev låst.
Manglende data for effektmål	**Lav**	Data er opgjort på ITT-populationen, og der foreligger data på de effektmål, der er beskrevet i studieprotokollen.
Risiko for bias ved indsamlingen af data	**Lav**	Dobbeltblindet, placebo-kontrolleret studie.
Risiko for bias ved udvælgelse af resultater, der rapporteres	**Lav**	Der foreligger data på de effektmål, der er beskrevet i studieprotokollen, og der er ingen indikation om selektiv rapportering.
Overordnet risiko for bias	**Lav**	Den overordnede risiko for bias er lav, da alle domæner har lav risiko for bias.

Bilag 2: GRADE

Klinisk spørgsmål 1 – filgotinib i kombination med MTX sammenlignet med adalimumab i kombination med MTX til behandling af behandlingsnaive patienter med moderat til svær kronisk leddegigt

Tabel 14. GRADE-evidensprofil for klinisk spørgsmål 1, FINCH 1, filgotinib vs. adalimumab

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	Filgotinib	Adalimumab	Relativ (95 % CI)	Absolut (95 % CI)	Sikkerhed	Vigtighed
ACR50, 52 uger												
1	RCT	Ingen	Alvorlig[a]	Ingen	Ingen	Ingen	296/475	192/325	RR: 1,06 [0,95; 1,19]	3,5 %-point [-3,2; 11,1]	⊕⊕⊕◯ MODERAT	KRITISK
Ophør grundet uønskede hændelser, 52 uger												
1	RCT	Ingen	Alvorlig[a]	Ingen	Alvorlig[b]	Ingen	26/475	18/325	RR: 0,99 [0,55; 1,77]	-0,1 %-point [-3,6; 3,1]	⊕⊕◯◯ LAV	KRITISK
Alvorlige infektioner, 52 uger												
1	RCT	Ingen	Alvorlig[a]	Ingen	Alvorlig[b]	Ingen	13/475	10/325	RR: 0,89 [0,36; 2,00]	-0,3 %-point [-3,0; 2,3]	⊕⊕◯◯ LAV	KRITISK
Ophør pga. manglende effekt, 52 uger												
1	RCT	Ingen	Alvorlig[a]	Ingen	Alvorlig[b]	Ingen	29/475	14/325	RR: 1,42 [0,76; 2,64]	1,8 %-point [-1,5; 4,9]	⊕⊕◯◯ LAV	VIGTIG

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	**Studie-design**	**Risiko for bias**	**Inkonsistens**	**Indirekthed**	**Unøjagtighed**	**Andre overvejelser**	**Filgotinib**	**Adalimumab**	**Relativ (95 % CI)**	**Absolut (95 % CI)**	**Sikkerhed**	**Vigtighed**
TSS, 52 uger												
1	RCT	Ingen	Alvorlig[a]	Ingen	Ingen	Ingen	365 /417	225/273	RR: 1,06 [1,00; 1,14]	5,2 %-point [-0,3; 11,1]	⨁⨁◯◯ LAV	VIGTIG
HAQ-DI, 52 uger												
1	RCT	Ingen	Alvorlig[a]	Ingen	Ingen	Ingen	348 /459	222/316	RR: 1,08 [0,99; 1,18]	5,7 %-point [-0,7; 12,7]	⨁⨁◯◯ LAV	VIGTIG
Kvalitet af den samlede evidens	LAV[c]											

[a] Der er nedgraderet ét niveau, da der kun var ét studie.

[b] Der er nedgraderet ét niveau, da konfidensintervallet indeholder indeholder mulighed for både positive og negative konklusioner.

[c] Den samlede evidenskvalitet er vurderet ud fra den laveste kvalitet af de kritiske effektmål.

Klinisk spørgsmål 3 – filgotinib sammenlignet med etanercept til behandling af behandlingsnaive patienter med moderat til svær kronisk leddegigt

Tabel 15. GRADE-evidensprofil for klinisk spørgsmål 3, DARWIN 2, filgotinib vs. placebo [19]

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	Filgotinib	Placebo	Relativ (95 % CI)	Absolut (95 % CI)	Sikkerhed	Vigtighed
ACR50, 12 uger												
1	RCT	Ingen	Alvorlig[a]	Ingen	Ingen	Ingen	30/69	8/72	RR: 3,91 [1,93; 7,93]	32,4 %-point [17,9; 45,3]	⊕⊕⊕◯ MODERAT	KRITISK
Ophør grundet uønskede hændelser, 12 uger												
1	RCT	Ingen	Alvorlig[a]	Ingen	Alvorlig[b]	Ingen	1/69	2/72	RR: 0,52 [0,05; 5,62]	-1,3 %-point [-8,2; 5,3]	⊕⊕◯◯ LAV	KRITISK
Alvorlige infektioner, 12 uger												
1	RCT	Ingen	Alvorlig[a]	Ingen	Alvorlig[b]	Ingen	1/69	0/72	RR: 3,13 [0,13; 75,53]	1,4 %-point [-3,8; 7,8]	⊕⊕◯◯ LAV	KRITISK
Ophør pga. manglende effekt, 12 uger												
1	RCT	Ingen	Alvorlig[a]	Ingen	Alvorlig[b]	Ingen	0/69	2/72	RR: 0,21 [0,01; 4,27]	-2,8 %-point [-9,6; 2,9]	⊕⊕◯◯ LAV	VIGTIG
TSS-ingen data												
-	-	-	-	-	-	-	-	-	-	-	-	VIGTIG

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	Filgotinib	Placebo	Relativ (95 % CI)	Absolut (95 % CI)	Sikkerhed	Vigtighed
HAQ-DI, 12 uger												
1	RCT	Ingen	Alvorlig[a]	Ingen	Ingen	Ingen	55/69	37/72	RR: 1,55 [1,20; 2,00]	28,3 %-point [12,7; 42,1]	⊕⊕⊕◯ MODERAT	VIGTIG
Kvalitet af den samlede evidens	LAV[c]											

[a] Der er nedgraderet ét niveau, da der kun var ét studie.

[b] Der er nedgraderet ét niveau, da konfidensintervallet indeholder indeholder mulighed for både positive og negative konklusioner.

[c] Den samlede evidenskvalitet er vurderet ud fra den laveste kvalitet af de kritiske effektmål.

Tabel 16. GRADE-evidensprofil for klinisk spørgsmål 3, Moreland et al., etanercept vs. placebo [21]

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	Filgotinib	Placebo	Relativ (95 % CI)	Absolut (95 % CI)	Sikkerhed	Vigtighed
ACR50, 3 måneder												
1	RCT	Ingen	Alvorlig[a]	Ingen	Ingen	Ingen	32/78	6/80	RR: 5,47 [2,42; 12,35]	33 %-point [20; 45]	⊕⊕⊕◯ MOERAT	KRITISK
Ophør grundet uønskede hændelser, 6 måneder												

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	Filgotinib	Placebo	Relativ (95 % CI)	Absolut (95 % CI)	Sikkerhed	Vigtighed
1	RCT	Ingen	Alvorlig[a]	Ingen	Alvorlig[b]	Ingen	2/78	3/80	RR: 0,68 [0,12; 3,98]	-1,2 %-point [-8,1; 5,6]	⨁⨁◯◯ LAV	KRITISK
Alvorlige infektioner – ingen data												
-	-	-	-	-	-	-	-	-	-	-	-	KRITISK
Ophør pga. manglende effekt, 12 uger												
1	RCT	Ingen	Alvorlig[a]	Ingen	Ingen	Ingen	12/78	42/80	RR: 0,29 [0,17; 0,51]	-37,1 %-point [-49,5; -22,7]	⨁⨁⨁◯ MOERAT	VIGTIG
TSS-ingen data												
-	-	-	-	-	-	-	-	-	-	-	-	VIGTIG
HAQ-DI – ingen data												
-	-	-	-	-	-	-	-	-	-	-	-	VIGTIG
Kvalitet af den samlede evidens	LAV[c]											

[a] Der er nedgraderet ét niveau, da der kun var ét studie.

[b] Der er nedgraderet ét niveau, da konfidensintervallet indeholder indeholder mulighed for både positive og negative konklusioner.

[c] Den samlede evidenskvalitet er vurderet ud fra den laveste kvalitet af de kritiske effektmål.

Application for the assessment of filgotinib (Jyseleca®) for the treatment of rheumatoid arthritis

Application to the Danish Medicines Council

18 December 2020

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1 Abbreviations

ACR	American College of Rheumatology
ATP	Adenosine triphosphate
bDMARD	Biologic disease-modifying-antirheumatic drug
CCP	Anticyclic citrullinated peptide
CRP	C-reactive protein
csDMARD	Conventional synthetic disease-modifying-antirheumatic drug
DAS28	Disease activity score based on 28 joints
DMARD	Disease-modifying-antirheumatic drug
EPAR	European Public Assessment Report
ET	Early termination
EULAR	European League Against Rheumatism
FACIT-fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
FAS	Full analysis set
HAQ-DI	Health Assessment Questionnaire Disability Index
IL	Interleukin
JAK	Janus-kinase
JIA	Juvenile idiopathic arthritis
LOCF	Last observation carried forward
MMRM	Mixed-effects model for repeated measures
MTX	Methotrexate
MTX-IR	Intolerance or inadequate response to methotrexate
NRI	Non-responder imputation
PBO	Placebo
PK	Pharmacokinetic
PP	Per protocol
RA	Rheumatoid arthritis
RCT	Randomized clinical trial
RF	Rheumatoid factor
SAP	Statistical analysis plan
SF-36	36-item Short Form Survey
tsDMARD	Targeted synthetic disease-modifying-antirheumatic drug
TSS	Total Sharp Score
TYK	Tyrosine kinase

2 Basic information

TABLE 1: CONTACT INFORMATION

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TABLE 2: OVERVIEW OF PHARMACEUTICAL PRODUCT

Proprietary name	Jyseleca
Generic name	Filgotinib
Marketing authorization holder in Denmark	Gilead Sciences
ATC code	L04AA45
Pharmacotherapeutic group	Janus kinase (JAK) inhibitor
Active substance(s)	Filgotinib
Pharmaceutical form(s)	Tablets for oral administration
Mechanism of action	Filgotinib is an adenosine triphosphate (ATP)-competitive and reversible inhibitor of the Janus kinase (JAK) family. JAKs are intracellular enzymes which transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane. JAK1 is important in mediating inflammatory cytokine signals, JAK2 in mediating myelopoiesis and erythropoiesis and JAK3 plays a critical role in immune homeostasis and lymphopoiesis. Within the signalling pathway, JAKs phosphorylate and activate signal transducers and activators of transcription (STATs) which modulate intracellular activity including gene expression. Filgotinib modulates these signalling pathways by preventing the phosphorylation and activation of STATs. In biochemical assays, filgotinib preferentially inhibited the activity of JAK1 and showed > 5-fold higher potency for JAK1 over JAK2, JAK3 and TYK2. In human cellular assays, filgotinib preferentially inhibited JAK1/JAK3-mediated signalling downstream of the heterodimeric cytokine receptors for IL-2, IL-4 and IL-15, JAK1/2-mediated IL-6, and JAK1/TYK2-mediated type I interferons, with functional selectivity over cytokine receptors that signal via pairs of JAK2 or JAK2/TYK2 (1).
Dosing regimen	The recommended dose of filgotinib for adult patients with rheumatoid arthritis is 200 mg once daily. A starting dose of 100 mg once daily is recommended for patients aged 75 years and older as clinical experience is limited.

Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Filgotinib is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs). Jyseleca may be used as monotherapy or in combination with methotrexate (MTX).
Other approved therapeutic indications	None.
Will dispensing be restricted to hospitals?	Yes.
Combination therapy and/or co-medication	Filgotinib may be used as monotherapy or in combination with methotrexate (MTX) (1).
Packaging – types, sizes/number of units, and concentrations	Filgotinib is available in 100 mg and 200 mg film-coated tablets. Pack size is 30 tablets per package.
Orphan drug designation	Filgotinib is not given orphan drug status.

3 Summary

Background

Gilead Sciences Inc. has requested the Danish Medicines Council (DMC) to evaluate filgotinib (Jyseleca®) for the standard treatment of adult patients with moderate to severe active rheumatoid arthritis (RA) who have an inadequate response to or who are intolerant to one or more disease-modifying antirheumatic drugs (DMARDs). Filgotinib is a selective Janus kinase (JAK) inhibitor and can be used as monotherapy or in combination with methotrexate (MTX). Filgotinib belongs to the targeted synthetic DMARD (tsDMARD) drug class.

Methods

The DMC protocol for filgotinib, outlined four clinical questions. We conducted a systematic literature search, using the search terms and criteria defined in the protocol. To answer clinical question 1, we applied the head-to-head comparison of filgotinib and adalimumab in the FINCH 1 trial. To answer clinical question 2 and accommodate the way the DMC has previously evaluated other bDMARD/tsDMARDs, we conducted a narrative description of filgotinib based on the FINCH 2 trial (2). To answer clinical question 3, we conducted an indirect comparison of filgotinib and etanercept with data from the DARWIN 2 trial, the study by Moreland et al. 1999 (3) and a post-hoc analysis of the JERA trial (4). In the systematic literature search, we did not identify any literature appropriate for answering clinical question 4.

Results

Clinical question 1: The assessment of clinical question 1 was based on the head-to-head comparison of filgotinib and adalimumab in the FINCH 1 trial. At week 52, 62.3% (95% CI: 57.9%; 66.6%) of the subjects had achieved an ACR50 response in the filgotinib arm and 59.1% (95% CI: 53.7%; 64.4%) of subjects in the adalimumab arm. 348 subjects (75.8%, 95% CI: 71.8%; 79.8%) in the filgotinib arm and 222 subjects (70.3%, 95% CI: 65.1%; 75.5%) in the adalimumab arm had achieved HAQ-DI response (reduction of ≥0.22 in HAQ-DI score from baseline) at week 52. 26 subjects (5.5%, 95% CI: 3.4%; 7.5%) in the filgotinib arm and 18 subjects (5.5%, 95% CI: 3.1%; 8.0%) in the adalimumab arm discontinued treatment due to AEs, and 13 subjects (2.7%, 95% CI: 1.2%; 4.3%) and 10 subjects (3.1%, 95% CI: 1.0%; 5.1%) experienced a serious infection, respectively. 29 subjects (6.1%, 95% CI: 4.0%; 8.3%) in the filgotinib arm and 14 subjects (4.3%, 95% CI: 2.1%; 6.5%) in the adalimumab arm discontinued treatment due to lack of effect. 365 subjects (87.5%, 95% CI: 84.2%; 90.8%) in the filgotinib arm and 225 subjects (82.4%, 95% CI: 77.7%; 87.1%) in the adalimumab arm had no radiographic progression at week 52 (mTSS ≤0 from baseline).

Clinical question 2: Due to a lack of relevant evidence on adalimumab bDMARD/tsDMARD treatment-experienced patients, the assessment of clinical question 2 consisted of a narrative description of filgotinib based on the FINCH 2 trial. In the FINCH 2 trial, filgotinib + MTX is compared with placebo + MTX. At week 24, 67 subjects (45.6%, 95% CI: 37.5%; 53.6%) in the filgotinib arm had achieved an ACR50 response and 99 subjects (68.8%, 95% CI: 61.2%; 76.3%) had a reduction of ≥0.22 in HAQ-DI score from baseline. 3 subjects (2.0%, 95% CI: -0.2%; 4.3%) treated with filgotinib discontinued treatment due to AEs, and only 1 subject (0.7%, 95% CI: -0.6%; 2.0%) experienced a serious infection during the 24 weeks. 12 subjects (8.2%, 95% CI: 3.7%; 12.6%) discontinued treatment with filgotinib due to lack of effect. Radiographic progression was not assessed in the FINCH 2 trial.

Clinical question 3: The assessment of clinical question 3 consisted of two indirect comparisons of filgotinib and etanercept as monotherapy in bDMARD/tsDMARD treatment-naïve and MTX-IR RA patients; one based on the DARWIN 2 trial and the study by Moreland et al. 1999, and another where data on relevant outcomes from Moreland et al. 1999 had been combined in a meta-analysis with data from a post-hoc analysis of the JERA trial. In the indirect comparison of the DARWIN 2 trial and Moreland et al. 1999, we estimated a risk ratio in ACR50 response of 0.72 (95% CI: 0.24; 2.10, p-value: 0.54) between filgotinib and etanercept, and a risk ratio in discontinuing treatment due to AEs of 0.76 (95% CI: 0.04; 14.71, p-value: 0.86). In the indirect comparison of DARWIN 2 and a meta-analysis of Moreland et al. 1999 and the JERA trial, we estimated a risk ratio in ACR50 response of 1.19 (95% CI: 0.39; 3.65, p-value: 0.76) and a risk ratio in discontinuing treatment due to AEs of 0.32 (95% CI: 0.02; 4.61, p-value: 0.41). However, the latter

analysis should be applied with caution due to a number of reasons; the JERA trial only included Japanese patients and the effect of etanercept might be underestimated because of the active comparator (MTX) in the JERA trial relative to the non-active comparator (placebo) in the DARWIN 2 trial and the study by Moreland et al. 1999. Furthermore, the MTX dose-regimen used in the JERA trial is not similar to the MTX dose-regimen in a Danish setting. This adds some uncertainty to the indirect comparison and have a substantial impact on the results. The indirect comparisons on occurrence of serious infections and treatment discontinuation due to lack of effect are subject to great uncertainties because of treatment arms with 0 observations. Thus, the analyses should be interpreted with caution. We estimated a risk ratio on occurrence of serious infections of 10.60 (95% CI: 0.12; 960.92, p-value: 0.30) and an corresponding absolute difference of 1.31% (95% CI: -10.95%; 1.45%) based on the DARWIN 2 trial and the JERA trial (no data available from the study by Moreland et al. 1999). Moreover, we estimated a risk ratio in discontinuing treatment due to lack of effect of 0.71 (95% CI: 0.03; 15.34, p-value: 0.83) and 0.98 (95% CI: 0.04; 22.58, p-value: 0.99) in the indirect comparison of the DARWIN 2 trial and Moreland et al. 1999 and the indirect comparison of the DARWIN 2 trial and a meta-analysis of Moreland et al. 1999 and the JERA trial, respectively. Overall, we did not estimate statistically significant differences between filgotinib and etanercept in the indirect comparisons. It was not possible to conduct an indirect comparison of the other outcomes specified in the DMC protocol on filgotinib, due to missing data.

Clinical question 4: It was not possible to identify relevant evidence for filgotinib and etanercept to answer clinical question 4.

4 Literature search

We conducted a systematic literature search, applying the search terms and criteria defined in the DMC protocol for filgotinib. The DMC has previously searched for literature containing direct comparisons between filgotinib and adalimumab and etanercept, respectively. They found one study containing a direct comparison between filgotinib in combination with MXT and adalimumab in combination with MTX in bDMARD/tsDMARD treatment-naïve patients (the FINCH 1 study). In this study, there is sufficient data to answer clinical question 1. Therefore, we have not searched for more literature to answer this clinical question.

However, the DMC did not find any literature containing a direct comparison between filgotinib in combination with MXT and adalimumab in combination with MTX in bDMARD/tsDMARD treatment-experienced patients (clinical question 2). Furthermore, no literature containing direct comparisons between filgotinib in monotherapy compared with etanercept in monotherapy in bDMARD/tsDMARD treatment-naïve patients (clinical question 3) or bDMARD/tsDMARD treatment-experienced patients (clinical question 4) was identified. To answer clinical question 2, 3 and 4, we have searched for articles applicable for indirect comparisons, which we have described below.

Databases and search strategy

We searched for relevant literature in PubMed and CENTRAL (via Cochrane Library) on October 13, 2020. We applied the search strings given in the DMC protocol for filgotinib. Search terms and number of hits in PubMed and CENTRAL can be found in Table 46 and Table 47 in Appendix 7.1.

The inclusion and exclusion criteria defined in the DMC protocol for filgotinib are listed in Table 48 in Appendix 7.1. In general, we excluded references with other patient populations than the ones specified in the protocol and references not reporting results on at least one of the defined critical or important outcomes measures. In addition, we excluded papers with any other design than randomised clinical trials (RCTs) and we excluded phase I and IIa RCTs. Figure 1 below provides a PRISMA flow diagram showing the number of references identified and the number of included and excluded references.

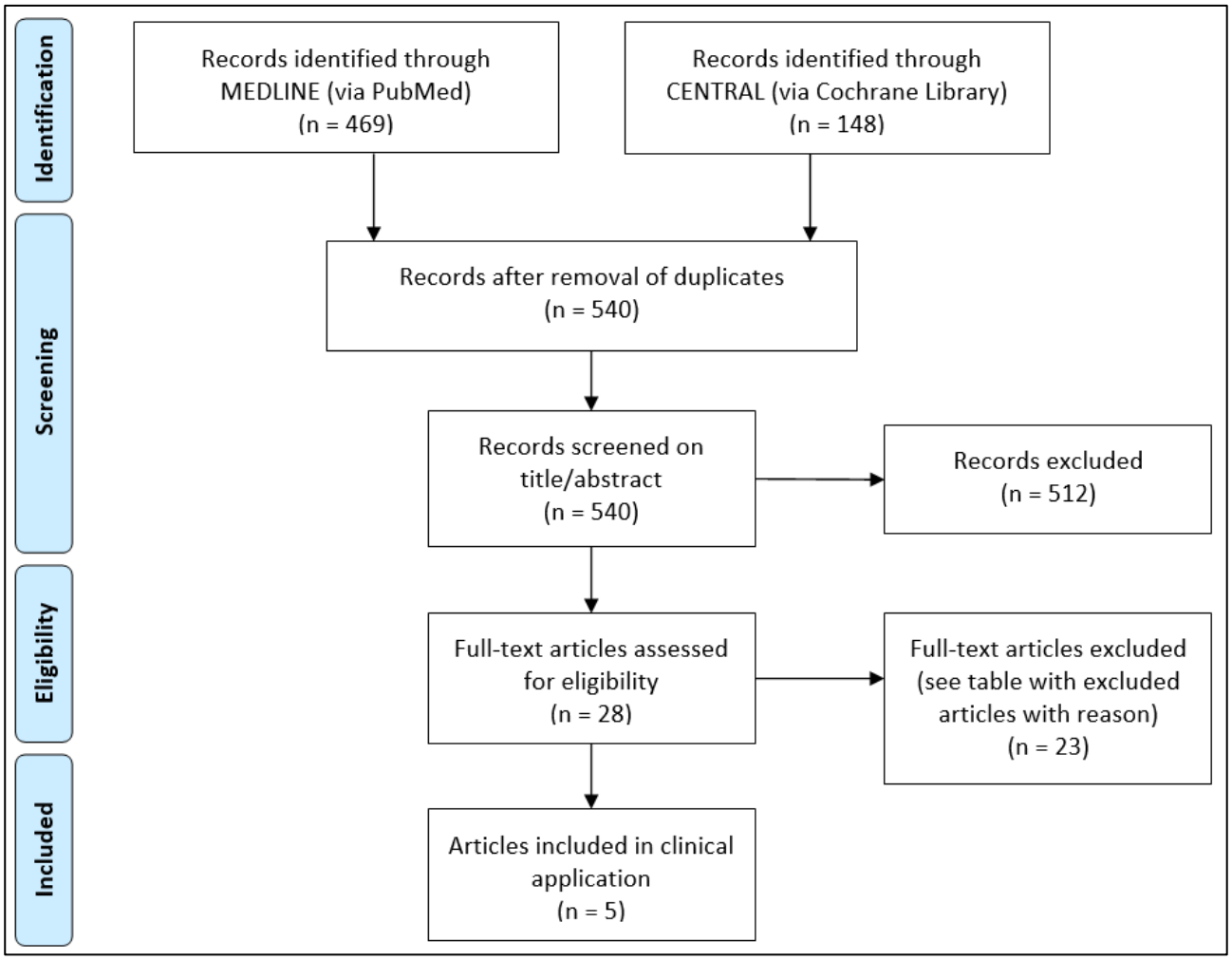

FIGURE 1: PRISMA FLOW DIAGRAM

We identified 469 records using PubMed and 148 records in CENTRAL. A total of 540 records were identified after duplicates were removed. All references were screened, and 512 records were excluded based on titles/abstracts. Subsequently, 28 full-text papers were assessed for eligibility. Of these, 23 references were excluded. The reasons for exclusion of each reference are provided in Table 49 in Appendix 7.1. In total, five references reporting results from four studies were included for the purpose of answering the clinical questions.

4.1 Relevant studies

In the literature search, we identified five relevant references for the assessment of filgotinib in addition to the FINCH 1 study identified by the DMC (Table 3).

TABLE 3: RELEVANT STUDIES INCLUDED IN THE ASSESSMENT OF FILGOTINIB

Reference (author, year, title, journal)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question
Not yet published in peer-reviewed journal[1]	FINCH 1	NCT02889796	*Start:* 30 August 2016 *End:* 20 June 2019 (5)	1
Genovese MC et al. (2019): Effect of filgotinib vs placebo on clinical response in patients with moderate to severe rheumatoid arthritis refractory to disease-modifying antirheumatic drug therapy: The FINCH 2 randomized clinical trial. JAMA. (2)	FINCH 2	NCT02873936	*Start:* 27 July 2016 *End:* 26 June 2018 (6)	2
Kavanaugh A et al. (2017): Filgotinib (GLPG0634/GS-6034), an oral selective JAK1 inhibitor, is effective as monotherapy in patients with active rheumatoid arthritis: results from a randomised, dose-finding study (DARWIN 2). Annals of the rheumatic diseases. (7)	DARWIN 2	NCT01894516	*Start:* July 2013 *End:* April 2015 (8)	3
Genovese M et al. (2018): Effect of filgotinib, a selective JAK 1 inhibitor, with and without methotrexate in patients with rheumatoid arthritis: patient-reported outcomes. Arthritis research & therapy. (9)	DARWIN 2	NCT01894516	*Start:* July 2013 *End:* April 2015 (8)	3
Moreland LW et al. (1999): Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. Annals of internal medicine. (3)	Not reported	Not reported	Not reported	3
Takeuchi T et al. (2020): Radiographic and clinical outcomes following etanercept monotherapy in Japanese methotrexate-naïve patients with active rheumatoid arthritis. Modern rheumatology. (4)	JERA	NCT00445770	*Start:* July 2006 *End:* July 2010 (10)	3

1: Abstract: Combe B et al.: Efficacy and safety of filgotinib for patients with rheumatoid arthritis with inadequate response to methotrexate: FINCH 1 52-week results. Ann Rheum Dis. 2020;79:320-321.

We identified one study (FINCH 2) investigating filgotinib in combination with MTX that is relevant for the bDMARD/tsDMARD treatment-experienced RA patient population receiving combination therapy (clinical question 2) (2). However, the literature search did not return any studies on adalimumab in combination with MTX for bDMARD/tsDMARD treatment-experienced patients. Accordingly, it is not possible to conduct an indirect comparison between filgotinib in combination with MTX and adalimumab in combination with MXT for the bDMARD/tsDMARD treatment-experienced patient population.

We identified three studies (published in four references) relevant for the bDMARD/tsDMARD treatment-naïve RA population receiving monotherapy (clinical question 3). The DARWIN 2 study assessed filgotinib as monotherapy compared with placebo in bDMARD/tsDMARD treatment-naïve patients where treatment with csDMARDs is not an option (defined as intolerance or inadequate response to MTX (MXT-IR)) (7,9). Two studies (the study by Moreland et al. 1999 and the JERA trial) report results on etanercept as monotherapy in bDMARD/tsDMARD treatment-naïve patients where treatment with csDMARDs is not an option (defined as MTX-IR) (3,4). The JERA trial only includes Japanese patients. The study by Moreland et al. 1999 and the JERA trial will be applied for the indirect comparison with the DARWIN 2 study.

The literature review did not return any studies on filgotinib or etanercept as monotherapy for bDMARD/tsDMARD treatment-experienced patients. This is in line with the literature review performed by the DMC for the chronic rheumatoid arthritis therapy area (11). As such, it is not possible to conduct an indirect comparison for clinical question 4.

4.2 Main characteristics of included studies

Information on the various trials described in the following section is obtained from the European Public Assessment Reports (EPAR) related to the respective drugs. If we were not able to find information on filgotinib in the EPAR, the clinical study reports (CSR) were applied instead. Trial information not provided in the following, such as baseline characteristics, outcomes and methods of analysis, can be found in section 7.2 in the appendix.

Table 4 gives an overview of the study designs, populations, treatments and primary as well as key secondary endpoints of the included studies.

TABLE 4: OVERVIEW OF THE INCLUDED STUDIES

Trial	Study design	Population	Treatments	Primary and key secondary endpoints
FINCH 1	Randomised, double-blind, PBO- and active-controlled, multicentre, parallel assignment trial	Adults with moderately to severely active RA who have inadequate response to ongoing stable MTX dose (MTX-IR) N=1,759	• Filgotinib 200 mg + MTX • Filgotinib 100 mg + MTX • Adalimumab + MTX • PBO + MTX	• Primary: ACR20 at Week 12 • Secondary: ACR20 at Weeks 4, 24, and 52; ACR50 and ACR70 at Weeks 4, 12, 24, and 52; DAS28-CRP score ≤3.2 at Week 12 and <2.6 at Week 24; change from baseline in mTSS at Week 24; HAQ-DI score at Week 12; ACR and EULAR response through 52 weeks; CDAI through 52 weeks and SDAI through 24 weeks; SF-36, FACIT-Fatigue scores, EQ-5D, and WPAI-RA scores
FINCH 2	Randomised, double-blind, PBO- and active-controlled, multicentre, parallel assignment trial	Adults with moderately to severely active RA who had inadequate response to bDMARD(s) treatment (bDMARD-IR) N=449	• Filgotinib 200 mg + csDMARD(s) • Filgotinib 100 mg +csDMARD(s) • PBO + csDMARD(s)	• Primary: ACR20 at Week 12 • Secondary: ACR20 at Weeks 4 and 24; ACR50 and ACR70 at Weeks 4, 12, and 24; DAS28-CRP score ≤3.2 at Week 12; HAQ-DI score at Week 12; ACR and EULAR response through 24 weeks; CDAI and SDAI through 24 weeks; SF-36, FACIT-Fatigue scores, EQ-5D, and WPAI-RA scores
DARWIN 2	Randomised, double-blind, PBO-controlled, parallel assignment trial	Adults with moderate-to-severe active RA who showed an inadequate response to MTX (MTX-IR)	• Filgotinib 50 mg QD • Filgotinib 100 mg QD • Filgotinib 200 mg QD • PBO	• Primary: ACR20 at Week 12 • Secondary: ACR 20/50/70, and ACR-N response (every visit); DAS28-CRP response (every visit); ACR/EULAR remission (every visit); EULAR response (every visit);

		N=283		CDAI/SDAI response (every visit); FACIT-Fatigue scale (Weeks 4, 12, and 24); SF-36 score (Weeks 4, 12, and 24); HAQ-DI scores (every visit); AEs, abnormal lab tests, vital signs, and ECG; PK and PD measures
Moreland et al. 1999	Randomised, double-blind, placebo-controlled trial with blinded joint assessors.	Patients with active rheumatoid arthritis who had an inadequate response to disease-modifying antirheumatic drugs. N= 234	• Twice-weekly subcutaneous injections of etanercept, 10 mg or 25 mg • Placebo for 6 months	• Primary end points: ACR 20/50 at 3 and 6 months. • Other end points were ACR70 responses at 3 and 6 months and other measures of disease activity at 3 and 6 months.
JERA	Phase III, randomised, controlled, double-blind, parallel-group, outpatient study	Japanese patients with active rheumatoid arthritis. N=550	• Etanercept 25 mg twice weekly s.c (n = 182) • Etanercept 10 mg twice weekly s.c (n = 192) • MTX 8 mg once weekly (n = 176)	• Primary efficacy endpoint was the change in modified total Sharp score using the modified Sharp/van der Heijde scoring system) from baseline to week 52. • Secondary radiographic efficacy endpoints included changes in mTSS from baseline to week 24 and changes in erosion score and joint space narrowing (JSN) from baseline to weeks 24 and 52, as well as the percentages of subjects with no progression of joint destruction (mTSS change ≤0, ≤0.5, ≤3, or smallest detectable difference, respectively, at week 52. • Other clinical efficacy endpoints included the number (%) of subjects achieving ACR 20/50/70 response rates over 52 weeks and other outcomes.

4.2.1 The FINCH 1 trial

The FINCH 1 trial was a phase III, randomised, double-blind (study participant and investigator), placebo and active substance-controlled multicentre parallel assignment trial. The study evaluated the efficacy and safety of filgotinib compared with adalimumab and placebo in patients with moderate to severe active RA who had inadequate response (IR) to ongoing stable MTX treatment (MTX-IR). The study consisted of four treatment arms:

- Filgotinib 200 mg orally once daily (n=475)
- Filgotinib 100 mg orally once daily (n=489)
- Adalimumab 40 mg/mL subcutaneously every other week (n=325)

- Placebo (n=475)

The trial design is illustrated in Figure 2.

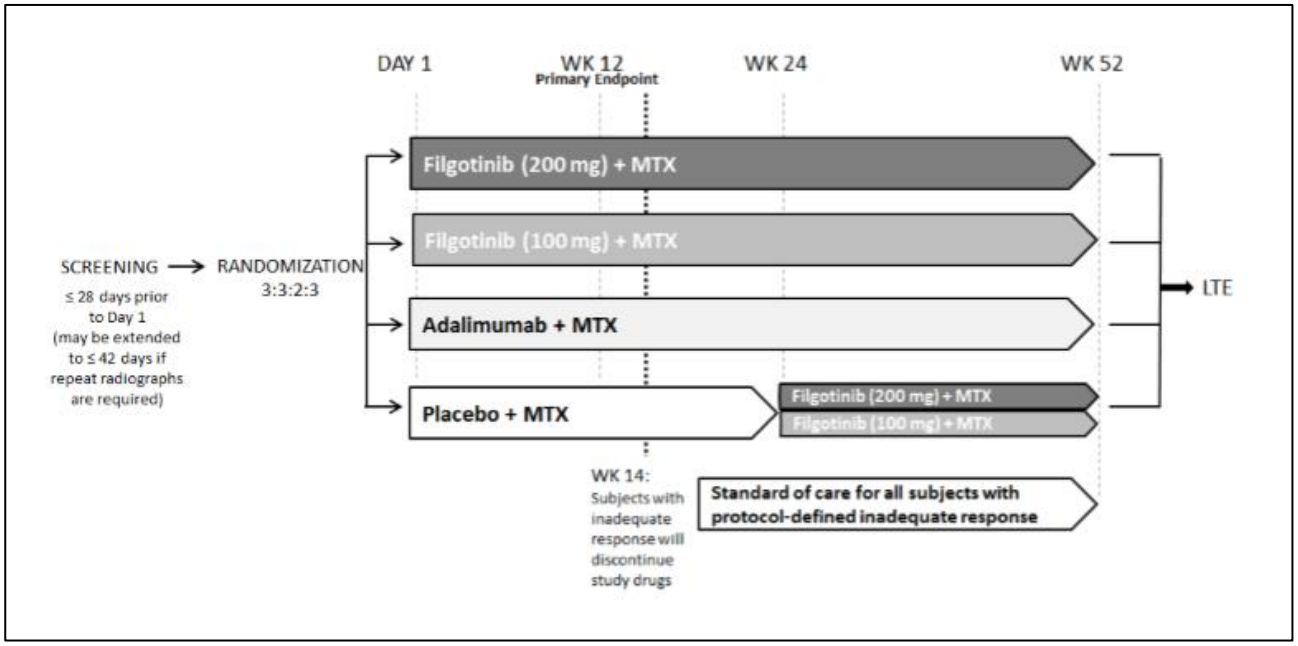

FIGURE 2: THE FINCH 1 TRIAL DESIGN. THE FIGURE SHOWS THE FOUR TREATMENT ARMS IN THE STUDY. LTE: LONG TERM EXTENSION. SOURCE: CSR (12).

2,582 subjects were screened and 1,759 were randomised to one of the treatment groups listed in Figure 2 in a 3:3:2:3 ratio. The randomisation was stratified by geographic region, prior treatment with bDMARDs and presence of rheumatoid factor (RF) or anticyclic citrullinated peptide (CCP) antibodies at screening. The randomisation was carried out with a computerised interactive web response system. Masking was achieved with filgotinib and adalimumab-matching placebos and a double-dummy technique. After all subjects completed the week 24 visit (or prematurely discontinued from the study prior to week 24), a planned week 24 analysis was conducted. A pre-specified sponsor team including members who were not actively involved in the conduct of the study reviewed the week 24 unblinded safety and efficacy analysis results.

Out of the 1,759 randomised subjects, four subjects (2 in the filgotinib 200 mg arm and 2 in the placebo arm) were randomised but not dosed. The 1,755 subjects who were randomised and received at least one dose of the study drug(s) were included in both the safety analysis set and full analysis set (FAS). Hence, the FAS and safety analysis populations were as follows:

- Filgotinib 200 mg: 475 subjects
- Filgotinib 100 mg: 480 subjects
- Adalimumab 40 mg/mL: 325 subjects
- Placebo: 475 subjects

The maximum follow-up time in the FINCH 1 trial was 52 weeks. At week 14, patients who had not achieved at least 20% improvement from baseline in both swollen joint count (SJC) and tender joint count (TJC) discontinued treatment with the study drug and went on to continue standard of care (SoC) for their RA. They continued study visits and assessment per protocol.

At week 24, patients in the placebo + MTX arm were blindly reassigned 1:1 to either the filgotinib 200 mg + MTX arm or filgotinib 100 mg + MTX arm (as shown in Figure 2). Patients who failed to maintain at least a 20% improvement from baseline in SJC and TJC, confirmed at two consecutive visits, discontinued treatment with the study drug but

continued with study visits and assessment per protocol. These patients went on to receive SoC, determined by the investigator. They also completed a follow-up visit 4 weeks after the last dose of study drug, regardless of dosing duration. Patients who had not discontinued treatment with the study drug when the follow-up time had completed could enrol into a separate long-term extension (LTE) trial: the FINCH 4 trial.

4.2.2 The FINCH 2 trial

Information on the FINCH 2 trial was available from the publication by Genovese et al. 2019 (2), the EPAR for filgotinib and the FINCH 2 CSR.

FINCH 2 was a phase III, randomised, multicentre, placebo-controlled double-blinded trial evaluating the efficacy and safety of filgotinib in combination with csDMARDs compared to placebo in combination with csDMARDs in patients with moderate to severe active RA who had experienced inadequate response or intolerance to at least one bDMARD (bDMARD-IR). All patients had to continue stable csDMARDs (methotrexate, hydroxychloroquine, sulfasalazine, or leflunomide). The study consisted of three treatment arms:

- Filgotinib 200 mg once daily (n=147)
- Filgotinib 100 mg once daily (n=153)
- Placebo (n=148)

An overview of the study design is proved in Figure 3.

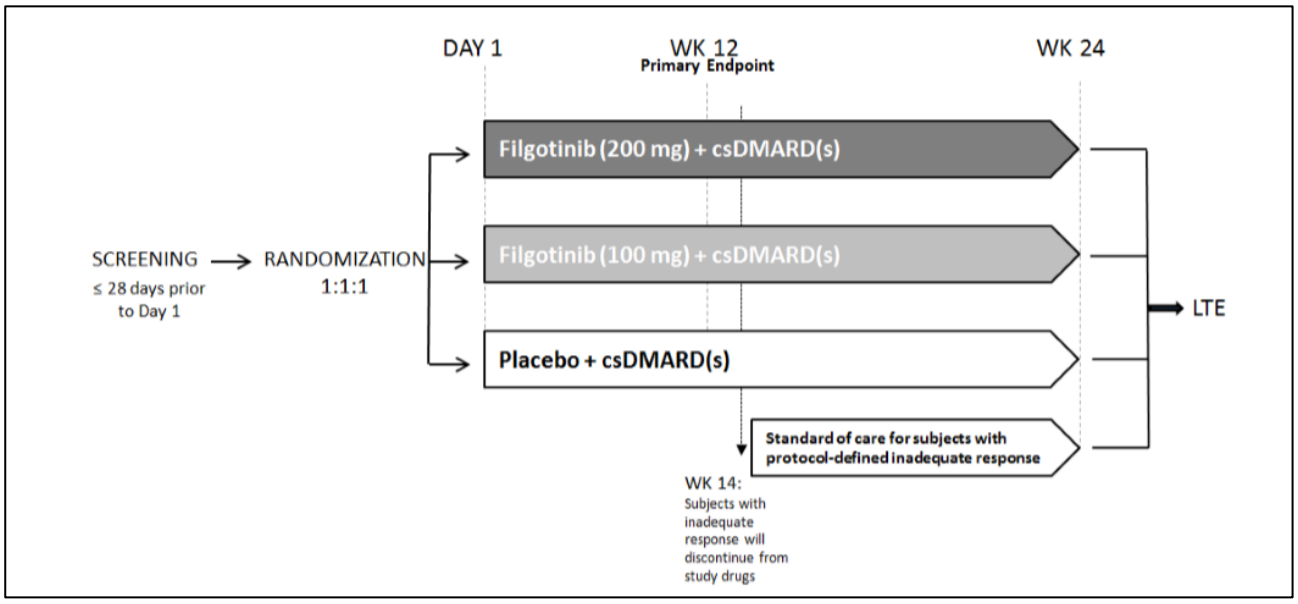

FIGURE 3: TRIAL DESIGN OF THE FINCH 2 TRIAL. UPON COMPLETION OF WEEK 24 OF THE DOSING PERIOD, ALL PATIENTS WHO HAD NOT DISCONTINUED THE STUDY DRUG DUE TO TOXICITY, REGARDLESS OF RESPONSE, WERE GIVEN THE OPTION TO SCREEN FOR ENROLMENT IN A SEPARATE LTE STUDY (THE FINCH 4 TRIAL). SOURCE: CSR (13).

Patients were randomised to each treatment arm shown in Figure 3 in a 1:1:1 ratio. Randomisation was stratified by geographic region, number of bDMARDs the patients had previously been exposed to (<3 or ≥3) and seropositivity of RF or anti-CCP antibodies at screening. The randomisation was done using a computerised interactive voice/web system (IXRS) system.

688 subjects were screened, and 449 subjects were randomised to a study drug. One subject who was randomised to the filgotinib 200 mg group did not receive the study drug.

Of the 448 subjects randomised and treated, 102 subjects (22.8%) prematurely discontinued study drugs (filgotinib 200 mg: 18 subjects, 12.2%; filgotinib 100 mg: 33 subjects, 21.6%; placebo: 51 subjects, 34.5%). Three subjects (2.0%) in the filgotinib 200 mg group, 5 subjects (3.3%) in the filgotinib 100 mg group, and 3 subjects (2.0%) in the placebo group discontinued study drugs due to an adverse event (AE). Twelve subjects (8.2%) in the filgotinib 200 mg group, 12 subjects (7.8%) in the filgotinib 100 mg group, and 32 subjects (21.6%) in the placebo group discontinued the study drugs due to lack of efficacy. The FAS and safety analysis set consisted of the 448 randomised subjects that received at least one study dose. The subject disposition is presented in Figure 4.

The maximum follow-up time in FINCH 2 was 24 weeks. At week 14, patients who had not achieved at least a 20% improvement from day 1 in the 66/68 swollen and tender joint counts (SJC66/TJC68) discontinued treatment with the study drug. These patients continued study visits and assessments per protocol and received SoC treatment. All patients who responded to treatment at week 14 continued treatment to week 24 Upon completion of week 24 of the dosing period, all patients who had not discontinued the study drug due to toxicity, regardless of response, were given the option to screen for enrolment in a separate long-term extension study (FINCH 4).

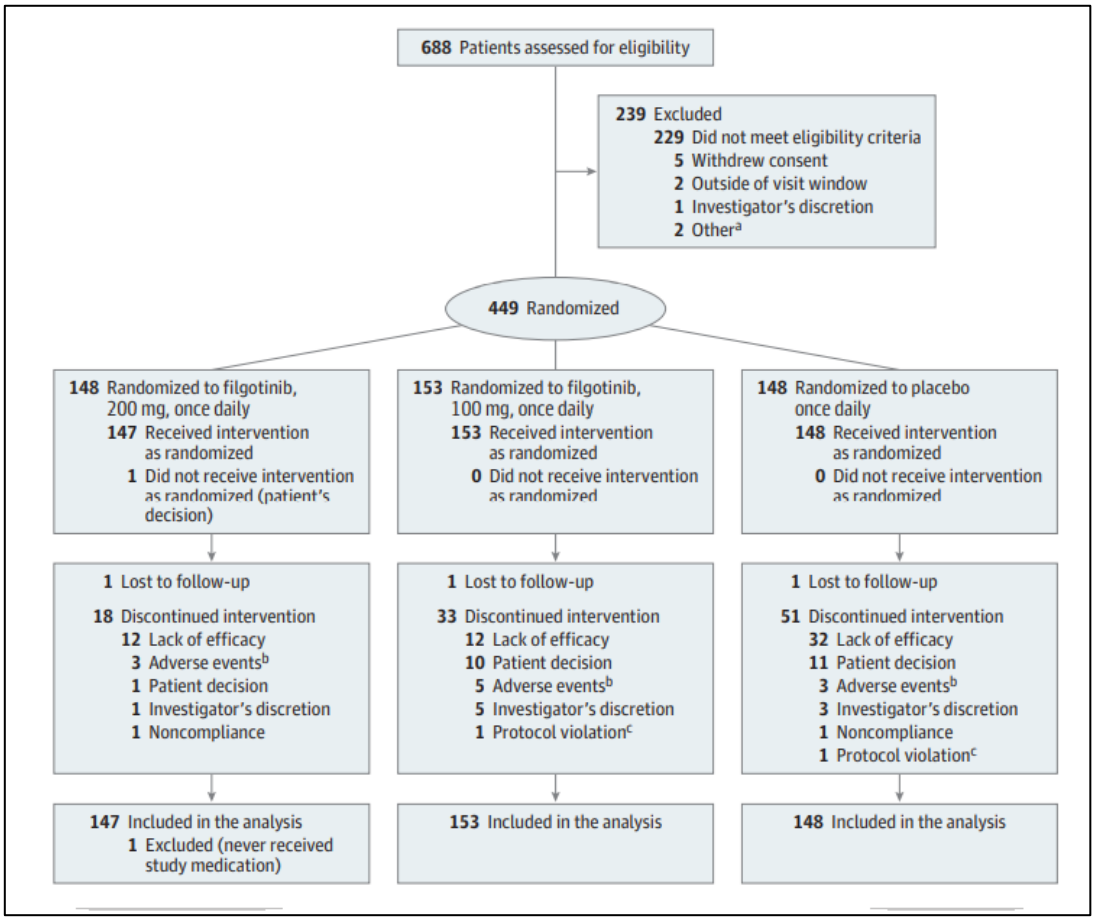

FIGURE 4: THE SUBJECT DISPOSITION IN THE FINCH 2 TRIAL. [A] NO ADDITIONAL INFORMATION WAS PROVIDED BY THE SITE INVESTIGATORS. [B] AES IN THE FILGOTINIB 200 MG ARM INCLUDED 1 CASE EACH (0.7%) OF ABNORMAL BLOOD ALKALINE PHOSPHATASE, GASTROESOPHAGEAL REFLUX DISEASE, AND MIGRAINE; IN THE FILGOTINIB 100 MG ARM INCLUDED 1 CASE EACH (0.7%) OF ANXIETY, HERPES ZOSTER, HOT FLUSH, MYOCARDIAL ISCHEMIA, AND OSTEITIS; AND IN THE PLACEBO ARM INCLUDED 2 CASES OF RA (1.4%) AND 1 CASE (0.7%) OF DECREASED LYMPHOCYTE COUNT. [C] A PATIENT IN THE FILGOTINIB 100 MG ARM REPORTED THEIR PARTNER'S PREGNANCY AT THE WEEK 4 VISIT THAT RESULTED IN THE PATIENT BEING REMOVED FROM THE STUDY AND RECORDED AS A PROTOCOL VIOLATION. A PATIENT IN THE PLACEBO GROUP RECEIVED PROTOCOL-PROHIBITED MEDICATION ON STUDY DAY 6 DUE TO SEVERE BODILY PAIN CAUSED BY RHEUMATOID ARTHRITIS (DEXAMETHASONE INTRA-ARTICULAR INJECTION AND DEXAMETHASONE INTRAVENOUS DRIP). SOURCE: GENOVESE ET AL 2019 (2).

4.2.3 The DARWIN 2 trial

Information on the DARWIN 2 trial was available from the EPAR for filgotinib, the DARWIN 2 CSR and the publications by Kavanaugh et al. 2017 and Genovese et al. 2018 (7,9).

The DARWIN 2 trial was a phase IIb, randomised, double-blinded, placebo-controlled, multicentre dose-finding study of filgotinib administered for 24 weeks as monotherapy to subjects with moderate to severe RA who had an inadequate response to MTX treatment. The trial consisted of the following four treatment arms:

- Filgotinib 50 mg once daily ((n=72)
- Filgotinib 100 mg once daily (n=70)
- Filgotinib 200 mg once daily (n=69)
- Placebo (n=72)

Treatment duration was 24 weeks. At week 12, all subjects on placebo and the subjects on the 50 mg dose who had not achieved a 20% improvement in swollen joint count (SJC66) and tender joint count (TJC68) were assigned (automatically via interactive voice/web response system (IXRS)) to 100 mg once daily in a blinded fashion and were to continue the study until week 24. Subjects in the other groups maintained their randomised treatment until week 24.

Subjects were randomly allocated to treatment according to a pre-specified randomisation scheme prepared by an independent statistician. Upon qualification for the study, subjects were randomised using a computerised IXRS system to placebo or one of the three doses of filgotinib (50 mg, 100 mg and 200 mg) in a 1:1:1:1 ratio (N=70 for each treatment group; total N=280), stratified by region and previous use of a bDMARD during a single clinical study setting.

The disposition of subjects in the DARWIN 2 trial is shown in Figure 5. 625 patients were screened and 287 randomised. 283 subjects were randomised and treated: 72 subjects started in the placebo group and 211 subjects started in one of the three filgotinib monotherapy groups. At week 12, all subjects in the placebo group and 15 non-responding subjects in the filgotinib 50 mg group were re-assigned to filgotinib 100 mg. The overall discontinuation rate was 9.2%, and there was no significant difference in the number of subjects who discontinued between filgotinib and placebo. In addition, no increased dropout rates were observed with increasing doses of filgotinib and no difference was observed in the dropout rate between the first and second 12 weeks of the study. The safety population included a total of 283 subjects who were randomised and received at least one dose of study drug. All 283 subjects in the safety population had post-baseline data or at least one efficacy parameter and were included in the intent-to-treat (ITT) population.

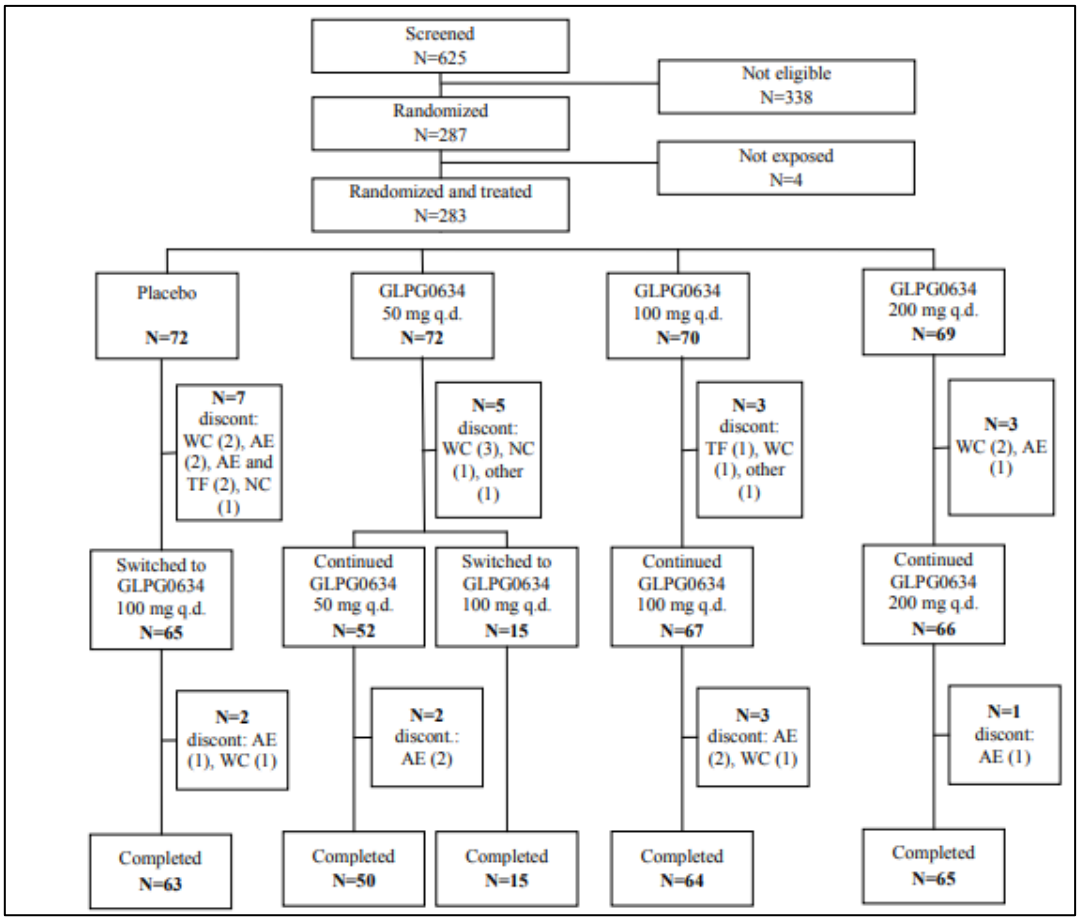

FIGURE 5: SUBJECT DISPOSITION IN THE DARWIN 2 TRIAL. GLPG0634: FILGOTINIB, WC: WITHDRAWAL OF CONSENT, NC: NON-COMPLIANCE, DISCONT.: DISCONTINUED. TF: TREATMENT FAILURE. SOURCE: CSR (14).

4.2.4 The study by Moreland et al. 1999

Moreland et al. 1999 present a phase II, randomised, double-blinded, placebo-controlled trial, investigating the treatment efficacy of etanercept in patients who previously had an inadequate response to between one and four DMARDs (e.g. azathioprine, methotrexate, sulfasalazine, penicillamine, hydroxychloroquine, or oral or injectable gold). The study consisted of three treatment arms:

- 10 mg etanercept subcutaneously (s.c) twice weekly (n=76)
- 25 mg etanercept s.c twice weekly (n=78)
- Placebo (n=80)

The treatment duration was 26 weeks. Patients were randomised with a blocked randomisation with stratification according to study site and equal allocation to treatments. Blinding was maintained until all patients completed six months of treatment and the database was locked.

246 patients were randomly assigned. An ITT analysis was performed on the 234 patients who were randomly assigned and received the study drug. 90% of patients had previously been treated with methotrexate; 22% were treated with methotrexate immediately before the DMARD washout period. 80 patients received placebo, 76 patients received 10 mg of etanercept, and 78 patients received 25 mg of etanercept twice weekly. Of the 234 subjects randomised, 97 subjects (41.5%) prematurely discontinued study drugs (etanercept 25 mg: 19 subjects, 24.3%; etanercept 10 mg: 24 subjects, 31.6%; placebo: 54 subjects, 67.5%). Most withdrawals occurred because of lack of efficacy. An overview of the subject disposition is provided in Figure 6.

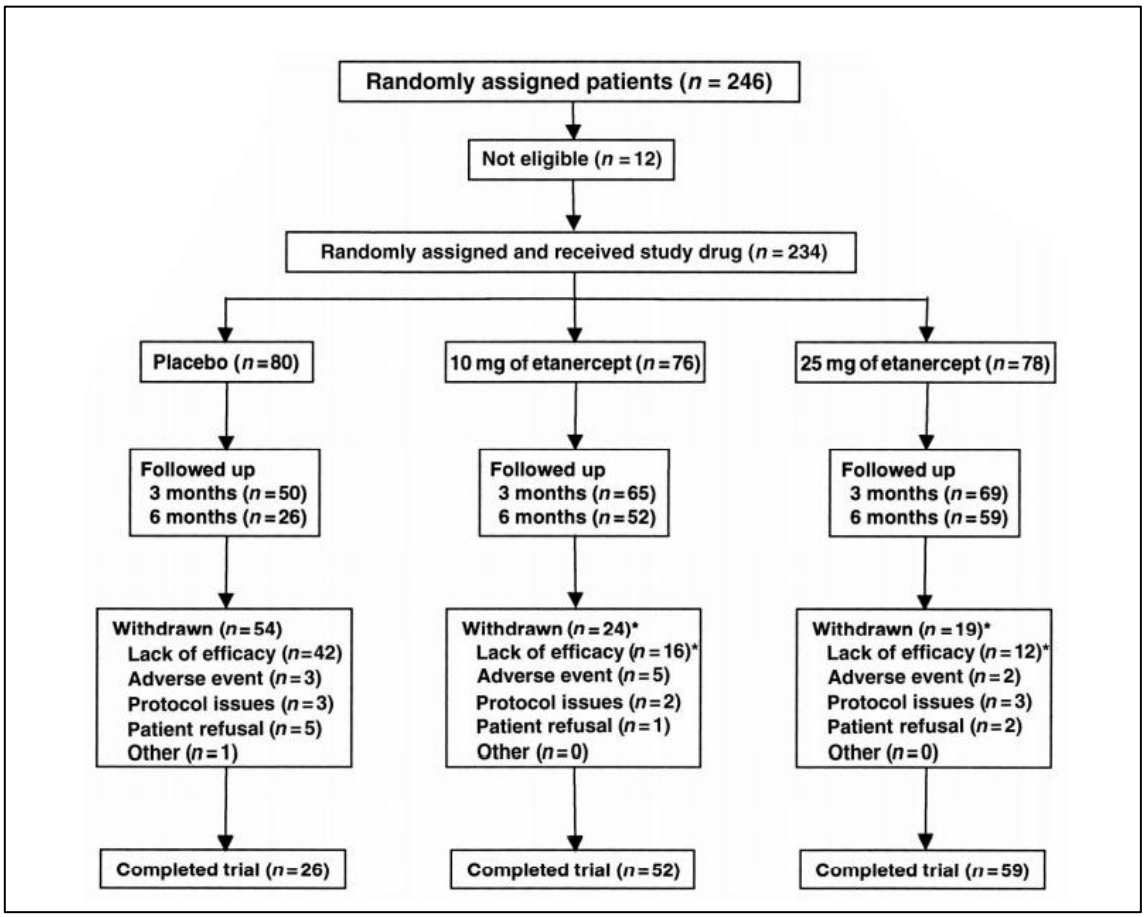

FIGURE 6: SUBJECT DISPOSITION IN THE STUDY BY MORELAND ET AL. 1999 (3). THE FIGURE SHOWS THE COMPLETION AND WITHDRAWAL BEFORE 6 MONTHS. *P-VALUE: <0.001 FOR EACH ETANERCEPT GROUP COMPARED WITH THE PLACEBO GROUP (LIKELIHOOD RATIO CHI-SQUARE TEST).

4.2.5 The JERA trial

In this section, we present the JERA trial. Information on the JERA trial was available from the articles by Takeuchi et al. 2013 and 2020 (4,15). Takeuchi et al. 2013 is the original article on the JERA trial, and Takeuchi et al. 2020 contains a post-hoc analysis. We considered including the JERA trial in the assessment of clinical question 3, but the original JERA trial included a mixed patient population of MTX-naïve and MTX-IR subjects. Therefore, we used the post-hoc analysis published in Takeuchi et al. 2020 (4), because the aim of the post-hoc analysis was to evaluate clinical, radiographic and functional outcomes following monotherapy with MTX or etanercept in patients who participated in the JERA trial and were separated into groups of MTX-naïve or MTX-IR subjects.

The post-hoc analysis was conducted based on data from the JERA trial; therefore, we describe the original article by Takeuchi et al. 2013 (15) followed by information on the post-hoc analysis in Takeuchi et al. 2020 (4). Additional information, such as baseline characteristics, outcomes and methods of analyses, can be found in the Appendix section 7.2.

The JERA trial was a phase III, randomised, double-blind, multicentre comparative study. The purpose of the JERA trial was to compare the radiographic and clinical effects of etanercept versus MTX over 52 weeks in Japanese subjects with active RA. Patients included in the JERA trial were a mix of MTX-naïve and MTX-IR patients. The trial consisted of three treatment arms:

- Etanercept 10 mg s.c twice weekly (n=192)
- Etanercept 25 mg s.c twice weekly (n=182)
- MTX (up to 8 mg) orally once weekly (n=176)

The allocation of subjects to the treatment groups was performed through the computerised randomisation enrolment (CORE) system. The initial MTX dose was 6 mg per week (divided into three doses, administered at 12±2 hours over a period of two days) at baseline and increased to 8 mg per week if an adequate response was reported at week 8. The study consisted of a screening period of 4 weeks, followed by a 52-week treatment period and a 4-week follow-up period.

In the JERA trial, the effect of etanercept might be underestimated because of the active comparator (MTX) relative to the non-active comparator (placebo) in the DARWIN 2 trial and the study by Moreland et al. 1999. In addition, as mentioned above the patient population in the JERA trial consists of Japanese patients, which may add some uncertainty to the indirect comparison. Moreover, the MTX dose administered in the study is lower than what is recommended by EULAR/Danish guidelines and the dose-regimen is also different from what the Danish rheumatology society NBV recommend for MTX. All together this trial is not directly comparable to the DARWIN 2 trial (and the study by Moreland et al. 1999). Because of these issues we have conducted two comparative analyses to answer clinical question 3, one including data from the JERA trial and one without including data from the JERA trial.

The subject disposition is shown in Figure 7.

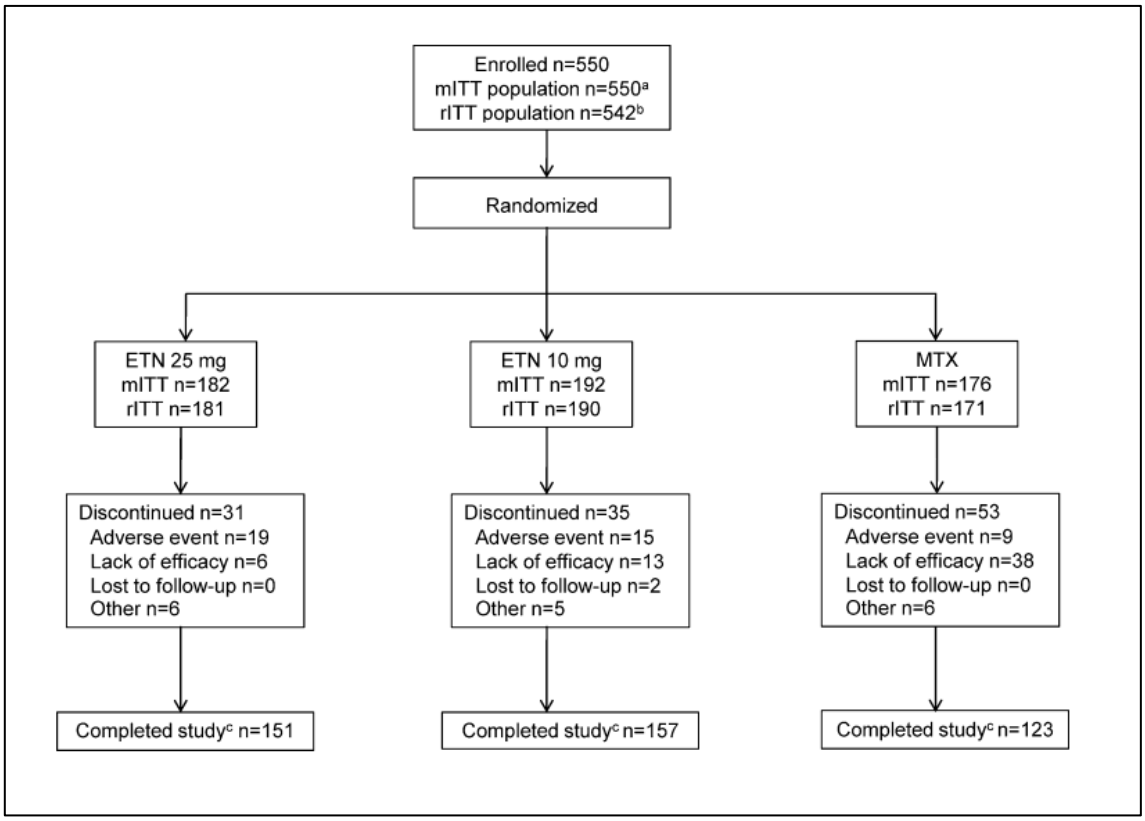

FIGURE 7: THE SUBJECT DISPOSITION IN THE JERA TRIAL. [A]ALL SUBJECTS IN THE MODIFIED INTENT-TO-TREAT (MITT) POPULATION WERE ALSO IN THE SAFETY POPULATION, [B]EIGHT SUBJECTS DID NOT HAVE BASELINE OR POST-BASELINE RADIOGRAPHIC DATA AND WERE NOT INCLUDED IN THE RADIOGRAPHIC INTENT-TO-TREAT (RITT) POPULATION, [C]ALL SUBJECTS WHO COMPLETED THE 52-WEEK TREATMENT PHASE ALSO COMPLETED THE 4-WEEK FOLLOW-UP PERIOD. ETN: ETANERCEPT, MTX: METHOTREXATE. SOURCE: TAKEUCHI ET AL (15).

All 550 randomised study subjects received at least one dose of study drug and were included in the modified intent-to-treat (mITT) and safety populations, which included all subjects who received at least one dose of the assigned drug. Of these, 542 subjects were included in the radiographic intent-to-treat (rITT) population, which included all subjects who received at least one dose of the assigned drug and provided radiographic data for the baseline and at least one post-baseline visit. The rITT did not include subjects who withdrew from the study within one month of the baseline visit (eight subjects with no post-baseline radiographic data were excluded).

Overall, 431 subjects (78.4 %) completed the study. Over the 52-week period, subjects in the MTX arm received a median weekly dose of 6 mg (mean 6.54 mg, SD 0.83). The rate of study discontinuation was significantly higher in the MTX treatment group than in the etanercept treatment groups, with 38 subjects (21.6 %) in the MTX group withdrawing due to lack of efficacy compared with six (3.3 %) in the etanercept 25 mg group and 13 (6.8 %) subjects in the etanercept 10 mg group. The number of subjects who withdrew due to AEs was comparable between groups (overall p-value = 0.173). (15)

The post-hoc analysis was conducted based on data from the JERA trial. Patients were grouped into MTX-naïve (never received MTX) and MTX-IR (those who were intolerant or had inadequate clinical response to MTX). The 550 RA patients included in the original JERA trial were included in the mITT and safety populations. 542 subjects were included in the rITT and grouped into MTX-naïve or MTX-IR. Table 5 shows the subject disposition in the MTX-naïve and MTX-IR groups.

TABLE 5: SUBJECT DISPOSITION IN THE POST-HOC ANALYSIS OF MTX-NAÏVE AND MTX-IR PATIENTS. SOURCE: (4).

	MTX-naïve	MTX-IR
Etanercept 10 mg	68	122
Etanercept 25 mg	60	121
MTX	68	103

5 Clinical questions

5.1 Clinical question 1: What is the value of filgotinib in combination with MTX compared with adalimumab in combination with MTX for bDMARD/tsDMARD treatment-naïve patients with moderate to severe chronic rheumatoid arthritis?

5.1.1 Presentation of relevant studies

In the search for literature containing a direct comparison of filgotinib and adalimumab in combination with MTX, the DMC identified the FINCH 1 trial. The FINCH 1 trial includes a head-to-head comparison of filgotinib and adalimumab in combination with MTX in bDMARD/tsDMARD treatment-naïve patients. The DMC protocol on filgotinib states that the FINCH 1 trial is sufficient evidence to answer clinical question 1, and we did not search for additional evidence.

In the following, we present results from the FINCH 1 trial for filgotinib 200 mg once daily and adalimumab 40 mg every other week on the relevant outcomes outlined in the protocol. We have used the EPAR for filgotinib as our primary data source but consulted the FINCH 1 CSR if the needed data was not available in the EPAR. As requested, we present data from the longest possible follow-up time in the study.

5.1.2 Results per study – The FINCH 1 trial

American College of Rheumatology 50% response (ACR50) – critical outcome

The primary endpoint of the FINCH 1 trial was the proportion of patients who achieve ACR20, and ACR50 was a secondary endpoint. Information on ACR50 was not available from the EPAR, and we consulted the CSR on the FINCH 1 trial and the SmPC for filgotinib (1).

ACR50 was analysed with logistic regression analysis with treatment groups and stratification factors such as geographic region, presence of RF or anti-CCP antibodies and prior exposure to bDMARD. Non-responder imputation (NRI) was applied.

Results for the FAS population (subjects who were randomised and received at least 1 dose of study drug) are presented in Table 6. At week 52, the proportion of subjects with ACR50 response was 62.3% (95% CI: 57.9%; 66.6%) in the filgotinib arm and 59.1% (95% CI: 53.7%; 64.4%) in the adalimumab arm.

TABLE 6: PROPORTION OF SUBJECTS WHO ACHIEVED ACR50 RESPONSE IN THE FILGOTINIB ARM AND IN THE ADALIMUMAB ARM AT WEEK 52 (FAS POPULATION).

Proportion of subjects who achieved ACR50 response	Filgotinib (N=475)	Adalimumab (N=325)	Source
ACR50 at week 52 – no. (%)	296 (62.3%)	192 (59.1%)	CSR/SmPC
95% CI	57.9%; 66.6%	53.7%; 64.4%	

Adverse events – critical endpoint

Results for AEs is measured in two ways: as the proportion of patients who discontinue treatment due to AEs, and as the proportion of patients who experience serious infections. Furthermore, the expert committee requests a description of the safety profiles of filgotinib and adalimumab, based on information from their respective summary of product characteristics (SmPCs), which is provided in section5.5. Discontinuation due to AEs and occurrence of

serious infections was assessed in the FINCH 1 trial. Our assessment of the AE outcome is based on the CSR on the FINCH 1 trial, because clinical safety data from phase II and phase III trials had been pooled in the EPAR.

All safety analyses were performed based on the safety analysis population, which included all subjects who received at least one dose of the study drug. AE data were summarised by treatment group using descriptive statistics.

Due to the re-randomisation of the placebo group at week 24, safety data and exposure comparison between the original active treatment groups (filgotinib and adalimumab) and placebo group were limited to the first 24 weeks. Comparison of filgotinib (200 mg) to the active comparator adalimumab (40 mg) is presented for the overall study duration. Across all treatment groups, most AEs that led to premature discontinuation of study drug were non-serious, Grade 1 or Grade 2 in severity, and were assessed by the investigator as not related to study drug. Throughout the overall study duration (52 weeks), 5.5% (95% CI: 3.4%; 7.5%) of the filgotinib arm and 5.5% (95% CI: 3.1%; 8.0%) of the adalimumab arm had discontinued treatment due to AEs. Results are presented in Table 7.

TABLE 7: PROPORTION OF SUBJECTS WHO DISCONTINUED TREATMENT DUE TO AES IN THE FILGOTINIB ARM AND IN THE ADALIMUMAB ARM THROUGH THE STUDY DURATION (SAFETY ANALYSIS POPULATION)

	Filgotinib (N=475)	Adalimumab (N=325)	Source
Proportion of subjects who discontinued treatment due to AEs – no. (%)	26 (5.5%)	18 (5.5%)	CSR
95% CI	3.4%; 7.5%	3.1%; 8.0%	

Results on the proportion of subjects who experience a serious infection are presented in Table 8. Results are shown for the overall study duration of 52 weeks.

The proportion of patients who experience serious infections was similar between the filgotinib and adalimumab group (2.7% vs. 3.1%). In the filgotinib group, 13 subjects experienced a serious infectious AE compared to 10 subjects in the adalimumab group.

TABLE 8: PROPORTION OF SUBJECTS WHO EXPERIENCE A SERIOUS INFECTION IN THE FILGOTINIB ARM AND IN THE ADALIMUMAB ARM (SAFETY ANALYSIS SET)

	Filgotinib (N=475)	Adalimumab (N=325)	Source
Proportion of subjects who experience a serious infection – no. (%)	13 (2.7%)	10 (3.1%)	CSR
95% CI	1.2%; 4.3%	1.0%; 5.1%	

Treatment discontinuation due to lack of effect – important outcome

Results for the overall study duration (52 weeks) are presented in Table 9. The filgotinib 200 mg FAS population consisted of 475 subjects. 77 subjects treated with filgotinib discontinued treatment prematurely (16.2%) and 29 subjects discontinued due to lack of effect corresponding to 6.1% (95% CI: 4.0%; 8.3%). The adalimumab FAS population consisted of 325 subjects. 59 subjects discontinued treatment with adalimumab prematurely (18.2%) and 14 subjects discontinued treatment due to lack of effect corresponding to 4.3% (95% CI: 2.1%; 6.5%) of the adalimumab FAS population.

TABLE 9: PROPORTION OF SUBJECTS WHO DISCONTINUED TREATMENT DUE TO LACK OF EFFECT IN THE FILGOTINIB AND ADALIMUMAB ARM (FAS POPULATION)

	Filgotinib (N=475)	Adalimumab (N=325)	Source
Proportion of subjects who discontinued treatment due to lack of effect – no. (%)	29 (6.1%)	14 (4.3%)	CSR
95% CI	4.0%; 8.3%	2.1%; 6.5%	

Total Sharp Score (TSS) after minimum 12 months – important outcome

We consulted the EPAR and the CSR on FINCH 1 in our assessment of proportion of patients without progression.

The proportion of subjects with no radiographic progression was defined as mTSS change ≤ 0. Radiographs were scored centrally by two independent readers blinded to chronological order, subject identifier and treatment group. mTSS change from baseline at week 52 included data from Campaign A (all radiographs through week 24) and Campaign B (radiographs through week 52 including re-reading of baseline and week 24 radiographs). Only observed values were used for analysis, no missing data imputation was performed. The proportion of subjects who were included in the mTSS analyses for each campaign were as follows: 81.5% (Campaign A), 77.3% (Campaign B), and 87.8% (417 patients) (Campaign B/A all available data at Week 52).

The proportion of subjects who had no radiographic progression at week 52 was defined as change from baseline in mTSS ≤0 analysed using a logistic regression analysis with treatment groups and stratification factors (geographic region, presence of RF or anti-CCP antibodies, prior exposure to bDMARDs) in the model. Subjects who did not have sufficient measurements to establish efficacy at week 12 were considered non-responders (i.e. NRI).

The proportion of subjects with no radiographic progression measured by an observed change from baseline in mTSS ≤0 is presented in Table 10. The proportion of subjects with change in mTSS ≤0 at week 52 was 87.5% (95% CI: 84.2%; 90.8%) in the filgotinib group versus 82.4% (95% CI: 77.7%; 87.1%) in the adalimumab group.

TABLE 10: PROPORTION OF SUBJECTS WITH NO RADIOGRAPHIC PROGRESSION (≤0 CHANGE FROM BASELINE IN MTSS) AT WEEK 52 (FAS POPULATION, OBSERVED CASES)

	Filgotinib (N=475)	Adalimumab (N=325)	Source
Campaign B/A at week 52 (all available data) - N	**417**	**273**	CSR
Proportion of subjects with no radiographic progression (≤0 change from baseline in mTSS) – no. (%)	365 (87.5%)	225 (82.4%)	
95% CI*	84.2%; 90.8%	77.7%; 87.1%	

*95% CI were based on normal approximation method with a continuity correction.

Health Assessment Questionnaire Disability Index (HAQ-DI) – important outcome

Improvement in HAQ-DI score is defined as a reduction of ≥0.22 from baseline and was evaluated in FINCH 1 with logistic regression analysis with treatment groups and stratification factors (geographic region, presence of RF or anti-CCP antibodies, prior exposure to bDMARDs) in the model.

Results are presented for the FAS population, however subjects with baseline HAQ-DI <0.22 were excluded from the analysis. 95% CI related to the response rates were based on normal approximation method with a continuity correction. Non-responder imputation (NRI) was applied. At week 52, 75.8% (95% CI: 71.8%; 79.8%) in the filgotinib group and 70.3% (95% CI: 65.1%; 75.5%) in the adalimumab group achieved response on the HAQ-DI, defined as a reduction of ≥0.22 in HAQ-DI from baseline. Results are presented in Table 11.

TABLE 11: PROPORTION OF SUBJECTS WHO ACHIEVED RESPONSE IN THE HAQ-DI OUTCOME IN THE FILGOTINIB ARM AND IN THE ADALIMUMAB ARM, AT WEEK 52

	Filgotinib (N=475)	Adalimumab (N=325)	Source
N	459	316	CSR
Proportion of subjects who achieved response in HAQ-DI (≥0.22 reduction from baseline) – no. (%)	348 (75.8%)	222 (70.3%)	
95% CI	71.8%; 79.8%	65.1%; 75.5%	

5.1.3 Comparative analyses related to clinical question 1

The protocol outlines two critical outcomes: ACR50 and AEs, and three important outcomes: treatment discontinuation due to lack of effect, TSS after minimum 12 months, and HAQ-DI. The comparative analyses of each outcome are described in the following subsections. An overview of the results of the comparative analyses is presented in Table 12 below and in the appendix, Table 60.

TABLE 12: OVERVIEW OF THE COMPARATIVE ANALYSES OF FILGOTINIB AND ADALIMUMAB IN COMBINATION WITH MTX IN BDMARD/TSDMARD-NAÏVE PATIENTS

Outcome	Absolut difference (95% CI)	Risk Ratio (95% CI)
Proportion of subjects who achieved ACR50 response	3.5 percentage points (-3.2%; 11.1%)	1.060 (0.945; 1.188)
Proportion of subjects who discontinue treatment due to an AEs	-0.1 percentage points (-3.6%; 3.1%)	0.988 (0.551; 1.773)
Proportion of subjects who experienced a serious infection	-0.3 percentage points (-3.0%; 2.3%)	0.889 (0.395; 2.004)
Proportion of subjects who discontinue treatment due to lack of effect	1.8 percentage points (-1.5%; 4.9%)	1.417 (0.761; 2.640)
Proportion of subjects without radiographic progression (defined as ≤0 change from baseline in mTSS)	5.2 percentage points (-0.3%; 11.1%)	1.063 (0.996; 1.135)
Proportion of subjects who achieved HAQ-DI response (defined as a reduction from baseline ≥0.22)	5.7 percentage points (-0.7%; 12.7%)	1.081 (0.990; 1.181)

Proportion of subjects who achieved ACR50 response

In the outcome “proportion of subjects who achieve ACR50 response”, the response rate in the filgotinib group was 62.3% versus 59.1% in the adalimumab group at week 52. The outcome was analysed with logistic regression and based on the estimated odds-ratio (OR), we have calculated the relative difference as a risk ratio between filgotinib and adalimumab using the formula in the DMC guideline (16). The absolute difference was calculated based on the risk ratio with the formula in the DMC guideline. The OR calculated with logistic regression was 1.160 and we calculated a risk ratio of 1.060 (95% CI: 0.945; 1.188, p-value = 0.320). An absolute difference of 3.5 percentage points (95% CI: -3.2%; 11.1%) was calculated, in favour of filgotinib. The difference was not beyond the minimal clinical difference (MCID) of 15% suggested by the DMC. Results are presented in Table 13.

TABLE 13: COMPARATIVE ANALYSIS OF THE PROPORTION OF SUBJECTS ACHIEVING ACR50 RESPONSE IN THE FILGOTINIB ARM AND ADALIMUMAB ARM AT WEEK 52

		Absolute difference			Relative difference		
	N	Difference	95% CI	p-value	Risk Ratio	95% CI	p-value
Filgotinib	475	3.5 percentage points	-3.2%; 11.1%	NA	1.060	0.945; 1.188	0.320
Adalimumab	325						

Adverse events – The proportion of subjects who discontinue treatment due to AEs

The proportion of subjects who discontinue treatment due to AEs was 5.5% in the filgotinib arm and 5.5% in the adalimumab arm, and we calculated an absolute difference of -0.1 percentage points (95% CI: -3.6%; 3.1%) and a risk ratio of 0.988 (95% CI: 0.551; 1.773, p-value = 0.969). The suggested MCID in the protocol is 5% and accordingly the calculated difference between filgotinib and adalimumab is not clinically relevant. The comparative analysis is presented in Table 14.

TABLE 14: COMPARATIVE ANALYSIS OF PROPORTION OF SUBJECTS WHO DISCONTINUE TREATMENT DUE TO AES IN THE FILGOTINIB AND ADALIMUMAB ARM THROUGHOUT THE STUDY DURATION

		Absolute difference			Relative difference		
	N	Difference	95% CI	p-value	Risk Ratio	95% CI	p-value
Filgotinib	475	-0.1 percentage points	-3.6%; 3.1%	0.969	0.988	0.551; 1.773	0.969
Adalimumab	325						

Adverse events – The proportion of subjects who experience a serious infection

2.7% of subjects in the filgotinib arm and 3.1% of subjects in the adalimumab arm experience a serious infection and there is an estimated absolute difference of -0.3 percentage points in favour of the filgotinib group (95% CI: -3.0%; 2.3%). We estimated the risk ratio to be 0.889 (95% CI: 0.395; 2.004, p-value = 0.777). The suggested MCID in the protocol is 5% and within this limit no clinical relevant difference is observed between filgotinib and adalimumab. The analysis is presented in Table 15.

TABLE 15: COMPARATIVE ANALYSIS OF THE PROPORTION OF SUBJECTS WHO EXPERIENCE A SERIOUS INFECTION IN THE FILGOTINIB AND ADALIMUMAB ARM THROUGHOUT THE STUDY DURATION

		Absolute difference			Relative difference		
	N	Difference	95% CI*	p-value	Risk Ratio	95% CI	p-value
Filgotinib	475	-0.3 percentage points	-3.0%; 2.3%	0.777	0.889	0.395; 2.004	0.777
Adalimumab	325						

*Absolute difference and 95% CI for the absolute difference in proportions were based on normal approximation method with a continuity correction.

The proportion of subjects who discontinue treatment due to lack of effect

We found that 29 subjects out of 475 (6.1%) in the filgotinib arm and 14 subjects out of 325 (4.3%) in the adalimumab arm discontinued treatment due to lack of effect. We calculated an absolute difference of 1.8 percentage points (95% CI: -1.5%; 4.5%) which is within the pre-specified MCID of 10% indicated by the DMC and the small absolute difference in the outcome indicates that the proportion of subjects who discontinue treatment due to lack of effect is similar in the two treatment groups. Results are presented in Table 16.

TABLE 16: COMPARATIVE ANALYSIS OF THE PROPORTION OF SUBJECTS WHO DISCONTINUE TREATMENT DUE TO LACK OF EFFECT IN THE FILGOTINIB ARM VERSUS THE ADALIMUMAB ARM THROUGHOUT THE STUDY DURATION

		Absolute difference			Relative difference		
	Results	**Difference**	**95% CI**	**p-value**	**Risk Ratio**	**95% CI**	**p-value**
Filgotinib	6.1%	1.8 percentage points	-1.5%; 4.9%	0.268	1.417	0.761; 2.640	0.272
Adalimumab	4.3%						

The proportion of subjects without radiographic progression (mTSS after minimum 12 months)

We found that 87.5% (95% CI: 84.2%; 90.8%) in the filgotinib group had a mean change from baseline ≤0 in mTSS versus 82.4% (95% CI: 77.7%; 87.1%) in the adalimumab group. The outcome was analysed with logistic regression and based on the estimated OR, we calculated the relative difference as a risk ratio between filgotinib and adalimumab using the formula in the DMC guideline (16). The absolute difference was calculated based on the risk ratio with the formula in the DMC guideline. The OR calculated with logistic regression was 1.510 and we calculated a risk ratio of 1.063 (95% CI: 0.996; 1.135, p-value = 0.068) indicating no statistically significant difference in the proportion of subjects with a mean change from baseline ≤0 in mTSS between the filgotinib and adalimumab at week 52. An absolute difference of 5.2 percentage points (95% CI: -0.3%; 11.1%) was calculated in favour of filgotinib, which was less than the MCID of 10% suggested by the DMC. However, it is worth mentioning that at week 52, change in mTSS from baseline was nominally significantly smaller for patients receiving filgotinib 200 mg versus adalimumab (Δ -0.43 [-0.66 to -0.20], P<0.001). The results on proportion of subjects with no radiographic progression are presented in Table 17.

TABLE 17: COMPARATIVE ANALYSIS OF PROPORTION OF SUBJECTS WITH NO RADIOGRAPHIC PROGRESSION (DEFINED AS ≤0 CHANGE FROM BASELINE IN MTSS) IN THE FILGOTINIB ARM VERSUS THE ADALIMUMAB ARM, AT WEEK 52

		Absolute difference			Relative difference		
	Results	**Difference**	**95% CI**	**p-value**	**Risk Ratio**	**95% CI**	**p-value**
Filgotinib	87.5%	5.2 percentage points	-0.3%; 11.1%	NA	1.063	0.996; 1.135	0.068
Adalimumab	82.4%						

Proportion of subjects achieving HAQ-DI response

We found a response rate of 75.8% in the filgotinib arm and a response rate of 70.3% in the adalimumab arm. The outcome was analysed with logistic regression and based on the estimated OR, we calculated the relative difference as a risk ratio between filgotinib and adalimumab using the formula in the DMC guideline (16). The absolute difference was calculated based on the risk ratio with the formula in the DMC guideline. The OR calculated with logistic regression was 1.338 and we calculated a risk ratio of 1.081 (95% CI: 0.990; 1.181, p-value = 0.084) indicating no significant difference in the HAQ-DI response rate between filgotinib and adalimumab at week 52. An absolute difference of 5.7 percentage points (95% CI: -0.7%; 12.7%) was calculated in favour of filgotinib, which was less than the MCID of 15% suggested by the DMC. Results are presented in Table 18.

TABLE 18: COMPARATIVE ANALYSIS OF PROPORTION OF SUBJECTS ACHIEVING HAQ-DI RESPONSE (DEFINED AS A REDUCTION FROM BASELINE ≥0.22), AT WEEK 52

	Result	Absolute difference			Relative difference		
		Difference	**95% CI**	**p-value**	**Risk Ratio**	**95% CI**	**p-value**
Filgotinib	75.8%	5.7 percentage points	-0.7%; 12.7%	NA	1.081	0.990; 1.181	0.084
Adalimumab	70.3%						

5.2 Clinical question 2: What is the value of filgotinib in combination with MTX compared with adalimumab in combination with MTX in bDMARD/tsDMARD treatment-experienced patients with moderate to severe chronic rheumatoid arthritis?

5.2.1 Presentation of relevant studies

In the systematic literature search, we identified the FINCH 2 study published by Genovese et al. 2019 (2). The FINCH 2 trial includes RA patients who have an inadequate response to bDMARDs (bDMARD-IR) and investigates filgotinib in combination with MTX.

We did not identify any studies for adalimumab in combination with MTX in bDMARD/tsDMARD-treatment-experienced RA patients. Likewise, the DMC's review of the therapy area did not identify studies for adalimumab in this patient population (11). However, they conclude that there is no basis for differentiating between biologics. We do not have any adalimumab studies to conduct a comparative analysis of filgotinib versus adalimumab to answer clinical question 2. We have examined earlier evaluations of bDMARD/tsDMARDs in RA patients conducted by the DMC to identify a method to answer clinical question 2 in the best way possible. Accordingly, we present a narrative description of filgotinib based on the FINCH 2 trial.

To perform the narrative description of filgotinib, we consulted the publication by Genovese et al. 2019, the EPAR on filgotinib and the FINCH 2 CSR. As requested in the protocol, we present data from the longest follow-up time in the FINCH 2 trial.

5.2.2 Results per study – The FINCH 2 trial

American College of Rheumatology 50% response (ACR50) – critical outcome

Information on ACR50 was not available in the EPAR; therefore, we consulted the FINCH 2 CSR, the publication by Genovese et al. 2019 and the SmPC for filgotinib (1,2).

ACR50 was a secondary endpoint in the FINCH 2 trial and was assessed at protocol-specified time points from day 1 through week 24 and was analysed with logistic regression analysis. Subjects who did not have sufficient measurements to establish efficacy at week 24 were considered non-responders (i.e. NRI imputation).

The proportion of subjects who achieved ACR50 response at week 24 was 45.6% (95% CI: 37.5%; 53.6%) in the filgotinib arm versus 18.2% (95% CI: 12.0%; 24.5%) in the placebo arm. The pairwise comparison showed a statistically significant difference in ACR50 response (p-value = <0.001). The proportion of subjects who achieved ACR50 response in the filgotinib arm versus the placebo group is presented in Table 19.

TABLE 19: PROPORTION OF SUBJECTS WHO ACHIEVED ACR50 RESPONSE IN THE FILGOTINIB ARM AND THE PLACEBO ARM AT WEEK 24 (FAS POPULATION WITH NRI)

	Filgotinib (N=147)	Placebo (N=148)	Source
Proportion of subjects who achieved ACR50 response – no. (%)	67 (45.6%)	27 (18.2%)	CSR/Genovese et al. 2019, SmPC (1,2)
95% CI	37.5%; 53.6%	12.0%; 24.5%	
P-value	<0.001		
Odds-ratio from logistic regression	3.755		

Adverse events – critical endpoint

AEs are measured in two ways: as the proportion of patients who discontinue treatment due to AEs, and as the proportion of patients who develop serious infections. Furthermore, the expert committee requests a description of the safety profiles of filgotinib and adalimumab, based on information from their respective SmPCs, which is provided in section 0. Discontinuation due to AEs and occurrence of serious infections were assessed in the FINCH 2 trial.

All safety analyses were performed based on the safety analysis population, which included all subjects who received at least one dose of the study drug. AE data were summarised by treatment group using descriptive statistics.

From weeks 0 to 24, three subjects (2.0%, 95% CI: -0.2%; 4.3%) in the filgotinib group and three subjects (2.0%, 95% CI: -0.2%; 4.3%) in the placebo group prematurely discontinued study drugs due to AEs. Most AEs that led to discontinuation of study drugs were considered by the investigator as related to study drugs, except for localised infection in the filgotinib group and RA in the placebo group. Results on treatment discontinuation for the safety analysis population are presented in Table 20.

TABLE 20: PROPORTION OF SUBJECTS WHO DISCONTINUED TREATMENT DUE TO AES IN THE FILGOTINIB ARM AND PLACEBO ARM (SAFETY ANALYSIS SET) FROM WEEKS 0 TO 24

	Filgotinib (N=147)	Placebo (N=148)	Source
Proportion of subjects who discontinued treatment due to AEs – no. (%)	3 (2.0%)	3 (2.0%)	Genovese et al. 2019 and SmPC (1,2)
95% CI	-0.2%; 4.3%	-0.2%; 4.3%	

In the assessment of the proportion of subjects who experienced a serious infection, we found that one subject (0.7%, 95% CI: -0.6%; 2.0%) in the filgotinib group and two subjects (1.4%, 95% CI: -0.5%; 3.2%) in the placebo group developed a serious infection during the study period (weeks 0 to 24). Results on the proportion of subjects experiencing a serious infection in the safety analysis population are presented in Table 21.

TABLE 21: PROPORTION OF SUBJECTS WHO EXPERIENCED A SERIOUS INFECTION IN THE FILGOTINIB ARM AND THE PLACEBO ARM FROM WEEKS 0 TO 24 (SAFETY ANALYSIS POPULATION)

	Filgotinib (N=147)	Placebo (N=148)	Source
Proportion of subjects who experienced a serious infection – no. (%)	1 (0.7%)	2 (1.4%)	CSR/Genovese et al. 2019 and SmPC (1,2)
95% CI	-0.6%; 2.0%	-0.5%; 3.2%	

Treatment discontinuation due to lack of effect – important outcome

12 subjects (8.2%, 95% CI: 3.7%; 12.6%) in the filgotinib 200 mg group and 32 subjects (21.6%, 95% CI: 15.0%; 28.3%) in the placebo group discontinued study drugs due to lack of effect. Results for the FAS population are presented in Table 22.

TABLE 22: PROPORTION OF SUBJECTS WHO DISCONTINUED TREATMENT DUE TO LACK OF EFFECT IN THE FILGOTINIB ARM AND IN THE PLACEBO ARM (FAS POPULATION), AT WEEK 24

	Filgotinib (N=147)	Placebo (N=148)	Source
Proportion of subjects who discontinued treatment due to lack of effect – no. (%)	12 (8.2%)	32 (21.6%)	CSR/Genovese et al. 2019 and SmPC (1,2)
95% CI	3.7%; 12.6%	15.0%; 28.3%	

Total Sharp Score (TSS) after minimum 12 months – important outcome

TSS was not assessed in the FINCH 2 trial. Therefore, the narrative description of filgotinib in clinical question 2 does not include a description of the TSS outcome.

Health Assessment Questionnaire Disability Index (HAQ-DI) – important outcome

Pairwise comparisons of the percentages of subjects who achieved at least a 0.22-point improvement (decrease) in the HAQ-DI score from baseline in the filgotinib treatment group versus placebo (using NRI) from day 1 through week 24 was reported in the FINCH 2 trial.

At all post-baseline study visits from weeks two to 24, the percentage of subjects who achieved an improvement in HAQ-DI score (at least a reduction of 0.22-point from baseline) was higher in the filgotinib treatment group, compared with the placebo group. At week 24, 68.8% of subjects in the filgotinib arm had achieved an improvement in HAQ-DI score compared to 35.4% of subjects in the placebo arm. The result is statistically significant (p-value = <0.001). Results are presented in Table 23.

TABLE 23: PROPORTION OF SUBJECTS WHO ACHIEVED RESPONSE IN HAQ-DI SCORE (REDUCTION OF ≥0.22 FROM BASELINE) IN THE FILGOTINIB ARM AND THE PLACEBO ARM (FAS POPULATION), AT WEEK 24

	Filgotinib (N=144)	Placebo (N=144)	Source
Proportion of subjects who achieved response in HAQ-DI (reduction from baseline ≥ 0.22)	99 (68.8%)	51 (35.4%)	CSR/Genovese et al. 2019
95% CI	61.2%; 76.3%	27.6%; 43.2%	
p-value	<0.001		
Odds-ratio from logistic regression	4.482		

Note: Only percentages reported in CSR/Genovese et al. 1999. Patient numbers are calculated.

5.2.3 Comparative analyses

As mentioned above, we did not identify any studies with data on adalimumab in bDMARD/tsDMARD treatment-experienced patients in the systematic literature search. Therefore, we were not able to perform comparative analyses of filgotinib and adalimumab in the requested population.

5.3 Clinical question 3: What is the value of filgotinib in monotherapy compared with etanercept as monotherapy in bDMARD/tsDMARD treatment-naïve patients with moderate to severe chronic rheumatoid arthritis?

5.3.1 Presentation of relevant studies

In the literature search, we identified three studies relevant for clinical question 3. The DARWIN 2 trial assessed filgotinib as monotherapy compared with placebo in bDMARD/tsDMARD treatment-naïve patients where treatment with csDMARD is not an option (defined as intolerance or inadequate response to MTX (MXT-IR)) (7,9). Two studies (the study by Moreland et al. 1999 and a post-hoc analysis of the JERA trial) report results on etanercept as monotherapy in bDMARD/tsDMARD treatment-naïve patients where treatment with csDMARD is not an option (MTX-IR) (3,4). The study by Moreland et al. 1999 and the post-hoc analysis of the JERA trial will be applied for the indirect comparison with the DARWIN 2 trial. However, there are some shortcomings with the JERA trial (see section 4.2.5). Thus, we have conducted two comparative analyses to answer clinical question 3, one including data from the JERA trial and one without including data from the JERA trial.

As requested, we present data from the longest follow-up time in the DARWIN 2 trial, which was 12 weeks, with results on filgotinib compared to placebo. In the study by Moreland et al. 1999, the follow-up time was six months. However, where possible we report results at three months of follow-up, which is more comparable to the 12 weeks of follow-up in the DARWIN 2 trial. In the post-hoc analysis of the JERA trial the follow-up time was 52 weeks. However, where possible, we report results at 12 weeks of follow-up, which is comparable to the 12 weeks of follow-up in the DARWIN 2 trial.

In the following, we present results on the relevant outcomes outlined in the DMC protocol on filgotinib from the DARWIN 2 trial, the study by Moreland et al. 1999 and the post-hoc analysis of the JERA trial in three separate sections. Subsequently, we present results on the indirect comparison between filgotinib and etanercept.

5.3.2 Results per study – the DARWIN 2 trial

American College of Rheumatology 50% response (ACR50) – critical outcome

Information on ACR50 was not available from the EPAR, and we consulted the publication by Kavanaugh et al. 2017 (7). ACR50 was a key secondary endpoint in the DARWIN 2 trial and assessed at every visit from baseline to week 24. However, at week 12, all patients in the placebo arm were reassigned to receive filgotinib. Thus, the longest follow-up on ACR50 in both the filgotinib and placebo arm is 12 weeks.

The proportion of subjects who achieved ACR50 response at week 12 was 43.5% (95% CI: 31.8%; 55.2%) in the filgotinib arm versus 11.1% (95% CI: 3.9%; 18.4%) in the placebo arm (Table 24). The results on this outcome are for the non-responder imputation ITT population.

TABLE 24: PROPORTION OF SUBJECTS WHO ACHIEVED ACR50 RESPONSE IN THE FILGOTINIB ARM AND THE PLACEBO ARM AT WEEK 12 (NON-RESPONDER IMPUTATION ITT POPULATION)

	Filgotinib (N=69)	Placebo (N=72)
Proportion of subjects who achieved ACR50 response – no. (%)	30 (43.5%)	8 (11.1%)
95% CI	31.8%; 55.2%	3.9%; 18.4%

Adverse events – critical outcome

Results for AEs are measured in two ways: as the proportion of patients who discontinue treatment due to AEs, and as the proportion of patients who experience serious infections. Furthermore, DMC requests a description of the safety profile of filgotinib, based on information from the SmPC. This is provided in section 0. Treatment discontinuation due to AEs and occurrence of serious infections were assessed in the publication by Kavanaugh et al. 2017 (7).

Only one subject in the filgotinib arm discontinued treatment due to AEs, while two subjects in the placebo arm discontinued treatment due to AEs. The proportion of subjects that discontinued treatment due to AEs from baseline to week 12 was 1.4% (95% CI: -1.4%; 4.3%) in the filgotinib arm and 2.8% (95% CI: -1.0%; 6.6%) in the placebo arm (Table 25). Results on this outcome are for the safety population (all randomised patients who received at least one dose of study drug).

TABLE 25: PROPORTION OF SUBJECTS WHO DISCONTINUED TREATMENT DUE TO AES IN THE FILGOTINIB ARM AND THE PLACEBO ARM AT WEEK 12 (SAFETY POPULATION)

	Filgotinib (N=69)	Placebo (N=72)
Proportion of subjects who discontinued treatment due to AEs – no. (%)	1 (1.4%)	2 (2.8%)
95% CI	-1.4%; 4.3%	-1.0%; 6.6%

Only one subject in the filgotinib arm (1.4%, 95% CI: -1.4%; 4.3%) experienced a serious infection from baseline to week 12 (Table 26). No subjects in the placebo arm experienced a serious infection. Results on this outcome are for the safety population.

TABLE 26 PROPORTION OF SUBJECTS WHO EXPERIENCED A SERIOUS INFECTION IN THE FILGOTINIB ARM AND THE PLACEBO ARM AT WEEK 12 (SAFETY POPULATION)

	Filgotinib (N=69)	Placebo (N=72)
Proportion of subjects who experienced a serious infection – no. (%)	1 (1.4%)	0 (0.0%)
95% CI	-1.4%; 4.3%	0.0%; 0.0%

Treatment discontinuation due to lack of effect – important outcome

Treatment discontinuation due to lack of effect was assessed in the publication by Kavanaugh et al. 2017 (7).

None of the subjects in the filgotinib arm discontinued treatment due to lack of effect, while two subjects in the placebo arm (2.8%, 95% CI: -1.0%; 6.6%) discontinued treatment due to lack of effect (defined as AEs and treatment failure) (Table 27). Results on this outcome are for the safety population.

TABLE 27: PROPORTION OF SUBJECTS WHO DISCONTINUED TREATMENT DUE TO LACK OF EFFECT IN THE FILGOTINIB ARM AND THE PLACEBO ARM AT WEEK 12 (SAFETY POPULATION)

	Filgotinib (N=69)	Placebo (N=72)
Proportion of subjects who discontinued treatment due to lack of effect – no. (%)	0 (0.0%)	2 (2.8%)
95% CI	0.0%; 0.0%	-1.0%; 6.6%

Total Sharp Score (TSS) after minimum 12 months – important outcome

TSS was not recorded in DARWIN 2. Thus, it is not possible to conduct an indirect comparison between filgotinib and etanercept on this outcome measure.

Health Assessment Questionnaire Disability Index (HAQ-DI) – important outcome

HAQ-DI response was assessed in the publication by Kavanaugh et al. 2017 (7). Subjects with a reduction of ≥0.22 in HAQ-DI score from baseline will be regarded as responders in the assessment of this outcome.

The proportion of subjects who achieved a HAQ-DI response at week 12 was 79.7% (95% CI: 70.2%; 89.2%) in the filgotinib arm and 51.4%% (95% CI: 39.8%; 62.9%) in the placebo arm (Table 28). Results on this outcome are for the ITT population.

TABLE 28: PROPORTION OF SUBJECTS WHO ACHIEVED RESPONSE ON THE HAQ-DI IN THE FILGOTINIB ARM AND THE PLACEBO ARM AT WEEK 12 (ITT POPULATION)

	Filgotinib (N=69)	Placebo (N=72)
Proportion of subjects who achieved response on HAQ-DI (≥0.22 change) – no. (%)	55 (79.7%)	37 (51.4%)
95% CI	70.2%; 89.2%	39.8%; 62.9%

5.3.3 Results per study – Moreland et al. 1999

American College of Rheumatology 50% response (ACR50) – critical outcome

ACR50 was one of the primary outcomes in the study by Moreland et al. 1999 and assessed at two weeks, three months, and six months (3). For this outcome measure, we report results at three months of follow-up, which is more comparable to the 12 weeks of follow-up for filgotinib in the DARWIN 2 trial.

The proportion of subjects who achieved ACR50 response at three months was 41% (95% CI: 30%; 52%) in the etanercept arm and 8% (95% CI: 2%; 14%) in the placebo arm (Table 29). At six months the ACR50 response did not change significantly (etanercept: 40%; placebo: 5%). The number of patients in the etanercept and placebo groups reflect the number of patients randomised to each group and withdrawals were counted as treatment failure. Moreland et al. 1999 only provide percentages; therefore, we have calculated the patient numbers.

TABLE 29: PROPORTION OF SUBJECTS WHO ACHIEVED ACR50 RESPONSE IN THE ETANERCEPT ARM AND THE PLACEBO ARM AT 3 MONTHS (WITHDRAWALS WERE COUNTED AS TREATMENT FAILURE)

	Etanercept (N=78)	Placebo (N=80)
Proportion of subjects who achieved ACR50 response – no. (%)	32 (41%)	6 (8%)
95% CI	30%; 52%	2%; 14%

Note: Only percentages (without decimals) reported in Moreland et al. (1999). Patient numbers are calculated.

Adverse events – critical outcome

Results for AEs are measured in two ways: as the proportion of patients who discontinue treatment due to AEs, and as the proportion of patients who experience serious infections. Furthermore, the expert committee requests a description of the safety profile of etanercept, based on information from the SmPC. This is provided in section 0 compared with the safety profile of filgotinib. Treatment discontinuation due to AEs was assessed in the publication by Moreland et al. 1999 (3). However, the study does not provide results on serious infections. Thus, the study by Moreland et al. 1999 will not be applied in the comparative analyses regarding serious infections.

Two subjects in the etanercept arm discontinued treatment due to AEs, while three subjects in the placebo arm discontinued treatment due to AEs during the six months study period. No data on three months, which is more comparable with the 12 weeks of follow-up on the DARWIN 2 trial, were available. The proportion of subjects that discontinued treatment due to AEs from baseline to six months was 2.6% (95% CI: -0.9%; 6.1%) in the etanercept arm and 3.8% (95% CI: -0.4%; 7.9%) in the placebo arm (Table 30). Results on this outcome are for the safety population (all randomised patients who received at least one dose of study drug).

TABLE 30: PROPORTION OF SUBJECTS WHO DISCONTINUED TREATMENT DUE TO AES IN THE ETANERCEPT ARM AND THE PLACEBO ARM AT 6 MONTHS (SAFETY POPULATION)

	Etanercept (N=78)	Placebo (N=80)
Proportion of subjects who discontinued treatment due to AEs – no. (%)	2 (2.6%)	3 (3.8%)
95% CI	-0.9%; 6.1%	-0.4%; 7.9%

Treatment discontinuation due to lack of effect – important outcome

Treatment discontinuation due to lack of effect was assessed in the publication by Moreland et al. 1999 (3).

The proportion of subjects who discontinued treatment due to lack of effect from baseline to six months was 15.4% (95% CI: 7.4%; 23.4%) in the etanercept arm and 52.5% (95% CI: 41.6%; 63.4%) in the placebo arm (Table 31). Most treatment discontinuations in the study occurred because of lack of efficacy (63.2% and 77.8% in the etanercept group and placebo group, respectively). Results on this outcome are for the safety population.

TABLE 31: PROPORTION OF SUBJECTS WHO DISCONTINUED TREATMENT DUE TO LACK OF EFFECT IN THE ETANERCEPT ARM AND THE PLACEBO ARM AT 6 MONTHS (SAFETY POPULATION)

	Etanercept (N=78)	Placebo (N=80)
Proportion of subjects that discontinued treatment due to lack of effect – no. (%)	12 (15.4%)	42 (52.5%)
95% CI	7.4%, 23.4%	41.6%; 63.4%

Total Sharp Score (TSS) after minimum 12 months – important outcome

Moreland et al. 1999, do not report on TSS (3).

Health Assessment Questionnaire Disability Index (HAQ-DI) – important outcome

In the study by Moreland et al. 1999 (3), there are no results on the proportion of subjects achieving HAQ-DI response (defined as a reduction of ≥0.22 from baseline). Instead improvement in HAQ-DI scores (defined as mean change from baseline) at week 2, 3 months and 6 months is reported (Table 4 in Moreland et al. 1999). Thus, the study by Moreland et al. 1999 will not be applied in the comparative analyses on this outcome measure.

5.3.4 Results per study – The JERA trial

The JERA trial compared MTX with etanercept as monotherapy in Japanese patients with RA. Results on the JERA trial were first published in 2013 by Takeuchi et al. (15). In 2020, Takeuchi et al. conducted and published a post-hoc analysis on data from the JERA trial comparing outcomes in patients who were MTX-naïve versus MTX-IR (4). In the indirect comparison with filgotinib we will apply the results from the MTX-IR subgroup published in Takeuchi et al.

2020. However, there are a number of shortcomings with applying the JERA trial in the indirect comparison with filgotinib (we refer to section 4.2.5 for an elaboration on this).

American College of Rheumatology 50% response (ACR50) – critical outcome

ACR50 response was assessed over 52 weeks. In the post-hoc analysis by Takeuchi et al. 2020, ACR50 response rates were analysed using the Cochran-Mantel-Haenszel approach, stratified by study centre. For this outcome measure, we report results at 12 weeks of follow-up, which is comparable to the 12 weeks of follow-up for filgotinib in the DARWIN 2 trial.

The proportion of subjects who achieved ACR50 response at week 12 was 39% (95% CI: 30%; 48%) in the etanercept arm and 18% (95% CI: 11%; 25%) in the MTX arm (Table 32). Takeuchi et al. 2020 only provide percentages in a graph (Figure 1 in Takeuchi et al. 2020). We estimated the percentages from the graph and calculated the patient numbers provided in Table 32. Results on this outcome are for the modified ITT population, which included patients who received at least one dose of study treatment.

TABLE 32: PROPORTION OF SUBJECTS WHO ACHIEVED ACR50 RESPONSE IN THE ETANERCEPT ARM AND THE MTX ARM AT WEEK 12 (MODIFIED ITT POPULATION)

	Etanercept (N=122)	MTX (N=108)
Proportion of subjects who achieved ACR50 response – no. (%)	48 (39%)	19 (18%)
95% CI	30%; 48%	11%; 25%

Note: Percentages estimated from graph at week 12 (Figure 1 in Takeuchi et al. 2020). Patient numbers are calculated.

Adverse events – critical outcome

Results for AEs are measured in two ways: as the proportion of patients who discontinue treatment due to AEs, and as the proportion of patients who develop serious infections. Furthermore, the expert committee requests a description of the safety profile of etanercept, based on information from the SmPC. This is provided in section 0 compared with the safety profile of filgotinib. Treatment discontinuation due to AEs and occurrence of serious infections was assessed in the publication by Takeuchi et al. 2020.

In the etanercept arm, 14 subjects discontinued treatment due to AEs, while five subjects in the MTX group discontinued treatment due to AEs. The proportion of subjects who discontinued treatment due to AEs from baseline to week 52 was 11.5% (95% CI: 5.8%; 17.1%) in the etanercept arm and 4.6% (95% CI: 0.7%; 8.6%) in the MTX arm (Table 33). No data on 12 weeks, which is comparable with the 12 weeks of follow-up on the DARWIN 2 trial, were available. The results on this outcome are for the safety population (all randomised patients who received at least one dose of study drug).

TABLE 33: PROPORTION OF SUBJECTS WHO DISCONTINUED TREATMENT DUE TO AES IN THE ETANERCEPT ARM AND THE MTX ARM AT WEEK 52 (SAFETY POPULATION)

	Etanercept (N=122)	MTX (N=108)
Proportion of subjects who discontinued treatment due to AEs – no. (%)	14 (11.5%)	5 (4.6%)
95% CI	5.8%; 17.1%	0.7%; 8.6%

Only one subject in the MTX arm (0.9%, 95% CI: -0.9%; 2.7%) experienced a serious infection from baseline to week 52 (Table 35). No subjects in the etanercept arm experienced a serious infection. Results on this outcome are for the safety population.

TABLE 34 PROPORTION OF SUBJECTS WHO EXPERIENCED A SERIOUS INFECTION IN THE ETANERCEPT ARM AND THE MTX ARM AT WEEK 52 (SAFETY POPULATION)

	Etanercept (N=122)	MTX (N=108)
Proportion of subjects who experienced a serious infection – no. (%)	0 (0.0%)	1 (0.9%)
95% CI	0.0%; 0.0%	-0.9%; 2.7%

Treatment discontinuation due to lack of effect – important outcome

Treatment discontinuation due to lack of effect was assessed in the publication by Takeuchi et al. 2020 (4).

The proportion of subjects who discontinued treatment due to lack of effect from baseline to week 52 was 2.5% (95% CI: -0.3%; 5.2%) in the etanercept arm and 21.3% (95% CI: 13.6%; 29.0%) in the MTX arm (Table 35). Results on this outcome are for the safety population.

TABLE 35: PROPORTION OF SUBJECTS WHO DISCONTINUED TREATMENT DUE TO LACK OF EFFECT IN THE ETANERCEPT ARM AND THE MTX ARM AT WEEK 52 (SAFETY POPULATION)

	Etanercept (N=122)	MTX (N=108)
Proportion of subjects who discontinued treatment due to lack of effect – no. (%)	3 (2.5%)	23 (21.3%)
95% CI	-0.3%; 5.2%	13.6%; 29.0%

Total Sharp Score (TSS) after minimum 12 months – important outcome

The mTSS was assessed in the publication by Takeuchi et al. 2020 (4) and analysed using the Cochran-Mantel-Haenszel approach, stratified according to the study centre. Changes from baseline in mTSS were analysed using an ANCOVA model based on rank-transformed data. For missing radiographic data, the linear interpolation or extrapolation method was used for the analysis of radiographic efficacy.

The proportion of subjects with no radiographic progression measured by a change from baseline in mTSS ≤0 is presented in Table 36. The proportion of subjects with change in mTSS ≤0 at week 52 was 41.3% (95% CI: 32.5%; 50.1%) in the etanercept arm and 25.2% (95% CI: 16.9%; 33.6%) in the MTX arm (Table 36). Results on this outcome is for the radiographic ITT population. The radiographic ITT population included all patients who received at least one dose of study treatment and had radiographic data at baseline and at least one post-baseline visit. It did not include patients who withdrew from the study within one month of the baseline visit.

TABLE 36: PROPORTION OF SUBJECTS WITH NO RADIOGRAPHIC PROGRESSION (DEFINED AS ≤0 CHANGE FROM BASELINE IN MTSS) IN THE ETANERCEPT ARM AND THE MTX ARM AT WEEK 52 (RADIOGRAPHIC ITT POPULATION)

	Etanercept (N=121)	MTX (N=103)
Proportion of subjects with no radiographic progression (≤0 change in mTSS) – no. (%)	50 (41.3%)	26 (25.2%)
95% CI	32.5%; 50.1%	16.9%; 33.6%

Health Assessment Questionnaire Disability Index (HAQ-DI) – important outcome

There are no results on the proportion of subjects who achieved HAQ-DI response (defined as a reduction of ≥0.22 from baseline) in MTX-IR subpopulation. The post-hoc analysis only reports changes in HAQ-DI score throughout the

study duration (52 weeks) in a graph (Figure 6 in Takeuchi et al. 2020 (4)). These results are not feasible for the indirect comparison with filgotinib. Thus, the post-hoc analysis of the JERA trial will not be applied in the comparative analyses on this outcome measure.

5.3.5 Comparative analyses

In this section, we present the comparative analysis of filgotinib and etanercept as monotherapy in bDMARD/tsDMARD treatment-naïve patients. This comparative analysis is based on an indirect comparison between filgotinib and etanercept and will be used to answer clinical question 3. The relative and absolute differences are estimated with Buchers' method (17,18) (please see appendix 7.4.3 for a description of this method).

Effects of filgotinib versus placebo have been studied in the DARWIN 2 trial and the effects of etanercept versus placebo has been studied in the study by Moreland et al. 1999. In addition, the effects of etanercept versus MTX have been studied in the post-hoc analysis of the JERA trial. In the JERA trial, the effect of etanercept might be underestimated because of the active comparator (MTX) relative to the non-active comparator (placebo) in the DARWIN 2 trial and the study by Moreland et al. 1999. In addition, the patient population in the JERA trial consists of Japanese patients, which may add some uncertainty to the indirect comparison (see section 4.2.5). Moreover, the results on the proportion of subjects who achieved ACR50 response were only provided in a graph. Therefore, we had to estimate the proportion from the graph, which also makes the applicability of the JERA trial for the indirect comparison with filgotinib challenging.

Because the DMC requests data from every study with data on the outlined outcomes in the specified patient population, we have decided to conduct two indirect comparisons: one applying the filgotinib data from the DARWIN 2 trial compared with the etanercept data from the study by Moreland et al. 1999, and another applying the filgotinib data from the DARWIN 2 trial compared with etanercept data from both the study by Moreland et al. 1999 and the JERA trial. For the latter, we have conducted a meta-analysis between the relative differences in the two etanercept studies (the study by Moreland et al. 1999 and the JERA trial). For this purpose, we chose the random effects meta-analysis, because this allows for differences in the treatment effects from study to study, whereas a fixed effects meta-analysis assumes all studies estimate the same (fixed) treatment effect (please see appendix 7.4.2 for a description of the random effects meta-analysis method).

The protocol outlines two critical outcomes: ACR50 and AEs, and three important outcomes: treatment discontinuation due to lack of effect, TSS after minimum 12 months, and HAQ-DI. The comparative analyses of each outcome are described in the following subsections. An overview of the results of the comparative analyses is presented in Table 37 below and in the appendix in Table 61 and Table 62.

TABLE 37: OVERVIEW OF THE COMPARATIVE ANALYSES OF FILGOTINIB COMPARED TO ETANERCEPT AS MONOTHERAPY IN BDMARD/TSDMARD TREATMENT-NAÏVE PATIENTS

Outcome	Based on DARWIN 2 trial and the study by Moreland et al. 1999		Based on the DARWIN 2 trial and a meta-analysis between the study by Moreland et al. 1999 and JERA trial	
	Absolut difference (95% CI)	Risk Ratio (95% CI)	Absolut difference (95% CI)	Risk Ratio (95% CI)
Proportion of subjects who achieved ACR50 response	-11.67% (-31.02%; 45.20%)	0.72 (0.24; 2.10)	7.76% (-24.39%; 60.00%)	1.19 (0.39; 3.65)
Proportion of subjects who discontinue treatment due to an AEs	-0.61% (-2.46%; 35.17%)	0.76 (0.04; 14.71)	-5.41% (-7.82%; 28.92%)	0.32 (0.02; 4.61)
Proportion of subjects who experienced a serious infection	NA	NA	1.31% (-10.95%; 1.45%)*	10.60 (0.12; 960.92)*
Proportion of subjects who discontinue treatment due to lack of effect	-4.43% (-14.88%; 84.62%)	0.71 (0.03; 15.34)	-0.17% (-7.18%; 92.50%)	0.98 (0.04; 22.58)
Proportion of subjects without radiographic progression (defined as ≤0 change from baseline in mTSS)	NA	NA	NA	NA
Proportion of subjects who achieved HAQ-DI response (defined as a reduction from baseline ≥0.22)	NA	NA	NA	NA

Note: *Based on the DARWIN 2 trial and the JERA trial. The study by Moreland et al. 1999 does not provide results on serious infections.

Proportion of subjects who achieved ACR50 response

In the indirect comparison of the "proportion of subjects who achieved an ACR50 response", based on the DARWIN 2 trial and the study by Moreland et al. 1999, the estimated risk ratio for filgotinib versus etanercept was 0.72 (95% CI: 0.24; 2.10). The result is not statistically significant (p-value: 0.54) (Table 38). The estimated absolute difference (assuming event rate for etanercept) was -11.67% with a wide confidence interval overlapping 0% (95% CI: -31.02%; 45.20%).

TABLE 38: INDIRECT COMPARISON OF PROPORTION OF SUBJECTS WHO ACHIEVED AN ACR50 RESPONSE FOR FILGOTINIB VERSUS ETANERCEPT AT WEEK 12/3 MONTHS*: BASED ON THE DARWIN 2 TRIAL AND THE STUDY BY MORELAND ET AL. 1999.

Relative difference Filgotinib versus placebo		Relative difference Etanercept versus placebo		Relative difference Filgotinib versus etanercept			Absolute difference assuming event rate for etanercept**	
Risk Ratio	95% CI	Risk Ratio	95% CI	Risk Ratio	95% CI	p-value	Difference	95% CI
3.91	1.93; 7.93	5.47	2.42; 12.35	0.72	0.24; 2.10	0.54	-11.67%	-31.02%; 45.20%

Note: *Outcome measured at week 12 for filgotinib in the DARWIN 2 trial and at 3 months for etanercept in the study by Moreland et al. 1999; **Event rate for etanercept from the study by Moreland et al. 1999.

In the indirect comparison on "proportion of subjects who achieved an ACR50 response", based on the DARWIN 2 trial and a meta-analysis between the study by Moreland et al. 1999 and the JERA trial, the estimated risk ratio for filgotinib versus etanercept was 1.19 (95% CI: 0.39; 3.65). The result is not statistically significant (p-value: 0.76) (Table 39). The estimated absolute difference (assuming event rate for etanercept) was 7.76% again with a wide confidence interval overlapping 0% (95% CI: -24.39%; 60.00%).

TABLE 39: INDIRECT COMPARISON OF PROPORTION OF SUBJECTS WHO ACHIEVED AN ACR50 RESPONSE FOR FILGOTINIB VERSUS ETANERCEPT AT WEEK 12/3 MONTHS*: BASED ON THE DARWIN 2 TRIAL AND A META-ANALYSIS BETWEEN THE STUDY BY MORELAND ET AL. 1999 AND THE JERA TRIAL.

Relative difference Filgotinib versus placebo		Relative difference Etanercept versus placebo		Relative difference Filgotinib versus etanercept			Absolute difference assuming event rate for etanercept**	
Risk Ratio	95% CI	Risk Ratio	95% CI	Risk Ratio	95% CI	p-value	Difference	95% CI
3.91	1.93; 7.93	3.28	1.38; 7.80	1.19	0.39; 3.65	0.76	7.76%	-24.39%; 60.00%

Note: *Outcome measured at week 12 for filgotinib in the DARWIN 2 trial, at 3 months for etanercept in the study by Moreland et al. 1999, and at week 12 for etanercept in the JERA; **Event rate for etanercept from the study by Moreland et al. 1999 and the JERA trial.

As mentioned previously the protocol specifies that the MCID for ACR50 is 15 percentage points. In both of the analyses the difference is less than 15% suggesting that there is no clinically relevant difference between filgotinib and etanercept for ACR50 with a MCID set at 15%.

Adverse events – The proportion of subjects who discontinue treatment due to AEs

In the indirect comparison of the "proportion of subjects who discontinue treatment due to AEs", based on the DARWIN 2 trial and the study by Moreland et al. 1999, the estimated risk ratio for filgotinib versus etanercept was 0.76 (95% CI: 0.04; 14.71). The result is not statistically significant (p-value: 0.86) (Table 40). The estimated absolute difference (assuming event rate for etanercept) was -0.61% with a wide confidence interval overlapping 0% (95% CI: -2.46%; 35.17%).

TABLE 40: INDIRECT COMPARISON OF PROPORTION OF SUBJECTS WHO DISCONTINUE TREATMENT DUE TO AES FOR FILGOTINIB VERSUS ETANERCEPT AT WEEK 12/6 MONTHS*: BASED ON THE DARWIN 2 TRIAL AND THE STUDY BY MORELAND ET AL. 1999.

Relative difference Filgotinib versus placebo		Relative difference Etanercept versus placebo		Relative difference Filgotinib versus etanercept			Absolute difference assuming event rate for etanercept**	
Risk Ratio	95% CI	Risk Ratio	95% CI	Risk Ratio	95% CI	p-value	Difference	95% CI
0.52	0.05; 5.62	0.68	0.12; 3.98	0.76	0.04; 14.71	0.86	-0.61%	-2.46%; 35.17%

Note: *Outcome measured at week 12 for filgotinib in the DARWIN 2 trial and at 6 months for etanercept in the study by Moreland et al. 1999; **Event rate for etanercept from the study by Moreland et al. 1999.

In the indirect comparison of the "proportion of subjects who discontinue treatment due to AEs", based on the DARWIN 2 trial and a meta-analysis between the study by Moreland et al. 1999 and the JERA trial, the estimated risk ratio for filgotinib versus etanercept was 0.32 (95% CI: 0.02; 4.61). The result is not statistically significant (p-value: 0.41) (Table 41). The estimated absolute difference (assuming event rate for etanercept) was -5.41% with a wide confidence interval overlapping 0% (95% CI: -7.82%; 28.92%).

TABLE 41: INDIRECT COMPARISON OF PROPORTION OF SUBJECTS WHO DISCONTINUE TREATMENT DUE TO AES FOR FILGOTINIB VERSUS ETANERCEPT AT WEEK 12/6 MONTHS/WEEK 52*: BASED ON THE DARWIN 2 TRIAL AND A META-ANALYSIS BETWEEN THE STUDY BY MORELAND ET AL. 1999 AND THE JERA TRIAL.

Relative difference Filgotinib versus placebo		Relative difference Etanercept versus placebo		Relative difference Filgotinib versus etanercept			Absolute difference assuming event rate for etanercept**	
Risk Ratio	95% CI	Risk Ratio	95% CI	Risk Ratio	95% CI	p-value	Difference	95% CI
0.52	0.05; 5.62	1.61	0.49; 5.30	0.32	0.02; 4.61	0.41	-5.41%	-7.82%; 28.92%

Note: *Outcome measured at week 12 for filgotinib in the DARWIN 2 trial, at 6 months for etanercept in the study by Moreland et al. 1999, and at week 52 for etanercept in the JERA trial; **Event rate for etanercept from the study by Moreland et al. 1999 and the JERA trial.

In the protocol a MCID of 5 percentage points has been suggested for this outcome. In the two indirect comparisons presented above, we found that the absolute and relative differences are numerically better for filgotinib versus etanercept, indicating that fewer subjects discontinue treatment due to AEs among patients treated with filgotinib versus patients treated with etanercept. However, both indirect comparisons find differences that are not statistically significant.

Adverse events – The proportion of subjects who experienced a serious infection

In the study by Moreland et al. 1999 this outcome was not reported. In both the DARWIN 2 trial and the JERA trial there are treatment arms with zero observations. In the DARWIN 2 trial, one subject in the filgotinib arm and zero subjects in the placebo arm experienced a serious infection, while zero subjects in the etanercept arm and one subject in the MTX arm experienced a serious infection in the JERA trial. Thus, to calculate the risk ratios, we have applied the standard method and added 0.5 to all cells in the 2x2 tables. It should be noted that this results in great uncertainties with the calculated risk ratios and the indirect comparison should be interpreted with caution. Because of zero observations in the etanercept arm we have estimated the absolute difference between filgotinib and etanercept assuming event rate for filgotinib.

In the indirect comparison of the "proportion of subjects who experienced a serious infection", based on the DARWIN 2 trial and the JERA trial, the estimated risk ratio for filgotinib versus etanercept was 10.60 (95% CI: 0.12; 960.92). The result is not statistically significant (p-value: 0.30) (Table 42). The estimated absolute difference (assuming event rate for filgotinib) was 1.31% with a wide confidence interval overlapping 0% (95% CI: -10.95%; 1.45%).

TABLE 42: INDIRECT COMPARISON OF PROPORTION OF SUBJECTS WHO EXPERIENCED A SERIOUS INFECTION FOR FILGOTINIB VERSUS ETANERCEPT AT WEEK 12/52*: BASED ON THE DARWIN 2 TRIAL AND THE JERA TRIAL.

Relative difference Filgotinib versus placebo**		Relative difference Etanercept versus placebo**		Relative difference Filgotinib versus etanercept			Absolute difference assuming event rate for filgotinib***	
Risk Ratio	95% CI	Risk Ratio	95% CI	Risk Ratio	95% CI	p-value	Difference	95% CI
3.13	0.13; 75.53	0.30	0.01; 7.17	10.60	0.12; 960.92	0.30	1.31%	-10.95%; 1.45%

Note: *Outcome measured at week 12 for filgotinib in the DARWIN 2 trial and at week 52 for etanercept in the JERA trial; **In both the DARWIN 2 trial and the JERA trial there are treatment arms with zero observations. Thus, to calculate the risk ratios, we have applied the standard method and added 0.5 to all cells in the 2x2 tables; ***Event rate for etanercept from the DARWIN 2 trial.

In the protocol a MCID of five percentage points has been suggested for this outcome. In the indirect comparison presented above, we found no statistically significant differences between filgotinib and etanercept on proportion of

subjects who experienced a serious infection. Again, it should be emphasised that these analyses are based on very few observations and the calculated risk ratios and indirect comparison are subject to great uncertainty.

The proportion of subjects who discontinue treatment due to lack of effect

In the DARWIN 2 trial, there were zero observations of discontinuation of treatment due to lack of effect in the filgotinib arm. Thus, to calculate the risk ratio for filgotinib versus placebo, we applied the standard method and added 0.5 to all cells in the 2x2 table. As described above, it should be noted that this results in great uncertainties with the calculated risk ratio and the indirect comparison should be interpreted with caution. In the indirect comparison of the "proportion of subjects who discontinue treatment due to lack of effect", based on the DARWIN 2 trial and the study by Moreland et al. 1999, the estimated risk ratio for filgotinib versus etanercept was 0.71 (95% CI: 0.03; 15.34). The result is not statistically significant (p-value: 0.83) (Table 43). The estimated absolute difference (assuming event rate for etanercept) was -4.43% with a wide confidence interval overlapping 0% (95% CI: -14.88%; 84.62%).

TABLE 43: INDIRECT COMPARISON OF PROPORTION OF SUBJECTS WHO DISCONTINUE TREATMENT DUE TO LACK OF EFFECT FOR FILGOTINIB VERSUS ETANERCEPT AT WEEK 12/6 MONTHS*: BASED ON THE DARWIN 2 TRIAL AND THE STUDY BY MORELAND ET AL. 1999.

Relative difference Filgotinib versus placebo**		Relative difference Etanercept versus placebo		Relative difference Filgotinib versus etanercept			Absolute difference assuming event rate for etanercept***	
Risk Ratio	95% CI	Risk Ratio	95% CI	Risk Ratio	95% CI	p-value	Difference	95% CI
0.21	0.01; 4.27	0.29	0.17; 0.51	0.71	0.03; 15.34	0.83	-4.43%	-14.88%; 84.62%

Note: *Outcome measured at week 12 for filgotinib in the DARWIN 2 trial and at 6 months for etanercept in the study by Moreland et al. 1999; **In the DARWIN 2 trial there are zero observations in the filgotinib arm. Thus, to calculate the risk ratio, we have applied the standard method and added 0.5 to all cells in the 2x2 table; ***Event rate for etanercept from the study by Moreland et al. 1999.

In the indirect comparison of the "proportion of subjects who discontinue treatment due to lack of effect", based on the DARWIN 2 trial and a meta-analysis between the study by Moreland et al. 1999 and the JERA trial, the estimated risk ratio for filgotinib versus etanercept was 0.98 (95% CI: 0.04; 22.58). The result is not statistically significant (p-value: 0.99) (Table 44). The estimated absolute difference (assuming event rate for etanercept) was -0.17% with a wide confidence interval overlapping 0% (95% CI: -7.18%; 92.50%).

TABLE 44: INDIRECT COMPARISON OF PROPORTION OF SUBJECTS WHO DISCONTINUE TREATMENT DUE TO LACK OF EFFECT FOR FILGOTINIB VERSUS ETANERCEPT AT WEEK 12/6 MONTHS/WEEK 52*: BASED ON THE DARWIN 2 TRIAL AND A META-ANALYSIS BETWEEN THE STUDY BY MORELAND ET AL. 1999 AND THE JERA TRIAL.

Relative difference Filgotinib versus placebo**		Relative difference Etanercept versus placebo		Relative difference Filgotinib versus etanercept			Absolute difference assuming event rate for etanercept***	
Risk Ratio	95% CI	Risk Ratio	95% CI	Risk Ratio	95% CI	p-value	Difference	95% CI
0.21	0.01; 4.27	0.21	0.09; 0.51	0.98	0.04; 22.58	0.99	-0.17%	-7.18%; 92.50%

Note: *Outcome measured at week 12 for filgotinib in the DARWIN 2 trial, at 6 months for etanercept in the study by Moreland et al. 1999, and at week 52 for etanercept in the JERA trial; **In the DARWIN 2 trial there are 0 observations in the filgotinib arm. Thus, to calculate the risk ratio, we have applied the standard method and added 0.5 to all cells in the 2x2 table; ***Event rate for etanercept from the study by Moreland et al. 1999 and the JERA trial.

In the protocol, a MCID of 10 percentage points has been suggested for this outcome. In the two indirect comparisons presented above, we found that the absolute and relative differences are numerically better for filgotinib versus etanercept, indicating that fewer subjects discontinue treatment due to lack of effect among patients treated with filgotinib versus patients treated with etanercept. However, both indirect comparisons find differences that are not statistically significant. Again, it should be emphasised that these analyses are based on zero observations in the filgotinib arm (DARWIN 2 trial) and the calculated risk ratio and indirect comparisons are subject to great uncertainty.

The proportion of subjects without radiographic progression (TSS after minimum 12 months)

It is not possible to estimate the absolute or relative difference in effect on the outcome for the "proportion of subjects without radiographic progression (≥0 change from baseline in mTSS)". In the DARWIN 2 trial and the study by Moreland et al. 1999, results on the TSS outcome were not reported.

The proportion of subjects who achieved HAQ-DI response

It is not possible to estimate the absolute or relative difference in effect on the outcome "proportion of subjects who achieved HAQ-DI response (reduction of ≥0.22 from baseline)". In the study by Moreland et al. 1999 and the JERA trial, this outcome was not reported.

5.4 Clinical question 4: What is the value of filgotinib in monotherapy compared to etanercept in monotherapy in bDMARD/tsDMARD treatment-experienced patients with moderate to severe chronic rheumatoid arthritis?

Unfortunately, we were not able to identify any clinical trials assessing the effect of filgotinib as monotherapy in the requested subpopulation. Thus, we were not able to present a comparative analysis or a narrative description for this clinical question.

5.5 Description of safety profiles from the summary of product characteristics (SmPC)

The expert committee has requested a narrative description of the safety profiles of filgotinib, adalimumab and etanercept based on their respective SmPCs (1,19,20). Overall, the safety profile of filgotinib is similar to the safety profiles of adalimumab and etanercept. Many of the reported AEs in the SmPC for filgotinib are also reported in the SmPC for adalimumab and etanercept (e.g. nausea, infections, opportunistic infections such as tuberculosis, and severe infections). Furthermore, the management of these AEs are similar for all three products. In Table 45, AEs observed in filgotinib clinical trials are listed by system organ class and frequency, classified as common (≥ 1/100 to < 1/10) and uncommon (≥ 1/1,000 to < 1/100).

TABLE 45: ADVERSE EVENTS FROM THE FILGOTINIB SMPC AND THE FREQUENCY. SOURCE: (1).

Frequency*	Adverse event
Infections and infestations	
Common	Urinary tract infection and upper respiratory tract infection
Uncommon	Herpes Zoster Pneumonia
Blood and lymphatic system disorders	
Uncommon	Neutropenia
Metabolism and nutrition disorders	
Uncommon	Hypercholesterolaemia
Nervous system disorders	
Common	Dizziness
Gastrointestinal disorders	
Common	Nausea
Investigations	
Uncommon	Blood creatine phosphokinase increased

*Frequency based on placebo-controlled pre-rescue period (week 12), pooled across FINCH 1 and 2 and DARWIN 1 and 2, for patients who received filgotinib 200 mg.

According to the SmPC for filgotinib, the AEs most frequently reported in patients treated with filgotinib are nausea, upper respiratory tract infections, urinary tract infection, and dizziness. The most frequently reported AEs in the SmPC for adalimumab are infections (such as nasopharyngitis, upper respiratory tract infection and sinusitis), injection site reactions (erythema, itching, haemorrhage, pain or swelling), headache and musculoskeletal pain. In the etanercept SmPC, the most frequently reported AEs are injection site reactions (pain, swelling, itching, reddening and bleeding at the puncture site), infections (such as upper respiratory infections, bronchitis, bladder infections) and skin infections, allergic reactions, development of autoantibodies, itching and fever.

Impaired spermatogenesis and histopathological effects on male reproductive organs (testes and epididymis) were observed with filgotinib in rats and dogs. At the no-observed-adverse-effect-levels (NOAELs) in dogs (the most sensitive species), the exposure margin is 2.7-fold at the 200 mg once daily dose in humans. The severity of the histological effects was dose-dependent. Spermatogenic and histopathological effects were not fully reversible at lower exposures and were irreversible at exposure margins of approximately 7- to 9-fold the exposure at the 200 mg once daily dose in humans. The potential effect of filgotinib on sperm production and male fertility in humans is currently unknown. The potential risk of reduced fertility or infertility should be discussed with male patients before initiating treatment. Preclinical data on fertility effects of adalimumab and etanercept are not available.

As mentioned above, infections are reported in the SmPCs of all three drugs. In the SmPC for filgotinib, the reported infections are upper respiratory tract infections, urinary tract infections, pneumonia, and herpes zoster. Most of the herpes zoster events involved a single dermatome and were non-serious. The most common serious infection

reported for filgotinib is pneumonia. The infections reported in the adalimumab SmPC are nasopharyngitis, upper respiratory tract infection, and sinusitis. Serious infections (including fatal infections, which occurred rarely) have been reported in patients treated with adalimumab and includes tuberculosis (including miliary and extra-pulmonary locations) and invasive opportunistic infections (e.g. disseminated or extrapulmonary histoplasmosis, blastomycosis, coccidioidomycosis, pneumocystis, candidiasis, aspergillosis and listeriosis). Sepsis, due to bacterial, mycobacterial, invasive fungal, parasitic, or viral agents, has also been reported with adalimumab. The serious infections reported with etanercept are sepsis, tuberculosis and opportunistic infections, including invasive fungal infections, listeriosis and legionellosis. These infections were due to bacteria, mycobacteria, fungi, viruses, and parasites (including protozoa).

Opportunistic infections and tuberculosis are mentioned in all three SmPCs, and patients should be screened for tuberculosis before initiating treatment with all three drugs. In placebo-controlled studies with background DMARDs, there were no opportunistic infections over 12 weeks, and in the MTX-controlled study FINCH 3, the frequency of opportunistic infections over 24 weeks was very low (0, 0.2% and 0 in the filgotinib 200 mg monotherapy and filgotinib 200 mg + MTX, respectively). The filgotinib SmPC does not specify what types of tuberculosis that have been reported with filgotinib. Cases of active tuberculosis, including miliary tuberculosis and tuberculosis with extra-pulmonary location, have been reported in patients treated with etanercept. In the adalimumab SmPC, reports included cases of pulmonary and extra-pulmonary (i.e. disseminated) tuberculosis. Other opportunistic infections, including invasive fungal infections have also been observed in patients receiving adalimumab. These infections have not consistently been recognised in patients taking TNF-antagonists (such as adalimumab) and this has resulted in delays in appropriate treatment, sometimes resulting in fatal outcomes.

Viral reactivation has also been reported in the SmPCs of all three products. In the filgotinib SmPC, reactivation of herpes zoster virus is listed as an uncommon AE with a frequency of 0.1 % for filgotinib 200 mg compared to 0.3% for placebo over 12 weeks in placebo-controlled studies with background DMARDs. Patients should be screened for hepatitis B and C virus and monitored for reactivation (patients with a history of hepatitis B and C where excluded from clinical trials). In the adalimumab SmPC, skin and soft tissue infections (including herpes zoster) are listed as a common AE and in the etanercept SmPC opportunistic infections that has been reported in association with etanercept include herpes zoster. Reactivation of hepatitis B has occurred in patients receiving a TNF-antagonist, including adalimumab and etanercept, and there have been reports of worsening of hepatitis C in patients receiving etanercept.

Malignancies have been reported in clinical studies of filgotinib, but clinical data are insufficient to assess the potential incidence of malignancies following exposure to filgotinib. However, Non-melanoma skin cancer (NMSC) is mentioned in all three SmPCs. Long-term safety evaluations are ongoing for patients treated with filgotinib. The adalimumab SmPC states that the rate (95% CI) of NMSC was 8.8 (6.0, 13.0) per 1,000 patient-years among adalimumab-treated patients. The etanercept SmPC states that NMSC has been observed in patients receiving etanercept and when combining the results of controlled clinical trials, more cases of NMSC were observed in patients receiving etanercept compared with control patients.

Events of deep venous thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients receiving JAK inhibitors including filgotinib. JAK inhibitors should be used with caution in patients with risk factors for DVT and PE (such as older age, obesity, a medical history of DVT/PE, or patients undergoing surgery and prolonged immobilisation). The same risk is not reported in the adalimumab or etanercept SmPC. Increases in lipids are reported in both the filgotinib and adalimumab SmPCs but not in the etanercept SmPC. Treatment with filgotinib was associated with dose-dependent increases in lipid parameters, including total cholesterol, and high-density lipoprotein (HDL) levels, while low-density lipoprotein (LDL) levels were slightly increased. LDL cholesterol returned to pre-treatment levels in the majority of patients who started statin therapy while taking filgotinib. In the adalimumab SmPC, increased lipids in the blood is listed as a very common undesirable effect.

6 References

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Synthetic Disease-Modifying Anti-Rheumatic Drug(s) (csDMARDs) to Subjects with Moderately to Severely Active Rheumatoid Arthritis Who Have an Inadequate Response to Biologic DMARD(s) Treatment (FINCH 2). 2018.

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7 Appendices

7.1 Literature search

7.1.1 Search terms and hits

We conducted the literature search on 13 October 2020, applying the search terms defined in the DMC protocol on filgotinib. Table 46 presents the search terms and number of hits found in PubMed, and Table 47 presents the search terms and number of hits found in CENTRAL.

TABLE 46: SEARCH TERMS AND HITS IN PUBMED (13 OCTOBER 2020)

#	Search terms	Comment	Hits
1	Arthritis, Rheumatoid[majr]	Terms for indication	92,853
2	rheumatoid arthriti*[ti] OR reumatoid arthriti*[ti] OR RA[ti]		65,549
3	#1 OR #2		103,664
4	GLPG0634[nm]	Terms for drugs	36
5	filgotinib[tiab] OR GLPG0634[tiab]		102
6	Adalimumab[majr]		1,424
7	adalimumab[tiab] OR Humira*[tiab] OR "ABP 501"[tiab]		7,171
8	Etanercept[majr]		770
9	etanercept[tiab] OR enbrel[tiab] OR ((TNFR*[tiab] OR TNF[tiab] OR TNT[tiab]) AND fusion[tiab] AND protein[tiab]) OR TNR-001[tiab]		8,263
10	#4 OR #5 OR #6 OR #7 OR #8 OR #9		13,331
11	("Randomized Controlled Trial"[pt] OR "Controlled Clinical Trial"[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR "Clinical Trials as Topic"[mh:noexp] OR randomly[tiab] OR trial[ti]) NOT ("Animals"[mh] NOT "Humans"[mh])	Filter for identification of randomised controlled trials (RCT)	1,261,248
12	#3 AND #10 AND #11	Combination of indication, drugs and RCT filter	763
13	Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Guideline[pt] OR Letter[pt] OR Review[pt] OR Systematic Review[pt] OR Meta-Analysis[pt]	Irrelevant publication types for exclusion	6,463,727
14	case report[ti] OR review[ti] OR meta-analysis[ti] OR animal[ti]		818,018
15	**#12 NOT (#13 OR #14)**	**Final search**	**469**

Note: majr = MeSH Major Topic, mh = MeSH Terms, nm = Supplementary Concept/Substance, pt = Publication type, ti = Title, tiab = Title/abstract, incl. author keywords.

TABLE 47: SEARCH TERMS AND HITS IN CENTRAL (13 OCTOBER 2020)

#	Search terms	Comment	Hits
1	MeSH descriptor: [Arthritis, Rheumatoid] this term only	Terms for indication	5,812
2	((rheumatoid OR reumatoid) NEXT arthritis):ti OR RA:ti		11,509
3	#1 OR #2		12,639
4	(filgotinib OR GLPG0634):ti,ab,kw	Terms for drugs	155
5	(adalimumab OR Humira*):ti,ab,kw		3,004
6	MeSH descriptor: [Adalimumab] explode all trees		744
7	(etanercept or enbrel* or TNR-001):ti,ab,kw		2,185
8	((TNFR* OR TNF OR TNT) AND fusion AND protein):ti,ab,kw		115
9	MeSH descriptor: [Etanercept] explode all trees		758
10	#4 OR #5 OR #6 OR #7 OR #8 OR #9		4,915
11	#3 AND #10	Combination of indication and drugs	1,603
12	conference abstract:pt OR review:pt OR meta-analysis:pt	Irrelevant publication types for exclusion	179,084
13	("clinicaltrials gov" OR trialsearch):so		332,961
14	NCT*:au		196,025
15	#12 OR #13 OR #14		512,211
16	#11 NOT #15		671
17	Embase:an NOT Pubmed:an	Identification of poster from Embase	349,980
18	**#16 AND #17**	**Final search**	**148**

Note: ti: Title, ab: Abstract, so: Source, kw: Keywords, controlled/index terms from the Medline and/or Embase databases, pt = Publication type.

7.1.2 Inclusion and exclusion criteria

We applied the inclusion and exclusion criteria defined in the DMC protocol on filgotinib. Table 48 presents the inclusion and exclusion criteria used in the search for relevant literature for clinical question 2-4.

TABLE 48: INCLUSION AND EXCLUSION CRITERIA USED IN THE SEARCH FOR RELEVANT LITERATURE.

Inclusion criteria	**Population:** Moderate to severe rheumatoid arthritis, bDMARD/tsDMARD treatment-experienced or treatment-naïve patients. For clinical question 3 and 4: patients where csDMARDs are not an option (e.g. MTX-IR). **Intervention(s):** Filgotinib (200 mg orally once daily) in combination with MTX; filgotinib (200 mg orally once daily); adalimumab (40 mg subcutaneously once every second week) in combination with MTX; etanercept (50 mg administered subcutaneously once weekly). **Comparator(s):** MTX and placebo; placebo; MTX **Outcomes:** Reporting one or more of the clinical outcome measures reported in the DMC protocol, i.e. American College of Rheumatology 50% response (ACR50), adverse events, discontinuation due to lack of efficacy, Total Sharp Score (TSS), Health Assessment Questionnaire Disability Index (HAQ-DI). **Study design:** Randomised clinical trial (RCT) **Language restrictions:** English
Exclusion criteria	**Study design:** Phase I or IIa studies

7.1.3 List of excluded literature

Table 49 lists all articles excluded after full-text assessment. We have indicated for which clinical question the article was potentially relevant and an explanation as to why the article was excluded.

TABLE 49: THE LIST OF EXCLUDED LITERATURE AFTER FULL-TEXT ASSESSMENT AND AN EXPLANATION AS TO WHY THE LITERATURE WAS EXCLUDED.

Reference	Potentially relevant for clinical question	Reason for exclusion
Aletaha D et al. (2019): Effect of disease duration and prior disease-modifying antirheumatic drug use on treatment outcomes in patients with rheumatoid arthritis. Annals of the rheumatic diseases. 78(12): 1609-1615.	Clinical question 2	Not relevant study population (only bDMARD/tsDMARD treatment-naïve patients)
Chen DY et al. (2009): Randomized, double-blind, placebo-controlled, comparative study of human anti-TNF antibody adalimumab in combination with methotrexate and methotrexate alone in Taiwanese patients with active rheumatoid arthritis. Journal of the Formosan Medical Association. 108(4): 310-9.	Clinical question 2	Not relevant study population (only bDMARD/tsDMARD treatment-naïve patients)
Keystone EC et al. (2004): Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate	Clinical question 2	Not relevant study population (only

therapy: a randomized, placebo-controlled, 52-week trial. Arthritis and rheumatism. 50(5): 1400-11.		bDMARD/tsDMARD treatment-naïve patients)
Keystone EC et al. (2014a): Clinical, functional, and radiographic implications of time to treatment response in patients with early rheumatoid arthritis: a post hoc analysis of the PREMIER study. The Journal of rheumatology. 41(2): 235-43.	Clinical question 2	Not relevant study population (only bDMARD/tsDMARD treatment-naïve patients)
Keystone EC et al. (2014b): Longterm effect of delaying combination therapy with tumor necrosis factor inhibitor in patients with aggressive early rheumatoid arthritis: 10-year efficacy and safety of adalimumab from the randomized controlled PREMIER trial with open-label extension. The Journal of rheumatology. 41(1): 5-14.	Clinical question 2	Not relevant study population (only bDMARD/tsDMARD treatment-naïve patients)
Strand V et al. (2012): Health-related quality of life outcomes of adalimumab for patients with early rheumatoid arthritis: results from a randomized multicenter study. The Journal of rheumatology. 39(1): 63-72.	Clinical question 2	Not relevant study population (only bDMARD/tsDMARD treatment-naïve patients)
Taylor PC et al. (2017): Baricitinib versus Placebo or Adalimumab in Rheumatoid Arthritis. The New England journal of medicine. 376(7): 652-662.	Clinical question 2	Not relevant study population (only bDMARD/tsDMARD treatment-naïve patients)
Weinblatt ME et al. (2003): Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. Arthritis and rheumatism. 48(1): 35-45.	Clinical question 2	Not relevant study population (only bDMARD/tsDMARD treatment-naïve patients)
Bathon JM et al. (2000): A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. The New England journal of medicine. 343(22): 1586-93.	Clinical question 3	Not relevant study population (MTX-naïve)
Bathon JM et al. (2006): Safety and efficacy of etanercept treatment in elderly subjects with rheumatoid arthritis. The Journal of rheumatology. 33(2): 234-43.	Clinical question 3	Not relevant stratification of the patient population (<65 years vs. ≥65 years)
Chen XX et al. (2016): A randomized, controlled trial of efficacy and safety of Anbainuo, a bio-similar etanercept, for moderate to severe rheumatoid arthritis inadequately responding to methotrexate. Clinical rheumatology. 35(9): 2175-83.	Clinical question 3	Not relevant intervention (Anbainuo, a biosimilar etanercept, in combination with MTX)
Genovese MC et al. (2002): Etanercept versus methotrexate in patients with early rheumatoid arthritis: two-year radiographic and clinical outcomes. Arthritis and rheumatism. 46(6): 1443-50.	Clinical question 3	Not relevant study population (MTX-naïve)
Kameda H et al. (2011): Continuation of methotrexate resulted in better clinical and radiographic outcomes than discontinuation upon starting etanercept in patients with rheumatoid arthritis: 52-week results from the JESMR study. The Journal of rheumatology. 38(8): 1585-92.	Clinical question 3	Not relevant comparator (treatment arms: etanercept vs. etanercept in combination with MTX)
Kavanaugh A et al. (2008): Improvements in clinical response between 12 and 24 weeks in patients with rheumatoid arthritis on etanercept therapy with or without methotrexate. Annals of the rheumatic diseases. 67(10): 1444-7.	Clinical question 3	Not relevant analyses (results for week 24 in week 12 non-responders and week 52 in week 24 non-responders)

Keystone EC et al. (2004): Once-weekly administration of 50 mg etanercept in patients with active rheumatoid arthritis: results of a multicenter, randomized, double-blind, placebo-controlled trial. Arthritis and rheumatism. 50(2): 353-63.	Clinical question 3	Not relevant intervention (concomitant MTX in >50% of patients)
Keystone E et al. (2009): Patients with moderate rheumatoid arthritis (RA) achieve better disease activity states with etanercept treatment than patients with severe RA. The Journal of rheumatology. 36(3): 522-31.	Clinical question 3	Not relevant stratification of the study population (moderate vs. severe RA)
Klareskog L et al. (2004): Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. Lancet (London, England). 363(9410): 675-81.	Clinical question 3	Not relevant study population (not MTX-IR and the majority were MTX-naïve)
Kosinski M et al. (2002): Health-related quality of life in early rheumatoid arthritis: impact of disease and treatment response. The American journal of managed care. 8(3): 231-40.	Clinical question 3	Not relevant study population (MTX-naïve)
Mathias SD et al. (2000): Health-related quality of life and functional status of patients with rheumatoid arthritis randomly assigned to receive etanercept or placebo. Clinical therapeutics. 22(1): 128-39.	Clinical question 3	Not relevant outcomes (only reports mean change from baseline on HAQ-DI, which is also presented in Moreland et al. 1999 in the same study population)
Moreland LW et al. (2001): Long-term safety and efficacy of etanercept in patients with rheumatoid arthritis. The Journal of rheumatology. 28(6): 1238-44.	Clinical question 3	Not relevant study design (pooled analysis with a combination of phase I, II and III studies and open label)
Moreland LW et al. (2006): Etanercept treatment in adults with established rheumatoid arthritis: 7 years of clinical experience. The Journal of rheumatology. 33(5): 854-61.	Clinical question 3	Not relevant study design (pooled analysis with a combination of phase I, II and III studies and open label) and no comparator
Takeuchi T et al. (2013): A phase 3 randomized, double-blind, multicenter comparative study evaluating the effect of etanercept versus methotrexate on radiographic outcomes, disease activity, and safety in Japanese subjects with active rheumatoid arthritis. Modern rheumatology. 23(4): 623-33.	Clinical question 3	Not relevant study population (combination of MTX-naïve and MTX-IR)
van der Heijde D et al. (2006): Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: two-year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial. Arthritis and rheumatism. 54(4): 1063-74.	Clinical question 3	Not relevant study population (not MTX-IR and the majority were MTX-naïve)

7.2 Main characteristics of included studies

Table 50, Table 51 and Table 52 include additional information on the main characteristics of the filgotinib trials: FINCH 1, FINCH 2 and DARWIN 2, respectively. Information in the tables was available from the EPAR on filgotinib and the CSRs related to the respective trials. Table 54 and Table 53 contain additional information on the two etanercept trials: the study by Moreland et al. 1999 (3) and the original and post-hoc analysis of the JERA trial (4,15), respectively.

TABLE 50: MAIN CHARACTERISTICS OF THE FINCH 1 STUDY.

Trial name	FINCH 1
NCT number	NCT02889796
Objective	Primary objective (12): • To evaluate the effects of filgotinib versus placebo for the treatment of signs and symptoms of rheumatoid arthritis (RA) as measured by the proportion of subjects achieving an American College of Rheumatology 20% improvement response (ACR20) at week 12 Secondary objectives (12): • To evaluate the effects of filgotinib versus placebo as measured by the proportion of subjects achieving Disease Activity Score for 28 joint count using c-reactive protein (DAS28[CRP]) ≤3.2 at week 12 • To evaluate the effect of filgotinib versus placebo on physical function as measured by change from baseline in the Health Assessment Questionnaire Disability Index (HAQ-DI) score at week 12 • To evaluate the effects of filgotinib versus placebo for the treatment of signs and symptoms of RA as measured by the proportion of subjects achieving DAS28(CRP) <2.6 at week 24 • To evaluate the effects of filgotinib versus placebo on preservation of joint structure as measured by change from baseline in the van der Heijde modified Total Sharp Score (mTSS) at week 24 • To evaluate the effects of filgotinib versus adalimumab for the treatment of signs and symptoms of RA as measured by the proportion of subjects achieving DAS28(CRP)≤3.2 at week 12 • To evaluate the safety and tolerability of filgotinib • To evaluate the effects of filgotinib on work productivity, fatigue, and general quality of life as measured by 36-Item Short Form Survey (SF-36), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue), Euro-QoL (5 Dimensions [EQ-5D]), and Work Productivity and Activity Impairment: Rheumatoid Arthritis (WPAI-RA)
Publications – title, author, journal, year	Title: Efficacy and safety of filgotinib for patients with rheumatoid arthritis with inadequate response to methotrexate: FINCH 1 primary outcome results Authors: Combe B, Kivitz A, Tanaka Y, van der Heijde D, Matzkies F, Bartok B, et al Journal, year: Annals of the Rheumatic diseases, 2019
Study type and design	Phase III, randomised, double-blind, placebo and active-controlled, multicentre, parallel assignment trial. Patients were randomised in a 3:3:2:3 ratio to filgotinib 200 mg, filgotinib 100 mg, adalimumab and placebo, all in combination with a stable dose of MTX. Randomisation was stratified by geographic region, prior exposure to bDMARDs and presence of RF or anti-CCP antibodies at screening, and was carried out using a computerised interactive web response system.

<table>
<tr><td></td><td>At week 14, subjects who had not achieved at least 20% improvement from day one in both swollen joint count (SJC) and tender joint count (TJC) discontinued investigational study drug dosing but continued with study visits and assessments per protocol. All subjects meeting this criterion who discontinued from investigational therapy were to receive standard of care treatment for RA as determined by the investigator.

At week 24, all subjects assigned to placebo who did not discontinue study drug were re-randomised 1:1 to either filgotinib 100 mg once daily or 200 mg once daily in a blinded fashion and continued in the study through week 52. Subjects previously randomised to filgotinib 100 or 200 mg or adalimumab continued their original randomisation group. All subjects on study drug were evaluated for loss of therapeutic response from week 30 through week 52.

Subjects who failed to maintain at least a 20% improvement from day 1 in TJC and SJC (confirmed at two consecutive visits) discontinued from investigational study drug therapy but continued with study visits and assessments per protocol. All subjects meeting this criterion who discontinued from investigational study drug dosing were to receive standard of care treatment for RA as determined by the investigator and were not eligible for enrolment in the separate LTE study (the FINCH 4 trial).

All subjects who received at least one dose of study drug and exited the study early completed an early termination visit at the time of study discontinuation, with a follow-up visit four weeks after the last dose of study drug (post-treatment week 4), regardless of dosing duration. At completion of the 52-week dosing period, subjects who had not discontinued assigned study drug dosing, were provided the option to enrol into the LTE study (FINCH 4 trial). (12)</td></tr>
<tr><td>Follow-up time</td><td>Follow-up at week 4, 12, 24 and 52. Maximum follow-up was 52 weeks.</td></tr>
<tr><td>Population (inclusion and exclusion criteria)</td><td>Inclusion criteria (from clinicaltrials.gov (5)):
• Have a diagnosis of RA (2010 ACR/EULAR criteria) and are ACR functional class I-III
• Have ≥6 swollen joints (from a swollen joint count based on 66 joints (SJC66) and ≥6 tender joints (from a tender joint count based on 68 joints (TJC68) at both screening and day 1
• Ongoing treatment with stable dose of MTX

Exclusion criteria (from clinical trials.gov (5)):
• Previous treatment with any JAK inhibitor</td></tr>
<tr><td>Intervention</td><td>Filgotinib 200 mg once daily + MTX (n=475)
Filgotinib 100 mg once daily + MTX (n=480)</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th>Baseline characteristics</th><th>Filgotinib 200 mg (n=475)</th><th>Filgotinib 100 mg (n=480)</th><th>Adalimumab (n=325)</th><th>Placebo (n=475)</th><th>Total (n=1,755)</th></tr>
<tr><td>Age, mean (SD)</td><td>52 (12.8)</td><td>53 (12.6)</td><td>53 (12.9)</td><td>53 (12.8)</td><td>53 (12.7)</td></tr>
<tr><td colspan="6">Age group, n (%)</td></tr>
<tr><td><65 years</td><td>398 (83.8%)</td><td>387 (80.6%)</td><td>258 (79.4%)</td><td>380 (80.0%)</td><td>1,423 (81.1%)</td></tr>
<tr><td>≥65 years</td><td>77 (16.2%)</td><td>93 (19.4%)</td><td>67 (20.6%)</td><td>95 (20.0%)</td><td>332 (18.9%)</td></tr>
<tr><td colspan="6">Sex at birth, n (%)</td></tr>
</table>
</td></tr>
</table>

Male	96 (20.2%)	81 (16.9%)	59 (18.2%)	84 (17.7%)	320 (18.2%)
Female	379 (79.8%)	399 (83.1%)	266 (81.8%)	391 (82.3%)	1,435 (81.8%)
Race, n (%)					
American Indian or Alaskan Native	26 (5.5%)	26 (5.4%)	19 (5.8%)	27 (5.7%)	98 (5.6%)
Asian	122 (25.7%)	115 (24.0%)	65 (20.0%)	109 (22.9%)	411 (23.4%)
Black or African American	6 (1.3%)	7 (1.5%)	10 (3.1%)	12 (2.5%)	35 (2.0%)
Native Hawaiian or Pacific Islander	1 (0.2%)	0	0	2 (0.4%)	3 (0.2%)
White	311 (65.5%)	324 (67.5%)	227 (69.8%)	319 (67.2%)	1,181 (67.3%)
Other	9 (1.9%)	7 (1.5%)	4 (1.2%)	5 (1.1%)	25 (1.4%)
Not permitted*	0	1 (0.2%)	0	1 (0.2%)	2 (0.1%)
Ethnicity, n (%)					
Hispanic or latino	67 (14.1%)	72 (15.0%)	55 (16.9%)	70 (14.7%)	264 (15.0%)
Non-hispanic or latino	404 (85.1%)	398 (82.9%)	267 (82.2%)	400 (84.2%)	1,469 (83.7%)
Not permitted	4 (0.8%)	10 (2.1%)	3 (0.9%)	5 (1.1%)	22 (1.3%)
BMI, mean kg/m^2 (SD)	26.7 (5.67)	26.4 (5.80)	26.9 (5.98)	27.0 (5.91)	26.7 (5.83)
Mean duration of RA from diagnosis, years (SD)	7.3 (7.39)	8.5 (8.21)	8.0 (7.40)	7.3 (7.25)	7.8 (7.60)
RF positive, n (%)	352 (74.1%)	362 (75.4%)	241 (74.2%)	365 (76.8%)	1,320 (75.2%)
Anti-CCP positive, n (%)	380 (80.0%)	381 (79.4%)	253 (77.8%)	378 (79.6%)	1,392 (79.3%)
RF positive + anti-CCP positive, n (%)	331 (69.7%)	332 (69.2%)	219 (67.4%)	333 (70.1%)	1,215 (69.2%)
Prior exposure to bDMARDs, n (%)	17 (3.6%)	17 (3.5%)	8 (2.5%)	6 (1.3%)	48 (2.7%)
Concurrent oral corticosteroid uses on first dose date, n (%)					
No	265 (55.8%)	273 (56.9%)	196 (60.3%)	269 (56.6%)	1,003 (57.2%)
Yes	210 (44.2%)	207 (43.1%)	129 (39.7%)	206 (43.4%)	752 (42.8%)
Mean dose, mg/day (SD)	6.2 (3.54)	6.1 (2.57)	5.9 (2.24)	5.9 (2.57)	6.0 (2.82)
Concurrent MTX use on first dose date, n (%)					
Yes	475 (100%)	480 (100%)	325 (100%)	475 (100%)	1,755 (100%)
Mean dose mg/week (SD)	15.3 (4.94)	15.5 (4.82)	15.4 (4.80)	14.8 (4.55)	15.2 (4.78)

	SJC 66, mean (SD)	15 (8.5)	15 (8.5)	16 (8.4)	16 (8.5)	16 (8.5)
	TJC 68, mean (SD)	25 (13.5)	25 (13.4)	24 (13.2)	24 (13.5)	24 (13.4)
	SJC 28, mean (SD)	11 (5.2)	11 (5.2)	11 (5.0)	11 (5.0)	11 (5.1)
	TJC 28, mean (SD)	15 (6.4)	15 (6.7)	15 (6.3)	15 (6.4)	15 (6.4)
	HAQ-DI total score, mean (SD)	1.59 (0.611)	1.55 (0.625)	1.59 (0.600)	1.63 (0.613)	1.59 (0.614)
	DAS28-CRP, mean (SD)	5.8 (0.88)	5.7 (0.95)	5.7 (0.88)	5.7 (0.91)	5.7 (0.91)
	SF-36 PCS, mean (SDSF-36 PCS, mean (SD	33.4 (7.17)	33.6 (7.75)	32.8 (7.74)	32.9 (7.11)	33.2 (7.42)
	SF-36 MCS, mean (SD)	43.9 (10.44)	44.6 (10.44)	44.1 (10.44)	43.4 (11.01)	44.0 (10.60)
	FACIT-Fatigue, mean (SD)	27.6 (10.68)	27.8 (10.60)	27.2 (10.20)	26.9 (10.34)	27.4 (10.48)
	Patient's Pain Assessment, mean (SD)	65 (20.4)	64 (20.1)	65 (19.4)	66 (19.0)	65 (19.7)
	Patient's Global Assessment Disease Activity, mean (SD)	67 (19.2)	65 (19.7)	67 (19.1)	68 (18.7)	67 (19.2)
	Physician Global Assessment Disease Activity, mean (SD)	66 (16.0)	65 (16.5)	67 (15.5)	66 (16.2)	66 (16.1)
	SDAI, mean, (SD)	41.2 (12.26	40.2 (12.79)	40.6 (11.85	41.2 (12.37)	40.8 (12.36)
	CDAI, mean (SD)	39.5 (11.85)	38.6 (12.23)	39.2 (11.47)	39.6 (11.66)	39.2 (11.83)
	hsCRP, mean mg/L (SD)	16.13 (21.005)	16.74 (22.982)	14.56 (18.003)	16.25 (24.051)	16.04 (21.914)

*Not permitted: Local regulations did not permit collection of race or ethnicity information.
bDMARD=biologic disease-modifying antirheumatic drug; BMI=body mass index; CCP=citric citrullinated peptide; CRP=C reactive protein; CDAI=Clinical Disease Activity Index; csDMARD=conventional synthetic disease-modifying antirheumatic drug; DAS28-CRP=Disease Activity Score based on 28 joints and C reactive protein value; FACIT=Functional Assessment of Chronic Illness Therapy; HAQ-DI=Health Assessment Questionnaire Disability Index; IR=inadequate response; MCS; mental component score; MTX=methotrexate; PBO=placebo; PCS=Physical Component Summary; QD=once per day; RA=rheumatoid arthritis; RF=rheumatoid factor; SD=standard deviation; SDAI=Simplified Disease Activity Index; SF-36=36-item Short Form Health Survey; SJC=swollen joint count; TJC=tender joint count; TNF=tumour necrosis factor.
Source: (12).

Primary and secondary endpoints	Primary endpoint (5): • Proportion of patients who achieve ACR20 response at week 12 Secondary endpoints (5):

	• Proportion of participants who achieve disease activity score based on 28 joints (DAS28) (C-reactive protein (CRP)) ≤ 3.2 at week 12 • Change from baseline in the health-assessment questionnaire - Disability Index (HAQ-DI) score at week 12 • Proportion of participants who achieve DAS28 (CRP) < 2.6 at week 24 • Change from baseline in the modified total sharp score (mTSS) at week 24 • Proportion of participants who achieve ACR 50% improvement (ACR50) at weeks 4, 12, 24 and 52. • Proportion of participants who achieve ACR 70% Improvement (ACR70) at weeks 4, 12, 24 and 52 • Proportion of participants who achieve ACR20 at weeks 4, 24 and 52. • Proportion of participants who achieve ACR20 over time from day 1 through week 52 • Proportion of participants who achieve ACR50 over time from day 1 through week 52 • Proportion of participants who achieve ACR70 over time from day 1 through week 52 • Change from baseline in individual components of the ACR response at weeks 4, 12, 24 and 52 and over time from day 1 through week 52 • Proportion of participants who achieve change in HAQ-DI of ≥ 0.22 at weeks 4, 12, 24 and 52, and over time from day 1 through week 52 • Change from baseline in DAS28 (CRP) at weeks 4, 12, 24 and 52, and over time from day 1 through week 52 • Proportion of participants who achieve DAS28 (CRP) ≤ 3.2 at Weeks 4, 24 and 52, and over time from day 1 through week 52 • Proportion of participants who achieve DAS28 (CRP) < 2.6 at weeks 4, 12 and 52, and over time from day 1 through week 52 • American College of Rheumatology N (ACR-N) at weeks 4, 12, 24 and 52, and over time from day 1 through week 52 • European League Against Rheumatism (EULAR) Response at weeks 4, 12, 24 and 52, and over time from day 1 through Week 52 • Change from baseline in Clinical Disease Activity Index (CDAI) at weeks 4, 12, 24 and 52, and over time from day 1 through week 52 • Change from baseline in Simplified Diagnostic Activity Index (SDAI) at weeks 4, 12, 24 and 52, and over time from day 1 through week 24 • Change from baseline in the mTSS at week 52 • Proportion of participants with no radiographic progression from baseline at weeks 24 and 52 • Absolute value and change from baseline in Short-form Health Survey (SF-36) at weeks 4, 12, 24 and 52, and over time from day 1 through week 52 • Absolute value and change from baseline in the Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-Fatigue) at weeks 4, 12, 24 and 52, and over time from day 1 through week 52

	• Absolute value and change from baseline in the Euro-Qol 5 Dimensions (EQ-5D) Patient-Reported Outcomes Survey at weeks 4, 12, 24 and 52, and over time from day 1 through week 52 • Absolute value and change from baseline in Work Productivity and Activity Impairment - Rheumatoid Arthritis (WPAI-RA) Patient-Reported Outcomes Survey at weeks 4, 12, 24 and 52, and over time from day 1 through week 52
Method of analysis	The primary efficacy endpoint was the proportion of subjects who achieved an ACR20 response at week 12. For the primary analysis, the ACR20 response rate at week 12 for filgotinib 200 mg was compared with placebo for a superiority test at the 2-sided 0.05-level. A logistic regression analysis with treatment groups and stratification factors in the model was used. Subjects who did not have sufficient measurements to establish efficacy at week 12 were considered non-responders (non-responder imputation, NRI). Hypothesis testing of the secondary efficacy endpoints began after the testing of the primary efficacy endpoint reached statistical significance and was conducted according to the hierarchical testing principle at the 2-sided 0.05 level. Nominal p-values are provided for comparisons that followed a nonsignificant result ($p \geq 0.05$), in the hierarchical testing procedure and for those that were not included in the testing procedures. ACR20 and mTSS are included in the hierarchical testing procedure, p-values are not reported as nominal for other endpoints that are highly correlated with ACR20 and mTSS (i.e. ACR50, ACR70, erosion score, and joint space narrowing) as applicable. Nominal p-values are also reported for the results of all supportive and sensitivity analyses. Binary endpoints (i.e. ACR20/50/70, HAQ-DI≥0.22, DAS28(CRP)≤3.2 and DAS28(CRP)<2.6) were analysed using logistic regression analysis with treatment groups and stratification factors (geographic region, presence of RF or anti-CCP antibodies, prior exposure to bDMARDs) in the model. Subjects who did not have sufficient measurements to establish efficacy at week 12 were considered as non-responders for these analyses (NRI). The changes from baseline for continuous endpoints (i.e., HAQ-DI score, mTSS, SF-36 PCS, and FACIT-Fatigue score) were analysed using the mixed-effects model for repeated measures (MMRM) that included data at postbaseline visits. Subjects who had a baseline value and at least one postbaseline value were included in the analysis. The MMRM models were used to evaluate treatment effect on score changes from baseline, with baseline value, stratification factors, treatment, visit, and treatment-by-visit interaction included as fixed effects and subject as the random effect. In addition to the FAS, the primary and key secondary endpoints were also evaluated using the Per-Protocol (PP) analysis set, as well as using additional sensitivity analysis methods that included observed case (OC), last observation carried forward (LOCF), multiple imputation (MI), and tipping point analysis; LOCF was used for binary endpoints only. Analyses of the primary and secondary efficacy endpoints, as well as other secondary efficacy endpoints (ACR50 and ACR70 response rates over time and changes from baseline in individual ACR components) were also conducted using all available data, including assessments collected under standard of care. Endpoints were analysed at protocol-specified time points during the placebo-controlled period from day 1 through week 24, and through week 52. These endpoints included the primary and secondary endpoints in addition to ACR20/50/70 response rates, changes in individual ACR components, composite measures of disease activity, and other patient-reported outcomes, including measures of health-related quality of life. Statistical methods were described in two statistical analysis plans (SAPs). These two different SAPs reflect differences in endpoints assessed and hierarchical testing sequences based on feedback from local regulatory authorities. One SAP describes an analysis

	hierarchy based on feedback from the United States Food and Drug Administration (FDA) (SAP1), and the other SAP is based on the analysis hierarchy specified in the protocol (12).
Subgroup analyses	Subgroup analyses comparing each filgotinib group with the placebo group were performed for the primary endpoint at week 12 for the following subgroups: • age (on the first dosing date of study drug, <65 or ≥65 years); • sex at birth (male or female); • race; • baseline weight (<60 kg, ≥60 kg to <100 kg, or ≥100 kg); • geographic region (A, B, C, D, or E); • prior exposure to bDMARDs (Yes or No); • presence of RF or anti-CCP Antibody (Yes or No); • duration of RA diagnosis on the first dosing date of study drug (<1 year, ≥1 to<5years, ≥5 to <10 years, or ≥10 years); • disease activity on the first dosing date of study drug (DAS28[CRP] ≤ 5.1 or DAS28[CRP]>5.1); • concurrent use of oral corticosteroids on the first dosing date of study drug (Yes or No); and • hsCRP at Baseline (≥4 mg/L or <4 mg/L). The proportion of subjects who achieved an ACR20 response was analysed using the Fisher exact test based on the NRI method for comparison between treatment groups. The number and percentage of subjects with an ACR20 response were provided for each treatment group within the subgroups. Subgroup analyses for the proportion of subjects who achieved DAS28(CRP)<2.6 and the proportion of subjects who achieved DAS28(CRP) ≤ 3.2 were performed using the Fisher exact test based on the NRI method. The change from baseline in HAQ-DI was analysed using the MMRM method with baseline value, treatment, visit, and treatment-by-visit interaction included as fixed effects and subjects being the random effect. The LS mean, LS mean difference, SE, and 95% CI were presented. The change from baseline in mTSS, change from baseline in SF-36 PCS, and change from baseline in FACIT-Fatigue were analysed using the MMRM model. Descriptive statistics for actual values and change from baseline were presented for each treatment group within the subgroup (12).

TABLE 51: MAIN CHARACTERISTICS OF THE FINCH 2 STUDY.

Trial name	FINCH 2
NCT number	NCT02873936
Objective	The study had several objectives. The primary objective was to evaluate the effects of filgotinib versus placebo for the treatment of signs and symptoms of RA as measured by the proportion of subjects who achieved an ACR20 response at week 12 (13). Secondary objectives of this study were: • to evaluate the effects of filgotinib versus placebo for the treatment of signs and symptoms of RA as measured by the proportion of subjects achieving DAS28[CRP] ≤3.2 at week 12;

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to evaluate the effect of filgotinib versus placebo on physical function as measured by change from baseline in the HAQ-DI at week 12;
to evaluate the safety and tolerability of filgotinib; and
to evaluate the effects of filgotinib on work productivity, fatigue, and general quality of life as measured by SF-36, FACIT-Fatigue, Euro-Qol (5 Dimensions) (EQ-5D), and Work Productivity and Activity Impairment -Rheumatoid Arthritis (WPAI-RA) (13).

</td></tr>
<tr><td>Publications – title, author, journal, year</td><td>Title: Effect of Filgotinib vs Placebo on Clinical Response in Patients with Moderate to Severe Rheumatoid Arthritis Refractory to Disease-Modifying Antirheumatic Drug Therapy: The FINCH 2 Randomized Clinical Trial.
Authors: MC. Genovese, K. Kalunian, J. Gottenberg, et al.
Journal and year: JAMA. 2019;322(4):315–325. doi:10.1001/jama.2019.9055</td></tr>
<tr><td>Study type and design</td><td>Randomised, double-blind, placebo and active-controlled, multicentre, parallel assignment phase III trial. Patients were randomised in a 1:1:1 ratio to either filgotinib 200 mg, filgotinib 100 mg or placebo. Randomisation was stratified by geographic region, number of bDMARDs previously exposed to (<3 or ≥3), and the presence of RF or anti-CCP antibody at screening and was carried out using a computerised IXRS system (13).</td></tr>
<tr><td>Follow-up time</td><td>Follow-up at week 4, 12 and 24. Maximum follow-up was 24 weeks.</td></tr>
<tr><td>Population (inclusion and exclusion criteria)</td><td>Inclusion criteria (from clinicaltrials.gov (6)):

Have a diagnosis of RA (2010 ACR/EULAR criteria for RA) and are ACR functional class I-III
Have ≥6 swollen joints (from swollen joint count based on 66 joints (SJC66) and ≥6 tender joints (from a tender joint count based on 68 joints (TJC68)) at screening day 1
Ongoing treatment with a stable prescription of 1 or 2 csDMARDs
Have received at least one bDMARD for the treatment of RA to which they had an inadequate response or were intolerant

Exclusion criteria (from clinicaltrials.gov (6)):

Previous treatment with any JAK inhibitor
From trial protocol: abnormal laboratory results, pregnancy and recent or active infection

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<tr><td>Intervention</td><td>Filgotinib was provided as 100 mg and 200 mg strength tablets. The tablets were beige, debossed with “GSI” on one side and “100” or “200” on the other side, capsule-shaped, biconvex, film-coated tablets for clinical use. Each tablet contained the equivalent of 100 mg or 200 mg filgotinib free base in the form of filgotinib maleate. In addition to the active ingredient, the tablets contained the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, fumaric acid, pregelatinized starch, silicon dioxide, magnesium stearate, macrogol/polyethylene glycol (PEG)3350, polyvinyl alcohol, talc, titanium dioxide, iron oxide yellow, and iron oxide red. Both tablets were administered once daily in combination with csDMARDs (13).</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th rowspan="2">Baseline characteristics</th><th colspan="2">Filgotinib QD dose groups</th><th rowspan="2">Placebo (n=148)</th><th rowspan="2">Total (n=448)</th></tr>
<tr><th>200 mg (n=147)</th><th>100 mg (n=153)</th></tr>
<tr><td>Age, mean (SD)</td><td>56 (12.5)</td><td>55 (12.0)</td><td>56 (12.1)</td><td>56 (12.2)</td></tr>
<tr><td colspan="5">Age group, n (%)</td></tr>
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<65 years	112 (76.2%)	117 (76.5%)	106 (71.6%)	335 (74.8%)
≥65 years	35 (23.8%)	36 (23.5%)	42 (28.4%)	113 (25.2%)
Sex at birth, n (%)				
Male	27 (18.4%)	34 (22.2%)	27 (18.2%)	88 (19.6%)
Female	120 (81.6%)	119 (77.8%)	121 (81.8%)	360 (80.4%)
Race, n (%)				
American Indian or Alaskan Native	7 (4.8%)	9 (5.9%)	10 (6.8%)	26 (5.8%)
Asian	15 (10.2%)	20 (13.1%)	15 (10.1%)	50 (11.2%)
Black or African American	14 (9.5%)	12 (7.8%)	21 (14.2%)	47 (10.5%)
White	110 (74.8%)	109 (71.2%)	97 (65.5%)	316 (70.5%)
Other	1 (0.7%)	3 (2.0%)	2 (1.4%)	6 (1.3%)
Not permitted*	0	0	3 (2.0%)	6 (1.3%)
BMI, mean kg/m^2 (SD)	30.5 (7.89)	30.3 (7.66)	29.8 (7.25)	30.2 (7.59)
Mean duration of RA from diagnosis, years (SD)	12.6 (9.48)	12.0 (7.74)	12.6 (10.30)	12.4 (9.20)
hsCRP level, mean mg/L (SD)	17.21 (18.275)	21.49 (28.206)	16.42 (18.321)	18.41 (22.249)
RF positive, n (%)	104 (70.7%)	107 (69.9%)	92 (62.2%)	303 (67.6%)
Anti-CCP positive, n (%)	99 (67.3%)	113 (73.9%)	105 (70.9%)	317 (70.8%)
RF positive + anti-CCP positive, n (%)	91 (61.9%)	102 (66.7%)	84 (56.8%)	277 (61.8%)
Number of prior bDMARDs, n (%)				
<3	110 (74.8%)	119 (77.8%)	114 (77.0%)	343 (76.6%)
≥3	37 (25.2%)	34 (22.2%)	34 (23.0%)	105 (23.4%)
Number of prior bDMARDs, n (%)				
0	0	0	1 (0.7%)	1 (0.2%)
1	73 (49.7%)	86 (56.2%)	77 (52.0%)	236 (52.7%)
2	37 (25.2%)	33 (21.6%)	36 (24.3%)	106 (23.7%)
3	19 (12.9%)	20 (13.1%)	19 (12.8%)	58 (12.9%)
4	9 (6.1%)	8 (5.2%)	2 (1.4%)	19 (4.2%)
≥5	9 (6.1%)	6 (3.9%)	13 (8.8%)	28 (6.3%)
Prior TNF bDMARD exposure, n (%)				
No	26 (17.7%)	19 (12.4%)	24 (16.2%)	24 (16.2%)
Yes ○ Adalimumab ○ Etanercept ○ Infliximab ○ Golimumab ○ Certolizumab	121 (82.3%) 53 (36.1%) 62 (42.2%) 37 (25.2%) 14 (9.5%) 4 (2.7%)	134 (87.6%) 68 (44.4%) 61 (39.9%) 29 (19.0%) 19 (12.4%) 7 (4.6%)	124 (83.8%) 63 (42.6%) 53 (35.8%) 34 (23.0%) 14 (9.5%) 3 (2.0%)	379 (84.6%) 184 (41.1%) 176 (39.3%) 100 (22.3%) 47 (10.5%) 14 (3.1%)
Prior non-TNF bDMARD exposure, n (%)				
No	74 (50.3%)	91 (59.5%)	73 (49.3%)	238 (53.1%)
Yes ○ Tocilizumab ○ Abatacept ○ Rituximab	73 (49.7%) 30 (20.4%) 25 (17.0%) 19 (12.9%)	62 (40.5%) 26 (17.0%) 20 (13.1%) 11 (7.2%)	75 (50.7%) 25 (16.9%) 34 (23.0%) 14 (9.5%)	210 (46.9%) 81 (18.1%) 79 (17.6%) 44 (9.8%)

○ Anakinra	2 (1.4%)	2 (1.3%)	0	4 (0.9%)
Concurrent oral steroid use on first dose date, n (%)				
No	79 (53.7%)	85 (55.6%)	77 (52.0%)	241 (53.8%)
Yes	68 (46.3%)	68 (44.4%)	71 (48.0%)	207 (46.2%)
Mean dose, mg/kg (SD)	6.4 (2.70)	6.3 (2.58)	6.2 (2.69)	6.3 (2.65)
Concurrent MTX use on first dose date, n (%)				
No	23 (15.6%)	26 (17.0%)	32 (21.6%)	81 (18.1%)
Yes	124 (84.4%)	127 (83.0%)	116 (78.4%)	367 (81.9%)
Mean dose, mg/week (SD)	15.5 (5.12)	16.2 (5.58)	15.5 (5.02)	15.8 (5.25)
Number of concurrent csDMARDs on first dose date, n (%)				
0	0	0	1 (0.7%)	1 (0.2%)
1	133 (90.5%)	135 (88.2%)	135 (91.2%)	403 (90.0%)
2	14 (9.5%)	18 (11.8%)	12 (8.1%)	44 (9.8%)
SJC 66, mean (SD)	18 (12.5)	17 (12.4)	17 (9.7)	17 (11.6)
TJC 68, mean (SD)	28 (16.1)	26 (15.4)	27 (15.5)	27 (15.7)
SJC 28, mean (SD)	12 (6.3)	12 (6.0)	12 (6.0)	12 (6.1)
TJC 28, mean (SD)	16 (7.7)	15 (6.8)	16 (6.9)	16 (7.1)
HAQ-DI total score, mean (SD)	1.70 (0.656)	1.64 (0.683)	1.65 (0.633)	1.67 (0.657)
DAS28-CRP, mean (SD)	5.9 (1.03)	5.9 (0.98)	5.9 (0.86)	5.9 (0.96)
SF-36 PCS, mean (SD)	30.4 (7.75)	31.7 (7.76)	31.1 (8.17)	31.1 (7.89)
SF-36 MCS, mean (SD)	44.5 (11.97)	44.2 (11.59)	44.3 (11.32)	44.3 (11.60)
FACIT-Fatigue, mean (SD)	24.2 (11.47)	23.7 (12.30)	25.4 (10.89)	24.4 (11.57)
Patient's Pain Assessment, mean (SD)	66 (21.6)	67 (21.7)	68 (19.9)	67 (21.0)
Patient's Global Assessment Disease Activity, mean (SD)	68 (20.6)	69 (20.2)	70 (18.0)	69 (19.6)
Physician Global Assessment Disease Activity, mean (SD)	69 (17.6)	68 (18.7)	66 (16.7)	67 (17.7)
SDAI, mean, (SD)	43.4 (14.64)	42.6 (14.16)	43.0 (12.33)	43.0 (13.72)
CDAI, mean (SD)	41.7 (14.23)	40.4 (13.23)	41.4 (12.00)	41.2 (13.17)

**Not permitted: Local regulations did not permit collection of race or ethnicity information. bDMARD=biologic disease-modifying antirheumatic drug; BMI=body mass index; CCP=citric citrullinated peptide; CRP=C reactive protein; CDAI=Clinical Disease Activity Index; csDMARD=conventional synthetic disease-modifying antirheumatic drug; DAS28-CRP=Disease Activity Score based on 28 joints and C reactive protein value; FACIT=Functional Assessment of Chronic Illness Therapy; HAQ-DI=Health Assessment Questionnaire Disability Index; IR=inadequate response; MCS; mental component score; MTX=methotrexate; PBO=placebo; PCS=Physical Component Summary; QD=once per day; RA=rheumatoid arthritis; RF=rheumatoid factor; SD=standard deviation; SDAI=Simplified Disease Activity Index; SF-36=36-item Short Form Health Survey; SJC=swollen joint count; TJC=tender joint count; TNF, tumour necrosis factor.*
Source: (13).

Primary and secondary endpoints	Primary endpoint (from clinicaltrials.gov (6)): • Proportion of participants who achieve ACR20 response at week 12 Secondary endpoint (from clinicaltrials.gov (6)): • Proportion of participants who achieve Disease Activity Score based on 28 joints (DAS28) (C-reactive protein (CRP)) ≤ 3.2 at week 12 • Change from baseline in the Health Assessment Questionnaire - Disability Index (HAQ-DI) Score at week 12 • Proportion of participants who achieve ACR 50% improvement (ACR50) at weeks 4, 12, and 24 • Proportion of participants who achieve ACR 70% improvement (ACR70) at weeks 4, 12, and 24 • Proportion of participants who achieve ACR20 at weeks 4 and 24 • Proportion of participants who achieve ACR20 over time from day 1 through week 24 • Proportion of participants who achieve ACR50 over time from day 1 through week 24 • Proportion of participants who achieve ACR70 over time from day 1 through week 24 • Change from baseline in individual components of the ACR Response at weeks 4, 12 and 24, and over time from day 1 through week 24 • Proportion of participants who achieve Change in HAQ-DI of ≥ 0.22 at weeks 4, 12 and 24, and over time from day 1 through week 24 • Change from baseline in DAS28 (CRP) at weeks 4, 12 and 24, and over time from day 1 through week 24 • Proportion of participants who achieve DAS28 (CRP) ≤ 3.2 at weeks 4 and 24, and over time from day 1 through week 24 • Proportion of participants who achieve DAS28 (CRP) < 2.6 at weeks 4 and 24, and over time from day 1 through week 24 • American College of Rheumatology N (ACR-N) at weeks 4, 12 and 24, and over time from day 1 through week 24 • European League Against Rheumatism (EULAR) Response at weeks 4, 12 and 24, and over time from day 1 through week 24 • Change from baseline in Clinical Diagnostic Activity Index (CDAI) at weeks 4, 12 and 24, and over time from day 1 through week 24 • Change from baseline in Simplified Diagnostic Activity Index (SDAI) at weeks 4, 12 and 24, and over time from day 1 through week 24 • Absolute value and change from baseline in Short-form Health Survey (SF-36) at weeks 4, 12 and 24, and over time from day 1 through week 24 • Absolute value and change from baseline in the Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-Fatigue) at weeks 4, 12 and 24, and over time from day 1 through week 24

	• Absolute value and change from baseline in the Euro-Qol 5 Dimensions (EQ-5D) Patient-Reported Outcomes Survey at weeks 4, 12 and 24, and over time from day 1 through week 24 • Absolute value and change from baseline in Work Productivity and Activity Impairment- Rheumatoid Arthritis (WPAI-RA) at weeks 4, 12 and 24, and over time from day 1 through week 24
Method of analysis	Efficacy assessments were carried out at day 1 and at weeks 2, 4, 8, 12, 14, 16, 20 and 24, or at ET (if applicable). The primary efficacy analysis used the FAS, which included all subjects who were randomised into the study and received at least one dose of study drugs. FAS was the primary analysis set for efficacy analyses. The primary endpoint for the study was the proportion of subjects who achieved an ACR20 response at week 12. The primary analyses consisted of a superiority test of filgotinib 200 mg compared with placebo based on the primary endpoint. Superiority was tested at the 2-sided 0.05-level. A logistic regression analysis with treatment groups and stratification factors in the model was used. Subjects who did not have sufficient measurements to establish efficacy at week 12 were considered non-responders (i.e., non-responder imputation (NRI)). If the superiority of filgotinib 200 mg over placebo was established, hypothesis testing for the secondary analyses was initiated. The superiority of filgotinib 200 mg or 100 mg over placebo was tested according to the hierarchical testing principle at the 2-sided 0.05-level. If a null hypothesis was not rejected, formal sequential testing was stopped, and only nominal significance was reported for the remaining hypotheses. Hypothesis testing for the secondary analyses was limited to key efficacy endpoints specific to each SAP. ACR20 at week 12 was also analysed with sensitivity analysis methods, including observed case (OC) or last observation carried forward (LOCF), and multiple imputation. The endpoint was also analysed using the per-protocol analysis set. ACR response components, such as the ACR50 and ARC70 were analysed with a pair-wise comparison of changes from baseline in each of the filgotinib treatment groups vs. placebo. Other secondary endpoints (HAQ-DI, DAS28(CRP) and SF-36) were analysed using the mixed-effects model for repeated measures (MMRM) that included all available data at postbaseline visits. Subjects that had a baseline value and at least one postbaseline value were included in the analysis. The MMRM models were used to evaluate treatment effect on score changes from baseline, with baseline value, stratification factors, treatment, visit, and treatment by visit interaction included as fixed effects and subject as the random effect. In addition to the FAS, the primary and key secondary endpoints analysed at week 12 were also evaluated using the Per-Protocol (PP) analysis set, as well as using additional sensitivity analysis methods that included observed case (OC) and last observation carried forward (LOCF) (for binary endpoints), multiple imputation, and tipping point analysis. The statistical methods used to analyse the endpoints mentioned above reflect regional differences in endpoints and hierarchical testing based on feedback from local health authorities. One SAP describes an analysis hierarchy based on feedback from the United States Food and Drug Administration (FDA) to support inclusion in the US label (SAP1) and the other SAP is based on the analysis hierarchy specified in the protocol (SAP2). All safety analyses were performed using the safety analysis set. AE data were summarised by treatment group using descriptive statistics. Clinical and laboratory AEs

	were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 21.0. the AEs of interest were identified using either standardised MedDRA queries (SMQs) or Gilead Medical Search Terms (MSTs). AEs of interest included all infections, serious infections, infections of interest (herpes zoster, active tuberculosis, opportunistic infections, and hepatitis B or C infections), adjudicated major adverse cardiovascular events (MACE), deep vein thrombosis and pulmonary embolism, malignancy (not including nonmelanoma skin cancer), nonmelanoma skin cancer, and gastrointestinal perforation. An independent cardiovascular safety endpoint adjudication committee (CVEAC) was formed to periodically review and adjudicate all potential MACE (13).
Subgroup analyses	The primary and secondary efficacy endpoints were examined using the following subgroups: • age (on the first dosing date of study drugs, <65 or ≥65); • sex at birth (male or female); • race; • baseline weight (<60kg, ≥60kg to <100kg, ≥100kg); • geographic region (A, B, C, or E); • presence of RF or anti-CCPAb (Yes or No); • duration of RA diagnosis on the first dosing date of study drugs (< 5 years, ≥5to<10years, ≥ 10 years); • number of prior bDMARDs exposure (<3 or ≥3; ≤1 or >1; 1, 2, or ≥3); • disease activity at baseline (DAS28[CRP] ≤5.1 or DAS28[CRP]>5.1); • concurrent use of MTX on the first dosing date of study drugs (Yes or No); • number of concurrent csDMARDs use on the first dosing date of study drugs(0-1or≥2); • concurrent use of oral corticosteroids on the first dosing date of study drugs (Yes or No); and • hsCRP at baseline (≥4mg/L or <4mg/L). Subgroup analyses comparing each filgotinib dose group with the placebo group were performed for the primary and secondary endpoints at week 12 and week 24. The proportion of subjects who achieved an ACR20 response was analysed using Fisher's exact test based on the NRI method for treatment group comparisons. The number and percentage of subjects who achieved an ACR20 response was also provided for each treatment group within the subgroups. The subgroup analysis for the proportion of subjects with DAS28(CRP) ≤3.2 and the proportion of subjects with DAS28(CRP) <2.6 was performed using Fisher's exact test based on the NRI method. The number and percentage of subjects with DAS28(CRP) ≤3.2 were also provided for each treatment group within the subgroups. The change from baseline in HAQ-DI was analysed using the MMRM method with baseline value, treatment, visit, and treatment by visit interaction included as fixed effects and subjects being the random effect. The LS mean, LS mean difference, SE, and 95% CI were presented. The change from baseline in SF-36 PCS and change from baseline in FACIT-Fatigue score was analysed similarly using the MMRM model, respectively. Descriptive statistics for actual values and change from baseline in HAQ-DI, SF-36 PCS, and FACIT-Fatigue score were also presented for each treatment group within the subgroups (13).

TABLE 52: MAIN CHARACTERISTICS OF THE DARWIN 2 TRIAL.

Trial name	DARWIN 2

NCT number	NCT01894516
Objective	Primary objective (14): • The primary objective of the study was to evaluate the efficacy, in terms of the percentage of subjects achieving an ACR20 response, of different doses of filgotinib given once daily compared to placebo at week 12. Secondary objectives (14): • To evaluate the efficacy in terms of the percentage of subjects achieving an ACR20, ACR50, ACR70, ACR-N, DAS28 (CRP), European League Against Rheumatism (EULAR) response and ACR/EULAR remission, CDAI, and SDAI with different doses of filgotinib given once daily compared to placebo at every visit • To evaluate the safety and tolerability of different doses of filgotinib in comparison with placebo • To characterise the population PK and PD of filgotinib and its metabolite (G254445) in subjects with RA and investigate the relationship between exposure and efficacy/safety/PD • To evaluate the effects of different doses of filgotinib administration on subjects' disability, fatigue, and quality of life
Publications – title, author, journal, year	Not applicable.
Study type and design	Study type and design: This was a phase IIb, double-blind, placebo-controlled, monotherapy study in subjects with moderately to severely active RA who had an inadequate response to MTX alone. A total of 280 subjects were planned to be randomised to one of three once daily dose regimens of filgotinib (50 mg, 100 mg, 200 mg) or to placebo. At week 12, all subjects on placebo and the subjects on the 50 mg dose who had not achieved a 20% improvement in swollen joint count 66 (SJC66) and tender joint count 68 (TJC68) were to be assigned (automatically via interactive voice/web response system [IXRS]) to 100 mg in a blinded fashion and were to continue the study until week 24. Subjects in the other groups were to maintain their randomised treatment until week 24. The planned treatment duration was 24 weeks. Blinding: The subject, the investigator, the study coordinator, the sponsor and the entire study processing team were to remain blinded to treatment assignment. The blind could be broken only if the investigator deemed it necessary for the safe treatment of a subject, and whenever possible, the medical monitor and sponsor should have been consulted before breaking the blind. If the blind was broken for any reason during the course of the study, the moment at which the blind was broken and all other relevant information was to be documented by the investigative site, INC Research and other sponsor designees as appropriate. The reason for breaking the blind was to be indicated and justified in the source documentation and in the eCRF. The blind could be broken by the investigator via the IXRS system. All subjects who were unblinded while on the study were to be withdrawn, with the reason for unblinding given as the reason for discontinuation from the study. If an AE led to unblinding, the AE should have been given as the reason for unblinding and the AE also had to be recorded in the eCRF. All subjects who were unblinded should have, where possible, completed the early discontinuation visit (EDV). Any AEs had to be followed until resolution. An unblinded interim analysis (i.e. unblinded at a treatment group level; not at a subject level) was performed when all subjects had completed the week 12 visit (14).

Follow-up time	24 weeks.
Population (inclusion and exclusion criteria)	Inclusion criteria from CSR (14): • Male or female subjects who were ≥18 years of age on the day of signing informed consent • Diagnosis of RA at least 6 months prior to screening and meeting the 2010 ACR/EULAR criteria of RA and ACR functional class I-III. • Had to have ≥6 swollen joints (from a SJC66) and ≥ 8 tender joints (from a TJC68) at screening and baseline. • Screening serum CRP ≥0.70 x ULN. Note that this inclusion criterion related to the serum CRP was not included in the original study protocol, which was more strict (CRP of ≥14 mg/dL); this numeric value was changed to 1.5xULN in the protocol amendment 1 and later decreased to 1.2xULN (in protocol amendment 3), and again to 0.7xULN (protocol amendment 5). • Had to have shown an inadequate response in terms of either lack of efficacy or toxicity to MTX. • Had to have agreed to be washed out from MTX for a period of ≥4 weeks before or during the screening period. • If taking oral steroids, these had to have been at a dose ≤10 mg/day of prednisone or prednisone equivalent and stable for ≥4 weeks prior to baseline. • If taking non-steroidal anti-inflammatory drugs (NSAIDs), these had to have been at a stable dose for ≥2 weeks prior to baseline. • The results of the following laboratory tests performed at the central laboratory at screening had to have been within the limits specified below: a) haemoglobin ≥ 10 g/dL (International System of Units [SI]: ≥ 100 g/L) b) WBCs ≥ 3.0 x 103 cells/mm3 (SI: ≥ 3.0 x 109 cells/L) c) neutrophils ≥ 2.0x103 cells/mm3 (SI: ≥ 2.0 x109 cells/L) d) lymphocytes ≥ 1.0 x 103 cells/mm3 (SI: ≥ 1.0 x 109 cells/L) e) platelets ≥ 100 x 103 cells/mm3 (SI: ≥ 100 x 109 cells/L) f) serum ALT and aspartate aminotransferase (AST) ≤1.5 x ULN g) total bilirubin level ≤1.25 x ULN h) ALP ≤1.5 x ULN i) lipase ≤1.5 x ULN and amylase ≤1.5 x ULN j) creatinine clearance >60 mL/min (creatinine clearance was calculated using the Cockroft-Gault formula). • Female subjects had to have a negative pregnancy test unless they were surgically sterile or had been post-menopausal for ≥1 year (12 consecutive months without menses); in case of doubt a determination of serum FSH could have been done with FSH levels >35 mI U/mL being confirmative for menopause. • Women of childbearing potential had to have used a medically acceptable means of birth control and had to have agreed to continue its use during the study and for ≥12 weeks after the last dose of study medication. Medically acceptable forms of birth control included oral contraceptives, injectable or implantable methods, intrauterine devices, tubal ligation (if performed >1 year before Screening) or double barrier contraception. • Sexually active men had to have agreed to use a medically acceptable form of contraception (double barrier) during the study and continue its use for ≥12 weeks after the last dose of study medication. • Had to have been able and willing to sign the ICF, as approved by the IEC/IRB, prior to screening evaluations and had to have agreed to the schedule of assessments. • Had to have been judged to be in good health, except for their RA, as determined by the investigator based upon the results of medical history, laboratory profile, physical examination, chest X-ray, and a 12-lead ECG performed during Screening.

	Exclusion criteria from CSR (14):
	• Current therapy with any non-biological DMARD, including oral or injectable gold, sulfasalazine, azathioprine, or D-penicillamine within four weeks prior to baseline, cyclosporine within eight weeks prior to baseline, and leflunomide within three months prior to baseline or a minimum of four weeks prior to baseline if after 11 days of standard cholestyramine therapy, with the exception of antimalarials, which had to be at a stable dose for ≥12 weeks prior to baseline.
	• Current or previous RA treatment with a biologic DMARD, except for biologic DMARDs:
	  ○ administered in a single clinical study setting;
	  ○ >6 months prior to screening (12 months for rituximab or other B cell depleting agents); and
	  ○ where the biologic DMARD was effective, and if discontinued, this could not have been due to lack of efficacy.
	• Previous treatment at any time with a cytotoxic agent, other than MTX, before screening. These agents included but were not limited to chlorambucil, cyclophosphamide, nitrogen mustard, or other alkylating agents.
	• Previous use of JAK inhibitors.
	• Receipt of an intra-articular or parenteral corticosteroid injection within four weeks prior to screening.
	• Known hypersensitivity to study medication ingredients or a significant allergic reaction to any drug as determined by the investigator, such as anaphylaxis requiring hospitalisation.
	• Positive serology for human HIV-1 or HIV-2 or hepatitis B or C or any history of hepatitis from any cause except for hepatitis A.
	• Immunocompromised subjects who in the opinion of the investigator were put at an unacceptable risk if participating in the study.
	• Previous history of symptomatic herpes zoster or herpes simplex infection within 12 weeks prior to screening or had a history of disseminated/complicated herpes zoster infection (multi-dermatomal involvement, ophthalmic zoster CNS involvement or postherpetic neuralgia).
	• Known active infection of any kind (excluding fungal infection of nail beds), or any major episode of infection requiring hospitalisation or treatment with parenteral (intramuscular or intravenous (i.v.) anti-infectives (antibiotics, antiviral, anti-fungals or anti-parasitic agents) within four weeks of the screening visit or completion of oral anti-infectives within two weeks of the screening visit.
	• Currently on any therapy for chronic infection (such as pneumocystis, cytomegalovirus, herpes simplex, herpes zoster and atypical mycobacteria).
	• History of any inflammatory rheumatological disorder other than RA, except secondary Sjogren's Syndrome.
	• Any surgical procedure, including bone/joint surgery/synovectomy (including joint fusion or replacement) within 24 weeks prior to the screening visit.
	• History of moderate to severe congestive heart failure (New York Heart Association class III or IV), recent (within 24 weeks prior to study entry) cerebrovascular accident and any other condition which, in the opinion of the investigator, would put the subject at risk by participating in the study.
	• History or current symptoms of gastrointestinal tract ulceration and/or diverticulitis.

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History of malignancy within the past five years (except for basal cell carcinoma of the skin or cervical carcinoma in situ that has been treated with no evidence of recurrence).
History of lymphoproliferative disease; or signs and symptoms suggestive of possible lymphoproliferative disease, including lymphadenopathy or splenomegaly.
History of active or latent tuberculosis (TB) infection as determined by either: a) positive QuantiFERON TB Gold test result b) chest radiograph (both posterior-anterior and lateral views), taken within three months prior to Screening and read by a qualified radiologist, with evidence of current active TB or old inactive TB symptoms of clinically significant illness in the 3 months before the initial study medication administration.
History of invasive infection (e.g., listeriosis and histoplasmosis).
Treatment with any drug known to have a well-defined potential for toxicity to a major organ in the last three months preceding the initial study medication administration.
Administration of a live vaccine within 90 days or an attenuated vaccine within 30 days prior to the initial study medication administration.
Participation in any investigational drug/device clinical study within four weeks prior to screening.
History within the previous two years or current evidence of drug or alcohol abuse.
If applicable to national or local legislation: history of being admitted to an institution under an administrative or court order.
Breastfeeding during the study.
Any condition or circumstances which, in the opinion of the investigator, could make a subject unlikely or unable to complete the study or comply with study procedures and requirements.
Significant blood loss (including blood donation [>500 mL]) or a transfusion of any blood product within 12 weeks prior to the initial study medication administration.

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<tr><td>Intervention</td><td>Filgotinib 50 mg once daily
Filgotinib 100 mg once daily
Filgotinib 200 mg once daily</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th></th><th>Placebo</th><th>Filgotinib 50 mg</th><th>Filgotinib 100 mg</th><th>Filgotinib 200 mg</th><th>Total</th></tr>
<tr><th></th><th>N=72</th><th>N=72</th><th>N=70</th><th>N=69</th><th>N=283</th></tr>
<tr><td>RA duration, years, Mean (SE)</td><td>9.46 (0.837)</td><td>8.63 (0.774)</td><td>8.57 (0.829)</td><td>8.68 (0.987)</td><td>8.84 (0.427)</td></tr>
<tr><td colspan="6">RA duration categories (years), n (%)</td></tr>
<tr><td>≥ 0.5-< 2</td><td>9 (12.5)</td><td>12 (16.7)</td><td>11 (15.7)</td><td>11 (15.9)</td><td>43 (15.2)</td></tr>
<tr><td>≥ 2-< 5</td><td>14 (19.4)</td><td>14 (19.4)</td><td>18 (25.7)</td><td>15 (21.7)</td><td>61 (21.6)</td></tr>
<tr><td>≥ 5-< 10</td><td>21 (29.2)</td><td>22 (30.6)</td><td>17 (24.3)</td><td>24 (34.8)</td><td>84 (29.7)</td></tr>
<tr><td>≥ 10-< 20</td><td>20 (27.8)</td><td>17 (23.6)</td><td>18 (25.7)</td><td>15 (21.7)</td><td>70 (24.7)</td></tr>
<tr><td>≥ 20</td><td>8 (11.1)</td><td>7 (9.7)</td><td>6 (8.6)</td><td>4 (5.8)</td><td>25 (8.8)</td></tr>
<tr><td>Mean (SE) CRP (mg/mL), Screening</td><td>37.34 (3.424)</td><td>32.00 (3.386)</td><td>35.38 (4.713)</td><td>33.74 (3.170)</td><td>34.62 (1.853)</td></tr>
<tr><td colspan="6">CRP categories (x ULN), Screening</td></tr>
<tr><td>≥ 0.7-≤ 1</td><td>2 (2.8)</td><td>9 (12.5)</td><td>1 (1.4)</td><td>3 (4.3)</td><td>15 (5.3)</td></tr>
<tr><td>> 1-< 1.2</td><td>2 (2.8)</td><td>2 (2.8)</td><td>3 (4.3)</td><td>4 (5.8)</td><td>11 (3.9)</td></tr>
<tr><td>≥ 1.2</td><td>68 (94.4)</td><td>61 (84.7)</td><td>66 (94.3)</td><td>62 (89.9)</td><td>257 (90.8)</td></tr>
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Mean (SE) CRP (mg/mL), Baseline	35.26 (4.434)	24.67 (3.257)	25.55 (4.247)	23.16 (2.492)	27.21 (1.864)
CRP categories (x ULN), Baseline					
< 0.7	7 (9.7)	11 (15.3)	13 (18.6)	15 (21.7)	46 (16.3)
≥ 0.7-≤ 1	4 (5.6)	5 (6.9)	7 (10.0)	5 (7.2)	21 (7.4)
> 1-< 1.2	6 (8.3)	2 (2.8)	5 (7.1)	5 (7.2)	18 (6.4)
≥ 1.2	55 (76.4)	54 (75.0)	45 (64.3)	44 (63.8)	198 (70.0)
Mean (SE) CRP (Baseline-Screening) (mg/mL)	-2.08 (3.680)	-7.33 (3.661)	-9.83 (3.707)	-10.57 (3.594)	-7.40 (1.832)
Mean (SE) corrected TJC68, Screening	24.396 (1.5041)	25.494 (1.8619)	25.823 (1.5085)	25.971 (1.5164)	25.412 (0.8008)
Mean (SE) corrected TJC68, Baseline	25.226 (1.4795)	25.580 (1.6204)	27.195 (1.7702)	26.242 (1.5057)	26.051 (0.7958)
Mean (SE) corrected TJC68 (Baseline-Screening)	0.831 (0.8697)	0.086 (1.0511)	1.373 (1.1474)	0.271 (1.1734)	0.639 (0.5299)
Mean (SE) corrected SJC66, Screening	16.314 (1.0783)	16.592 (1.2221)	18.932 (1.3463)	16.714 (1.1417)	17.130 (0.6003)
Mean (SE) corrected SJC66, Baseline	15.980 (0.8534)	16.969 (1.0735)	18.653 (1.4179)	15.740 (1.0465)	16.834 (0.5578)
Mean (SE) corrected SJC66 (Baseline-Screening)	-0.335 (0.8240)	0.377 (0.5860)	-0.279 (0.8659)	-0.974 (0.7311)	-0.296 (0.3783)
Mean (SE) DAS28 (CRP), Screening *	6.30 (0.087)	6.11 (0.117)	6.38 (0.089)	6.30 (0.101)	6.27 (0.050)
Mean (SE) DAS28 (CRP), Baseline	6.22 (0.099)	6.03 (0.105)	6.18 (0.101)	6.09 (0.102)	6.13 (0.051)
Mean (SE) DAS28 (CRP) (Baseline-Screening) *	0.08 (0.070)	-0.08 (0.083)	-0.20 (0.079)	-0.21 (0.073)	-0.14 (0.038)
Mean (SE) patient's global evaluation, Screening *	73.7 (1.90)	69.0 (2.38)	71.5 (2.30)	71.9 (2.20)	71.5 (1.10)
Mean (SE) patient's global evaluation, Baseline	71.1 (2.02)	68.6 (2.41)	71.5 (2.23)	68.9 (2.07)	70.0 (1.09)
Mean (SE) patient's global evaluation (Baseline-Screening) *	-2.8 (2.25)	-0.4 (1.82)	0.0 (2.25)	-3.0 (1.79)	-1.5 (1.02)

	Mean (SE) investigator global evaluation, Baseline **	70.4 (1.73)	68.2 (1.73)	72.0 (1.59)	67.7 (1.86)	69.6 (0.87)
	Mean (SE) patient pain evaluation, Baseline ***	71.6 (2.37)	71.0 (2.38)	72.6 (1.85)	68.1 (2.35)	70.9 (1.12)
	Mean (SE) HAQ-DI, Baseline ***	1.80 (0.058)	1.84 (0.068)	1.81 (0.068)	1.80 (0.063)	1.81 (0.032)
	Mean (SE) SDAI, Baseline **	45.730 (1.4789)	43.770 (1.5609)	46.608 (1.6538)	44.139 (1.5079)	45.071 (0.7750)
	Mean (SE) CDAI, Baseline **	42.168 (1.3272)	41.348 (1.4777)	44.052 (1.5383)	41.869 (1.4230)	42.362 (0.7204)
	RF-status, n (%)					
	Positive	57 (79.2)	53 (73.6)	51 (72.9)	50 (72.5)	211 (74.6)
	Negative	15 (20.8)	19 (26.4)	19 (27.1)	19 (27.5)	72 (25.4)
	Anti-CCP, n (%)					
	Positive	58 (80.6)	56 (77.8)	54 (77.1)	57 (82.6)	225 (79.5)
	Negative	14 (19.4)	16 (22.2)	16 (22.9)	12 (17.4)	58 (20.5)
	RF and anti-CCP combined, n (%)					
	RF+/ anti-CCP+	55 (76.4)	50 (69.4)	47 (67.1)	47 (68.1)	199 (70.3)
	RF+/ anti-CCP-	2 (2.8)	3 (4.2)	4 (5.7)	3 (4.3)	12 (4.2)
	RF-/ anti-CCP+	3 (4.2)	6 (8.3)	7 (10.0)	10 (14.5)	26 (9.2)
	RF-/ anti-CCP-	12 (16.7)	13 (18.1)	12 (17.1)	9 (13.0)	46 (16.3)

**N=71 instead of 72 in the placebo group.*
***N= 71 instead of 72 in the placebo group; 70 instead of 72 in the filgotinib 50 mg once daily dose group and 68 instead of 69 in the filgotinib 200 mg once daily dose group.*
****N= 71 instead of 72 in the placebo group and 70 instead of 72 in the filgotinib 50 mg once daily dose group.*
CCP=cyclic citrullinated peptide; CDAI=clinical diagnostic activity index; CRP=C-reactive protein; DAS28=disease activity score based on 28 joints; HAQ-DI=health assessment questionnaire-disability index; N=number of subjects per treatment group; n=number of subjects per category; RA=rheumatoid arthritis; RF=rheumatoid factor; SE=standard error; SDAI=simplified diagnostic activity index; SJC66=swollen joint count based on 66 joints; TCJ68=tender joint count based on 68 joints; ULN=upper limit of normal range.
Source: (14).

Primary and secondary endpoints

Primary endpoint (21):

- Percentage of subjects who achieved an ACR20 response at week 12.
  Time frame: Baseline - week 12

Secondary endpoints (21):

- Percentage of subjects who achieved an ACR20 response at every visit from week 1 to 24
- Percentage of subjects who achieved an ACR50 response at every visit from week 1 to 24
- Percentage of subjects who achieved an ACR70 response at every visit from week 1 to 24
- Percentage of subjects who achieved an ACR-N response at every visit from week 1 to 24
- Percentage of subjects who achieved a DAS28(CRP) at every visit from week 1 to 24
- Percentage of subjects who achieved an ACR/European League Against Rheumatism (EULAR) remission at every visit from week 1 to 24

	• Percentage of subjects who achieved a EULAR response at every visit from week 1 to 24 • Percentage of subjects who achieved a CDAI/SDAI response at every visit from week 1 to 24 • Change versus baseline in FACIT at weeks 4, 12 and 24 • Change versus baseline in Short Form-36 scores (quality of life assessment) at weeks 4, 12 and 24 • Change versus baseline in Subject's Disability (based on the HAQ-DI scores) at every visit from week 1 to 24 • The number of subjects with AEs, abnormal lab tests, vital signs, and electrocardiogram (ECG) from screening up to 10 days after last dose • To evaluate the safety and tolerability of filgotinib in comparison with placebo in terms of AEs, laboratory test abnormalities, vital signs, and ECG • The plasma levels of filgotinib and its metabolite as a measure of pharmacokinetics (PK) in week 4, 12 and 24 • To characterise the PK of filgotinib and its metabolite by measuring the amount in the plasma • The change versus baseline in levels of immune and inflammation-related parameters in whole blood and serum as a measure of pharmacodynamics (PD). Time frame: Baseline, week 1, 4, 12 and 24. To characterise the PD of filgotinib and its metabolite by measuring the levels of immune- and inflammation-related parameters in whole blood and serum
Method of analysis	Efficacy assessments were carried out at screening (joint counts, CRP, and Patient's Global Assessment of Disease Activity only); at baseline (Day -1); at weeks 1, 2, 4, 8, 12, 16, 20 and 24; and at the early discontinuation visit (EDV), if applicable. The parameters described below (apart from the FACIT Fatigue and SF-36) were used to compute the ACR, DAS28, SDAI, and CDAI scores. Furthermore, efficacy analysis was presented in two chapters: 1. Chapter 2: Analysis of the full 24-week study period 2. Chapter 3: Analysis of the second study period from week 12 onwards. All chapters used the original baseline visit as reference. Binary parameters (such as ACR20/50/70) were analysed with logistic regression model with factors treatment, region and previous use of biologics. Continuous parameters: Both the changes from baseline and the percent changes from baseline were to be described. Formal between-group comparisons were to be performed on the changes from baseline only, using an analysis of (co)variance (AN(C)OVA) model with factors treatment, baseline value, region, and previous use of biologics. Baseline was to be the last non-missing value prior to first dosing in the study. Time to (first) response (ACR20/50/70) was to be analysed using Kaplan-Meier survival techniques, and groups were to be compared against placebo using a Cox proportional hazards regression model with factors treatment, region, and previous use of biologics. (14) <u>Evaluation of Disease Activity</u> A joint assessor evaluated each of 68 joints for tenderness and each of 66 joints for swelling. <u>Patient's Global Assessment of Disease Activity</u>

	The Patient's Global Assessment of Disease Activity was recorded on a 0 to 100 mm visual analogue scale (VAS), with 0 indicating "very well" and 100 indicating "very poor" to the question "Considering all the ways arthritis affects you, how well are you doing today?" Physician's Global Assessment of Disease Activity The Physician's Global Assessment of Disease Activity was recorded on a 0 to 100 mm VAS, with 0 indicating "no disease activity" and 100 indicating "extreme disease activity". The evaluating physician and the subject had to complete the global assessments independently of each other. Health Assessment Questionnaire – Disability Index (HAQ-DI) The functional status of the subject was assessed using the HAQ-DI, a 20-question instrument assessing the degree of difficulty a person has in accomplishing tasks in 8 domains (dressing, arising, eating, walking, hygiene, reaching, gripping and errands/chores). The HAQ-DI total score ranges from 0 to 3 with higher scores indicating greater dysfunction. As part of the HAQ-DI, subjects were asked to assess their average pain during the last week on a 0 to 100 mm VAS, with 0 indicating "no pain" and 100 indicating "severe pain". This assessment had to be completed before the joint examination. This pain score was used to drive the ACR20/50/70. FACIT Fatigue Scale The FACIT fatigue scale (version 4) measures an individual's level of fatigue during their usual daily activities over the past week. It consists of 13 questions with a 7-day recall period on a 5-point Likert scale, with 0 indicating "not at all" and 4 indicating "very much". The total score ranges from 0 to 52. The higher the score, the better the quality of life. SF-36 The health-related quality of life of the subject was assessed using the SF-36 (version 2) with a 4-week recall period. This consists of 36 questions belonging to 8 domains in 2 components: • physical well-being: 4 domains: physical functioning (10 items), role physical (4 items), bodily pain (2 items), and general health perceptions (5 items) • mental well-being: 4 domains: vitality (4 items), social functioning (2 items), role emotional (3 items), and mental health (5 items) The remaining item (health transition) was not part of the above domains but is kept separately. These scales were rescaled from 0 to 100 (converting the lowest possible score to 0 and the highest possible score to 100), with higher scores indicating a better quality of life. Safety AEs were recorded and physical examinations, vital signs, 12-lead electrocardiogram (ECG) and laboratory assessments were performed. The analysis presented the results in two chapters: 1. Chapter 1: Analysis of the first study period, up to and including the week 12 visit. 2. Chapter 2: Analysis of the full 24 weeks study period. Statistical methods The efficacy analysis was performed on all subjects who used the study medication at least once and have postbaseline efficacy data. ACR20, ACR50, ACR70, ACR-N, EULAR response, and ACR/EULAR remission, components of the ACR, and DAS28, CDAI and SDAI

	at each post-dosing visit were analysed descriptively. Between-group comparisons were also done for each dose group versus the placebo group. The effects of different doses of filgotinib administration on subject's disability, fatigue and quality of life were also evaluated. Hommel's closed testing correction procedure was applied to adjust for multiplicity. This study was not powered for any formal comparison among the dose groups. Clinical safety was evaluated by assessing TEAEs, physical examinations, laboratory assessments, ECG, and vital signs results in a descriptive manner. Original results, changes, and percent changes from baseline (or from screening, depending on the parameter) were summarised for the laboratory data, vital signs, and ECG values. Values were categorised as low/normal/high according to normal ranges, and shift tables versus baseline were created to determine treatment-emergent abnormalities (14).
Subgroup analyses	The following subgroups were examined descriptively for ACR20 and DAS28 (CRP) change from baseline at week 12: • Per-protocol ACR20 and DAS28(CRP) • Various baseline disease characteristics ACR20 and DAS28(CRP) Furthermore, the baseline disease characteristics were split up for week 12 responders versus non-responders. (14)

TABLE 53: MAIN CHARACTERISTICS OF MORELAND ET AL. 1999 (3)

Trial name	Not reported.
NCT	Not reported.
Objective	To confirm the benefit of etanercept therapy of longer duration and simplified dosing in patients with rheumatoid arthritis.
Publications – title, author, journal, year	Title: Etanercept Therapy in Rheumatoid Arthritis A Randomized, Controlled Trial Author: Moreland et al. Journal and year: Annals of Internal Medicines 1999
Study type and design	Randomised, double-blind, placebo-controlled trial with blinded joint assessors. Patients were randomised to twice-weekly subcutaneous injections of etanercept, 10 or 25 mg, or placebo for six months.
Follow-up	Maximum follow-up was six months.
Population (inclusion and exclusion criteria)	Eligible patients were adults who were at least 18 years of age, met the American Rheumatism Association's diagnostic criteria for rheumatoid arthritis, and were in functional class I, II, or III. Patients were required to have had an inadequate response to one to four DMARDs (such as azathioprine, methotrexate, sulfasalazine, penicillamine, hydroxychloroquine, or oral or injectable gold); an inadequate response was defined as discontinuation of therapy because of lack of effect. If patients were receiving DMARDs, they were required to complete a DMARD washout period that lasted at least 1 month before starting study drug treatment. No DMARDs were permitted during the study. Patients had to have active disease at enrolment (before the DMARD washout period), defined as 12 or more tender joints, 10 or more swollen joints, and at least one of the following: • erythrocyte sedimentation rate of at least 28 mm/h; • C-reactive protein level greater than 20 mg/L; or • morning stiffness for at least 45 minutes.

	All patients were required to have aminotransferase levels no greater than twice the upper limit of normal, a haemoglobin level of 85 g/dL or greater, a platelet count of at least 125 000 cells/mm^3, a leukocyte count of 3500 cells/mm^3 or higher, and a serum creatinine level of 176.8 µmol/L (2 mg/dL) or less. Concomitant therapy with stable doses of oral corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs) was permitted. Corticosteroid doses could not exceed the equivalent of 10 mg of prednisone per day, and NSAID doses could not exceed the maximum dose recommended by the manufacturer. Patients could receive analgesics during the study except for the 24 hours before scheduled joint examinations. Intra-articular corticosteroids were not permitted during the study or beginning four weeks before enrolment. Because the inclusion criteria for this study were similar to the inclusion criteria for the previous three-month trial in rheumatoid arthritis, eight patients who received placebo in the three-month trial were enrolled in the current study.
Intervention	Etanercept 10 mg s.c twice weekly (for 6 months) Etanercept 25 mg s.c twice weekly (for 6 months)

Baseline characteristics

Characteristics	Placebo (n=80)	Etanercept	
		10 mg (n=76)	25 mg (n=78)
Mean age, y	51	53	53
Women, %	76	84	74
White, %	89	96	94
Mean duration of disease, y	12	13	11
Mean measures of disease activity			
Tender joints, n *	35	34	33
Swollen joints, n **	25	25	25
Duration of morning stiffness, hours	4.8	4.4	5.0
Physician's global assessment ***	6.9	6.9	6.9
Patient's global assessment ***	6.9	6.9	7.0
Pain (visual analogue scale) ****	6.5	6.6	6.7
Vitality domain (SF-36) *****	69	68	66
Mental health domain (SF-36) *****	42	41	42
Disability index (health assessment questionnaire)	1.7	1.7	1.6
Erythrocyte sedimentation rate, mm/h	39	44	35
C-reactive protein level, mg/dL	4.1	5.3	4.7
Rheumatoid-factor positive, %	79	82	79
Haemoglobin level, g/L	130	127	133
Platelet count, x 10^3 /µL	360	358	358
Albumin level, g/dL	37	36	36
Leukocyte count, x 10^3 /µL	8.7	9.3	10.2
Mean previous DMARDs, n	3.0	3.4	3.3
Previous DMARDs, %			
Methotrexate	90	92	87
Hydroxychloroquine	71	70	65
Gold, injectable	46	57	58
Sulfasalazine	35	54	51
Azathioprine	28	32	32
D-Penicillamine	21	30	22
Gold, oral	21	20	22
Concomitant medications			
Corticosteroids, %	58	66	81

	Mean daily corticosteroid dose (prednisone equivalent), mg	6.8	7.5	7.3
	Nonsteroidal anti-inflammatory drugs, %	84	67	67
	Patients requiring DMARD washout, %	48	46	45

**Range, 0–71.*
***Range, 0–68.*
**** 0 = best, 10 = worst.*
***** 0 = best, 3 = worst.*
****** 1 = best, 100 = worst.*
Source: (3).

Primary and secondary endpoints	The primary efficacy endpoints were 20% and 50% improvement in disease activity at 3 and 6 months. The 20% ACR response specifies a 20% reduction in tender joint count and swollen joint count and 20% improvement in at least three of the following: patient's assessment of pain, patient's global assessment, physician's global assessment, patient's assessment of disability, and acute phase reactant measures (either erythrocyte sedimentation rate or C-reactive protein level). Other efficacy end points included 70% ACR response at 3 and 6 months and percentage change from baseline at 3 and 6 months in the following: tender joint count, swollen joint count, duration of morning stiffness, patient's global assessment, physician's global assessment, patient's assessment of pain, quality of life, erythrocyte sedimentation rate, and C-reactive protein level. Response was also evaluated according to the Paulus index, defined as a 20% or 50% improvement in at least four of the following variables: tender joint scores, swollen joint scores, duration of morning stiffness, erythrocyte sedimentation rate, patient's global assessment, and physician's global assessment. (3)
Method of analyses	The ACR response rates and Paulus indices were compared by using the likelihood ratio chi-square test. Fisher's exact test was substituted when necessitated by low response rates (50% ACR response at 2 weeks and 70% ACR response). Patients who withdrew for any reason were counted as non-responders after withdrawal. Individual measures of disease activity were compared by using analysis of variance in which treatment, study site, and their interaction were the factors. The last available observation was used for dropouts. If the initial comparison of the three treatments was significant at the p-value 0.05 level, each pair of treatments was compared (also at the 0.05 level). This procedure controls the type I error at the 0.05 level. The Stuart–Maxwell chi-square test was used to test for normalisation of laboratory values (within treatment groups). We conducted all analyses by using version 6.12 of SAS software (SAS Institute, Cary, North Carolina) (3).
Subgroup analyses	None.

TABLE 54: MAIN CHARACTERISTICS OF THE JERA TRIAL

Trial name	A Randomised, Double-Blind, Multicenter, Comparative Study Evaluating the Efficacy and Safety of Etanercept and Methotrexate in Japanese Subjects With Active Rheumatoid Arthritis (JERA trial)
NCT	NCT00445770
Objective	The purpose of this study is to examine the effects of etanercept (10 mg and 25 mg) compared with methotrexate (up to 8 mg per week) on the slowing of joint destruction.
Publications – title, author, journal, year	Title: A phase 3 randomized, double-blind, multicenter comparative study evaluating the effect of etanercept versus methotrexate on radiographic outcomes, disease activity, and safety in Japanese subjects with active rheumatoid arthritis

<table>
<tr><td></td><td>Author: Takeuchi T, Miyasaka N, Zang C.
Journal and year: Modern Rheumatology, 2013 (15)

<u>Post-hoc analysis:</u>
Title: Radiographic and clinical effects of 10 mg and 25 mg twice weekly etanercept over 52 weeks in Japanese patients with active rheumatoid arthritis.
Author: Takeuchi T, Miyasaka N, Pedersen RD, Sugiyama N.
Journal and year: Modern Rheumatology, 2020 (22)

Title: Radiographic and clinical outcomes following etanercept monotherapy in Japanese methotrexate-naïve patients with active rheumatoid arthritis.
Author: Takeuchi T, Miyasaka N, Pedersen RD, Sugiyama N.
Journal and year: Modern Rheumatology, 2020 (4)</td></tr>
<tr><td>Study type and design</td><td>Phase III, randomised, multicentre, comparative study</td></tr>
<tr><td>Follow-up</td><td>Maximum follow-up time was 52 weeks.</td></tr>
<tr><td>Population (inclusion and exclusion criteria)</td><td>Inclusion criteria (10):
Must be Japanese and live in Japan
Must be age 20 to 75 years
Diagnosed less than or equal to 10 years from time of first visit
Exclusion criteria (10):
Anyone who has received etanercept or TNF-inhibitors such as infliximab or adalimumab in the past
Patient with other rheumatic diseases or conditions that could predispose the patient to infection
Pregnant or lactating women</td></tr>
<tr><td>Intervention</td><td>Etanercept 10 mg s.c twice weekly
25 mg etanercept s.c twice weekly</td></tr>
<tr><td>Baseline characteristics</td><td><u>Baseline characteristics of patients in JERA trial</u> (15)<u>:</u>

<table>
<tr><th>Characteristics</th><th>Etanercept 25 mg (n=182)</th><th>Etanercept 10 mg (n=192)</th><th>MTX (n=176)</th></tr>
<tr><td colspan="4">Demographic characteristics*</td></tr>
<tr><td>Age, years, mean (SD)</td><td>51.8 (11.1)</td><td>51.5 (12.2)</td><td>50.4 (11.9)</td></tr>
<tr><td colspan="4">Sex, n (%)</td></tr>
<tr><td>Male</td><td>37 (20.3)</td><td>38 (19.8)</td><td>36 (20.5)</td></tr>
<tr><td>Female</td><td>145 (79.7)</td><td>154 (80.2)</td><td>140 (79.6)</td></tr>
<tr><td>BMI, kg/m^2, mean</td><td>22.8</td><td>22.1</td><td>21.7</td></tr>
<tr><td>Prior corticosteroid use, n (%)</td><td>109 (59.9)</td><td>129 (67.2)</td><td>105 (59.7)</td></tr>
<tr><td>Prior NSAID use, n (%)</td><td>169 (92.9)</td><td>173 (90.1)</td><td>164 (93.2)</td></tr>
<tr><td>Prior MTX use, n (%)</td><td>122 (67.0)</td><td>123 (64.1)</td><td>108 (61.4)</td></tr>
<tr><td>Prior DMARD use including MTX, n (%)</td><td>182 (100.0)</td><td>192 (100.0)</td><td>176 (100.0)</td></tr>
<tr><td>Prior DMARD use excluding MTX, n (%)</td><td>154 (84.6)</td><td>155 (80.7)</td><td>148 (84.1)</td></tr>
<tr><td colspan="4">Baseline disease characteristics, mean (SD)*</td></tr>
<tr><td>Duration of disease, years</td><td>3.0 (2.6)</td><td>2.9 (2.7)</td><td>3.0 (2.7)</td></tr>
</table></td></tr>
</table>

RF+, n (%)	142 (78.0)	147 (75.6)	133 (75.6)
DAS	4.1 (0.9)	4.0 (0.9)	4.1 (1.0)
DAS28	5.8 (1.0)	5.7 (1.2)	5.8 (1.1)
Tender joint count	17.5 (11.2)	16.3 (10.6)	17.1 (10.8)
Swollen joint count	14.0 (8.8)	14.2 (9.0)	13.8 (7.8)
Physician global assessment	6.2 (1.9)	6.2 (1.8)	6.3 (2.0)
Patient global assessment	6.0 (2.0)	6.1 (2.2)	6.0 (2.3)
Patient General Health VAS	55.7 (21.7)	58.7 (23.1)	58.4 (24.0)
Pain VAS	52.6 (21.5)	54.4 (23.1)	54.9 (23.6)
CRP, mg/L	22.1 (24.2)	22.9 (29.8)	21.1 (22.3)
ESR, mm/h	43.7 (27.6)	42.0 (29.4)	42.6 (28.2)
HAQ-DI	1.1 (0.7)	1.2 (0.7)	1.0 (0.7)
Baseline disease characteristics, mean (SD)**	**Etanercept 25 mg (n=181)**	**Etanercept 10 mg (n=190)**	**MTX (n=171)**
mTSS, mean (SD)	41.98 (41.51)	45.17 (38.75)	43.01 (46.78)
mTSS progression rate, mean (SD) ***	25.11 (34.20)	31.42 (45.47)	27.82 (40.65)
Erosion score, mean (SD)	25.23 (23.88)	26.66 (22.11)	25.09 (26.30)
JSN score, mean (SD)	16.75 (19.11)	18.50 (19.14)	17.92 (21.93)

MTX: methotrexate, SD: standard deviation, BMI: body mass index, NSAID: non-steroidal anti-inflammatory drugs, DMARD: disease-modifying anti-rheumatic drugs, RF+: rheumatoid factor positive, DAS: disease activity score, 4 variables-ESR, DAS28: disease activity score in 28 joints, VAS: visual analogue scale, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, HAQ-DI: Health Assessment Questionnaire Disability Index, mTSS: modified total Sharp score, JSN: joint space narrowing, mITT: modified intent-to-treat, rITT: radiographic intent-to-treat.
**mITT population.*
***rITT population.*
****The baseline progression rate of mTSS was calculated by dividing the baseline mTSS by the duration of disease.*

Baseline characteristics of patients in post-hoc analysis (4):

Characteristics*	**MTX-naïve**				**MTX-IR**			
	MTX (n=68)	**ETN 10 mg (n=69)**	**ETN 25 mg (n=60)**	**P****	**MTX (n=108)**	**ETN 10 mg (n=123)**	**ETN 25 mg (N=122)**	**P****
Age, years	50.69 (13.22)	54.42 (12.54)	52.70 (11.94)	.226	50.22 (11.07)	49.80 (11.75)	51.37 (10.64)	.525
Female sex, n (%)	52 (76.47)	56 (81.16)	45 (75.00)	.675	88 (81.48)	98 (79.67)	100 (81.97)	.891
BMI, kg/m2	21.43 (2.98)	22.10 (3.52)	22.62 (3.59)	.137	21.82 (3.55)	22.09 (4.08)	22.82 (3.85)	.121
RA duration, years	2.26 (2.53)	1.97 (2.36)	2.13 (2.12)	.769	3.41 (2.76)	3.44 (2.78)	3.42 (2.74)	.996
Prior corticosteroid use, n (%)	35 (51.47)	40 (57.97)	32 (53.33)	.735	70 (64.81)	89 (72.36)	77 (63.11)	.265
Prior NSAID use, n (%)	63 (92.65)	62 (89.86)	56 (93.33)	.740	101 (93.52)	111 (90.24)	113 (92.62)	.630
CRP, mg/L	21.16 (20.85)	21.04 (23.23)	21.19 (22.87)	.999	21.11 (23.26)	23.89 (32.92)	22.53 (24.87)	.746

ESR, mm/h	41.04 (25.18)	42.59 (29.39)	44.85 (29.11)	.743	43.50 (30.07)	41.67 (29.58)	43.08 (26.99)	.878
RF positive, n (%)	57 (83.82)	50 (72.46)	43 (71.67)	.185	76 (70.37)	97 (78.86)	99 (81.15)	.135
Erosion score ¼ 0, n (%) ***	0 (0.00)	0 (0.00)	1 (1.67)	.306	0 (0.00)	1 (0.82)	0 (0.00)	1.000
PtGA	5.96 (2.01)	5.83 (2.04)	5.78 (2.19)	.885	6.04 (2.45)	6.29 (2.23)	6.02 (1.93)	.582
PGA	6.29 (1.92)	6.07 (1.67)	6.02 (1.82)	.648	6.36 (2.03)	6.32 (1.85)	6.29 (1.89)	.958
HAQ-DI score	0.95 (0.61)	1.12 (0.66)	1.03 (0.65)	.298	1.05 (0.67)	1.20 (0.67)	1.08 (0.68)	.200
TJC 71 joints	17.04 (10.27)	16.02 (9.28)	14.47 (7.66)	.286	17.16 (11.14)	16.46 (11.24)	18.96 (12.36)	.223
SJC 68 joints	13.47 (7.38)	13.49 (7.55)	12.33 (6.25)	.582	14.07 (8.10)	14.65 (9.69)	14.81 (9.74)	.818
DAS28-4ESR	5.77 (1.01)	5.70 (1.00)	5.66 (1.06)	.848	5.88 (1.21)	5.77 (1.26)	5.90 (1.00)	.639

BMI: body mass index; CRP: C-reactive protein; DAS28-4ESR: Disease Activity Score in 28 joints based on the erythrocyte sedimentation rate with four variables; ESR: erythrocyte sedimentation rate; ETN: etanercept; HAQ-DI: Health Assessment Questionnaire Disability Index; mITT: modified intent-to-treat; MTX: methotrexate; MTX-IR: patients intolerant to, or with an inadequate clinical response to, prior MTX treatment; NSAID: non-steroidal anti-inflammatory drug; PGA: physician global assessment; PtGA: patient global assessment; RA: rheumatoid arthritis; RF: rheumatoid factor; SJC: swollen joint count; TJC: tender joint count.

** Data are mean (standard deviation) unless otherwise noted.*

***The p values for variables presented as mean (standard deviation) are from one-way ANOVA with treatment as factor, while p values for variables presented as n (%) are from chi-square analysis, except 'RF positive' which were from two-tailed Fisher's exact test.*

****Evaluated in the radiographic intent-to-treat population.*

Source: Takeuchi et al. 2020 (4).

Primary and secondary endpoints

Primary outcome measures (10):

- Change from baseline in mTSS at week 52. mTSS = sum of erosion and JSN scores for 44 joints (16 per hand and 6 per foot). mTSS scores ranged from 0 (normal) to 448 (worst possible total score). Change = scores at observation minus score at baseline. An increase in mTSS from baseline represented disease progression and/or joint worsening, no change represented halting of disease progression, and a decrease represents improvement.

Secondary outcome measures (10):

- Change from baseline in mTSS at week 24. mTSS = sum of erosion and JSN scores for 44 joints (16 per hand and 6 per foot). mTSS scores ranged from 0 (normal) to 448 (worst possible total score). Change = scores at observation minus score at Baseline. An increase in mTSS from baseline represented disease progression and/or joint worsening, no change represented halting of disease progression, and a decrease represented improvement.

- Change from baseline in erosion score at weeks 24 and 52. Joint erosion score: erosion severity in 44 joints (16 per hand, 6 per foot). Each joint scored according to surface area involved, from 0 (no erosion) to 5 (extensive bone loss from more than one half of articulating bone). Because each side of foot joint was graded, maximum erosion score for foot joint was 10. Thus, maximum erosion score was 280. Change = score at observation minus score at baseline. An increase in score from baseline represented disease progression and/or joint worsening, no change represented halting of disease progression, and a decrease represented improvement.

	• Change from baseline in Joint Space Narrowing (JSN) score at weeks 24 and 52. JSN score: severity of JSN in 42 joints (15 per hand and 6 per foot), including subluxation, scored from 0 (no/normal JSN) to 4 (complete loss of joint space, bony ankylosis, or luxation). Maximum JSN score was 168. Change = scores at observation minus score at baseline. An increase in score from baseline represented disease progression and/or joint worsening, no change represented halting of disease progression, and a decrease represented improvement. • Percentage of participants with no progression of joint destruction at week 52. Absence of joint destruction defined by three categories (mTSS change <=0.5, <=3.0, and <smallest detectable difference [SDD] where SDDs were scores >3.0). mTSS = sum of erosion and JSN scores for 44 joints (16 per hand and 6 per foot). mTSS scores ranged from 0 (normal) to 448 (worst possible total score). • Change from baseline in Swollen Joint Count at weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, 48, and 52. American College of Rheumatology (ACR) swollen joint count was an assessment of 68 joints. Joints classified as either swollen or not swollen. Change = scores at observation minus score at Baseline, and total possible scores ranged from -68 to 68. An increase in swollen joints from baseline represented disease progression and/or joint worsening, no change represented halting of disease progression, and a decrease represented improvement. • Change from baseline in number of painful Joints on pressure or on motion at weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, 48 and 52. 71 joints assessed by the investigator using criteria based on pressure and joint manipulation. Change = scores at observation minus score at Baseline, and total possible scores ranged from -71 to 71. An increase in tender joint count from baseline represented disease progression and/or joint worsening, no change represented halting of disease progression, and a decrease represented improvement. • Change from baseline in Physician's Global Assessment of Symptoms at weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, 48 and 52. Physician Global Assessment of symptoms, assessed using a 11-point rating scale, where 0=asymptomatic and 10=severe symptoms. Change = scores at observation minus score at baseline. An increase in score from baseline represented disease progression and/or joint worsening, no change represented halting of disease progression, and a decrease represented improvement. • Change from baseline in Patient's Global Assessment at weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, 48 and 52. Patient's Global Assessment of symptoms, assessed using a 11-point rating scale, where 0=asymptomatic and 10=severe symptoms. Change = scores at observation minus score at baseline. An increase in score from baseline represented disease progression and/or joint worsening, no change represented halting of disease progression, and a decrease represented improvement. • Change from baseline in Mean Duration of Morning Stiffness at weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, 48 and 52. Morning stiffness in and around the joints lasting at least 1 hour before maximal improvement. Change = scores at observation minus score at baseline. An increase in stiffness duration from baseline represented disease progression and/or joint worsening, no change represented halting of disease progression, and a decrease represented improvement. • Change from baseline in Visual Analogue Scale for Pain (VAS pain) at weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, 48 and 52. 100 mm line (VAS) marked by participant. Intensity of pain range (over past week): 0mm = no pain to 100mm = worst possible pain. Change = scores at observation minus score at baseline. An increase in score from baseline represented disease

	progression and/or joint worsening, no change represented halting of disease progression, and a decrease represented improvement. • Change from baseline in VAS for Participant General Health at weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, 48 and 52. 100 mm line (VAS) marked by participant. Participants asked, "In general how would you rate your health over the last 2-3 weeks?" 0mm=very well to 100mm=extremely bad. Change = scores at observation minus score at baseline. An increase in score from baseline represented disease progression and/or joint worsening, no change represented halting of disease progression, and a decrease represented improvement. • Change from baseline in HAQ-DI Score at weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, 48 and 52. HAQ-DI: participant-reported assessment of ability to perform tasks: 1) dress/groom; 2) arise; 3) eat; 4) walk; 5) reach; 6) grip; 7) hygiene; and 8) common activities over past week. Each item scored on 4-point Likert scale from 0 to 3: 0=no difficulty; 1=some difficulty; 2=much difficulty; 3=unable to do. Change = scores at observation minus score at baseline and total possible scores ranged from -3 to 3. An increase in score from baseline represented disease progression and/or joint worsening and a decrease represented improvement. • Percentage of participants with an ACR20 Response. Time frame: baseline and weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, 48 and 52. ACR20 response: greater than or equal to (≥) 20 percent (%) improvement in tender joint count; ≥ 20% improvement in swollen joint count; and ≥ 20% improvement in at least 3 of 5 remaining ACR core measures: participant assessment of pain; participant global assessment of disease activity; physician global assessment of disease activity; self-assessed disability (disability index of the Health Assessment Questionnaire [HAQ]); and C-Reactive Protein (CRP). • Percentage of participants with an ACR50 Response. Time frame: baseline and weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, 48 and 52. ACR50 response: ≥ 50% improvement in tender joint count; ≥ 50% improvement in swollen joint count; and ≥ 50% improvement in at least 3 of 5 remaining ACR core measures: participant assessment of pain; participant global assessment of disease activity; physician global assessment of disease activity; self-assessed disability (disability index of the HAQ); and CRP. • Percentage of participants with an ACR70 Response. Time frame: baseline and weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, 48 and 52. ACR70 response: ≥ 70% improvement in tender joint count; ≥ 70% improvement in swollen joint count; and ≥ 70% improvement in at least 3 of 5 remaining ACR core measures: participant assessment of pain; participant global assessment of disease activity; physician global assessment of disease activity; self-assessed disability (disability index of the HAQ); and CRP. • Change from baseline in Disease Activity Score (DAS) at weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, 48 and 52. DAS: weighted calculation of joint tenderness score (Ritchie Articular Index[RAI]), swollen joint count of 44 joints, natural logarithm (ln) of erythrocyte sedimentation rate (ESR) in mm per hour (mm/hr), and general health (GH) using VAS. RAI defined as sum of 26 possible 0 to 3 tender scores. DAS = 0.53938 square root (√) (RAI) + 0.06465 (swollen joint count) + 0.330 (ln ESR) + 0.00722 (GH). Change from baseline = DAS at week x minus baseline DAS. Total DAS scores could range from 10 (worse outcome) to 0 (better outcome). • Change from baseline in Disease Activity Score in 28 Joints (DAS28) at weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, 48, and 52. DAS based on 28 painful joint counts, 28 swollen joint counts, ESR, and GH. DAS28 score calculated as 0.56 √ (28 painful joint count) + 0.28 √ (28 swollen joint count) + 0.70 (ln ESR mm/hr) + 0.014 GH. Change from baseline = DAS at week x minus baseline DAS. Total DAS scores could range from 10 (worse outcome) to 0 (better outcome).

	• Change from baseline in C-reactive Protein (CRP) at weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, 48 and 52. CRP: marker of inflammation. Higher level consistent with inflammation. Normal CRP-range: 0 to 1.0 milligrams per decilitre (mg/dL). • Change from baseline in Erythrocyte Sedimentation Rate (ESR) at weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, 48 and 52. ESR: laboratory test that provided a non-specific measure of inflammation. The test assessed the rate at which red blood cells fell in a test tube and was measured in mm/hour. Normal range: 0-30mm/h. Higher rate consistent with inflammation. • Other Outcome Measures: Comparison of Etanercept Serum Concentrations Between the 10 mg and 25 mg Etanercept Doses. Time frame: weeks 12, 24 and 52.
Method of analyses	The radiographic efficacy analysis was based on the rITT population, which included all subjects who received at least one dose of the assigned drugs and provided radiographic data for the baseline and at least one postbaseline visit and did not include subjects who withdrew from the study within one month of the baseline visit. The clinical efficacy analysis was based on the mITT population that included all subjects who received at least one dose of the assigned test article. The safety population included all subjects who received at least one dose of test article. The primary efficacy endpoint, the change in mTSS from baseline to 52 weeks, and other radiographic variables were analysed using the analysis of covariance (ANCOVA) model based on rank transformed data, adjusting for rank baseline, with study centre, prior MTX use, and treatment group as the factors in the model. The primary radiographic efficacy analysis was based on a 52-week annualised change in mTSS score. Radiographic non-progression using different cut-offs (mTSS change ≤0.0, ≤0.5, ≤3.0, and ≤ smallest detectable difference (SDD)) and ACR20/50/70 response rates were analysed using the Cochran–Mantel–Haenszel approach, stratified by study centre and prior MTX use, as were the evaluation of DAS28 remission and EULAR response rates. For continuous clinical efficacy endpoints, changes from baseline were analysed, using an ANCOVA model with baseline values as a covariate, and study centre, prior MTX use, and treatment as factors. For missing radiographic data, the linear interpolation or extrapolation method was used for the primary radiographic efficacy analysis. For missing clinical data, the last observation carried forward method was used for the primary clinical efficacy analyses. Descriptive statistics, such as means and standard deviations (SD), were provided for demographic data and baseline characteristics. Safety data during the study were compared between treatment groups using Fisher's exact test procedures for categorical endpoints and the ANCOVA model with a baseline value as covariate for continuous endpoints. For the subgroup analyses, subgroup-by-treatment interactions were tested for each group individually by adding a subgroup main effect and subgroup-by-treatment interaction term to the primary analysis model. Tables of means by treatment and subgroup were produced with pairwise comparisons (15).
Subgroup analyses	Takeuchi et al. 2013 included analyses that were performed to examine the relative efficacy of the treatments on mTSS change at week 52 in clinically relevant subgroups. These subgroups included prior MTX use (yes or no), baseline progression rate of mTSS (quartiles: ≤8.6, >8.6 and ≤15.6, >15.6 and ≤28.8, >28.8), tender joint count (quartiles: ≤9.0, >9.0 and ≤14.0, >14.0 and ≤22.0, >22.0), CRP (mg/dL quartiles: ≤0.3, >0.3 and ≤1.5, >1.5 and ≤3.0, and >3.0), and duration of disease (by ≤3 vs. >3 years) (15).

7.3 Results per study

Table 55, Table 56 and Table 57 include results on the outcomes requested in the DMC protocol on filgotinib from the filgotinib trials: FINCH 1, FINCH 2 and DARWIN 2, respectively. Information in the tables was available from the EPAR on filgotinib and the CSRs related to the respective trials in addition to the FINCH 2 publication (2) and the two DARWIN 2 publications (7,9). Table 58 and Table 59 contain results on the outcomes requested in the DMC protocol on filgotinib from the two etanercept trials: the study by Moreland et al. 1999 (3) and the JERA trial (4,15), respectively.

TABLE 55: RESULTS ON THE OUTCOME REQUESTED IN THE DMC PROTOCOL ON FILGOTINIB FROM THE FINCH 1 TRIAL

Trial name:				FINCH 1						
NCT number:				NCT02889796						
				Odds ratio for Filgotinib vs Adalimumab	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (%) 95% CI	OR (95% CI)	Difference	95% CI	*P* value	Risk ratio	95% CI	*P* value	
Proportion of subjects who achieved ACR50 response (week 52)	Filgotinib 200 mg + MTX	475	296 (62.3%) 95% CI: 57.9%; 66.6%	1.160 (0.866, 1.552)	3.5 percentage points	-3.2%; 11.1%	NA	1.060	0.945; 1.188	0.320	Relative difference estimated based on OR from logistic regression. The absolute difference was calculated based on the relative difference. Formulas from the DMC guideline were used.
	Adalimumab + MTX	325	192 (59.1%) 95% CI: 53.7%; 64.4%								
Proportion of subjects who discontinue treatment due to an AEs (week 52)	Filgotinib 200 mg + MTX	475	26 (5.5%) 95% CI: 3.4%; 7.5%	NA	-0.1 percentage points	-3.6%; 3.1%	0.969	0.988	0.551; 1.773	0.969	Absolute difference in proportions and relative difference presented as risk ratio. 95% CI in absolute difference calculated.
	Adali-mumab + MTX	325	18 (5.5%) 95% CI: 3.1%; 8.0%								
Proportion of subjects who experienced a serious infection (week 52)	Filgotinib 200 mg + MTX	475	13 (2.7%) 95% CI: 1.2%; 4.3%	NA	-0.3 percentage points	-3.0%; 2.3%	0.777	0.889	0.395; 2.004	0.777	Absolute difference in proportions and relative difference presented as risk ratio.
	Adali-mumab + MTX	325	10 (3.1%) 95% CI: 1.0%; 5.1%								

Proportion of subjects who discontinue treatment due to lack of effect (week 52)	Filgotinib 200 mg + MTX	475	29 (6.1%) 95% CI: 4.0%; 8.3%	NA	1.8 percentage points	-1.5%; 4.9%	0.268	1.417	0.761; 2.640	0.272	Absolute difference in proportions and relative difference presented as risk ratio. 95% CI in absolute difference calculated.
	Adalimumab + MTX	325	14 (4.3%) 95% CI: 2.1%; 6.5%							
Proportion of subjects without radiographic progression (defined as ≤0 change from baseline in mTSS) (week 52)	Filgotinib 200 mg + MTX	417	365 (87.5%) 95% CI: 84.2%; 90.8%	1.510 (0.983, 2.319)	5.2 percentage points	-0.3%; 11.1 %	NA	1.063	0.996; 1.135	0.068	Relative difference estimated based on OR from logistic regression. The absolute difference was calculated based on the relative difference. Formulas from the DMC guideline were used.
	Adalimumab + MTX	273	225 (82.4%) 95% CI: 77.7%; 87.1%							
Proportion of subjects who achieved HAQ-DI response (defined as a reduction from baseline ≥0.22) (week 52)	Filgotinib 200 mg + MTX	459	348 (75.8%) 95% CI: 71.8%; 79.8%	1.338 (0.966, 1.852)	5.7 percentage points	-0.7%; 12.7%	NA	1.081	0.990; 1.181	0.084	Relative difference estimated based on OR from logistic regression. The absolute difference was calculated based on the relative difference. Formulas from the DMC guideline were used.
	Adalimumab + MTX	316	222 (70.3%) 95% CI: 65.1%; 75.5%							

TABLE 56: RESULTS ON THE OUTCOMES REQUESTED IN THE DMC PROTOCOL ON FILGOTINIB FROM THE FINCH 2 TRIAL

Trial name:				FINCH 2						
NCT number:				NCT02873936						
				Odds ratio for Filgotinib vs Placebo	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (%) 95% CI	OR (95% CI)	Difference	95% CI	*P* value	Risk ratio	95% CI	*P* value	
Proportion of subjects who achieved ACR50 response (week 24)	Filgotinib 200 mg + MTX	147	67 (45.6%) 95% CI: 37.5%; 53.6%	3.755 (2.204, 6.398)	27.8 percentage points	13.1%; 49.2%	NA	2.468	1.692; 3.600	<0.000	Relative difference estimated based on OR from logistic regression. The absolute difference was calculated based on the relative difference. Formulas from the DMC guideline were used.
	Placebo + MTX	148	27 (18.2%) 95% CI: 12.0%; 24.5%								
Proportion of subjects who discontinue treatment due to an AEs (week 24)	Filgotinib 200 mg + MTX	147	3 (2.0%) 95% CI: -0.2%; 4.3%	NA	0.0 percentage points	-4.0%; 4.0%	0.993	1.01	0.21; 4.91	0.993	Absolute difference in proportions and relative difference presented as risk ratio. 95% CI in absolute difference calculated.
	Placebo + MTX	148	3 (2.0%) 95% CI: -0.2%; 4.3%								
Proportion of subjects who experienced a serious infection (week 24)	Filgotinib 200 mg + MTX	147	1 (0.7%) 95% CI: -0.6%; 2.0%	NA	-0.7 percentage points	-4.2%; 2.6%	0.566	0.51	0.05; 5.53	0.577	Absolute difference in proportions and relative difference presented as risk ratio. 95% CI in absolute difference calculated.
	Placebo + MYX	148	2 (1.4%) 95% CI: -0.5%; 3.2%								

Proportion of subjects who discontinue treatment due to lack of effect (week 24)	Filgotinib 200 mg + MTX	147	12 (8.2%) 95% CI: 3.7%; 12.6%	NA	-13.5 percentage points	-21.5%; -5.4%	0.001	0.42	0.23; 0.80	0.008	Absolute difference in proportions and relative difference presented as risk ratio. 95% CI in absolute difference calculated.
	Placebo + MTX	148	32 (21.6%) 95% CI: 15.0%; 28.3%							
Proportion of subjects without radiographic progression (defined as ≤0 change from baseline in mTSS)	Filgotinib 200 mg + MTX	NA		NA	NA			NA			NA
	Placebo + MTX									
Proportion of subjects who achieved HAQ-DI response (defined as a reduction from baseline ≥0.22) (week 24)	Filgotinib 200 mg + MTX	144	99 (68.8%) 95% CI: 61.2%; 76.3%	4.482 (2.690, 7.469)	35.7 percentage points	20.1%; 55.5%	NA	2.007	1.568; 2.568	0.000	Relative difference estimated based on OR from logistic regression. The absolute difference was calculated based on the relative difference. Formulas from the DMC guideline were used.
	Placebo + MTX	144	51 (35.4%) 95% CI: 27.6%; 43.2%							

TABLE 57: RESULTS ON THE OUTCOMES REQUESTED IN THE DMC PROTOCOL ON FILGOTINIB FROM THE DARWIN 2 TRIAL

Trial name:	DARWIN 2								
NCT number:	NCT01894516								
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (%) 95% CI	Difference	95% CI	*P* value	Risk ratio	95% CI	*P* value	
Proportion of subjects who achieved ACR50 response (week 12)	Filgotinib 200 mg	69	30 (43.5%) 95% CI: 31.8%; 55.2%	32.4 percentage points	17.9%; 45.3%	<0.001	3.91	1.93; 7.93	<0.001	Absolute difference in proportions and relative difference presented as risk ratio. 95% CI in absolute difference calculated.
	Placebo	72	8 (11.1%) 95% CI: 3.9%; 18.4%							
Proportion of subjects who discontinue treatment due to an AEs (week 12)	Filgotinib 200 mg	69	1 (1.4%) 95% CI: -1.4%; 4.3%	-1.3 percentage points	-8.2%; 5.3%	0.59	0.52	0.05; 5.62	0.59	Absolute difference in proportions and relative difference presented as risk ratio. 95% CI in absolute difference calculated.
	Placebo	72	2 (2.8%) 95% CI: -1.0%; 6.6%							
Proportion of subjects who experienced a serious infection (week 12)	Filgotinib 200 mg	69	1 (1.4%) 95% CI: -1.4%; 4.3%	1.4 percentage points	-3.8%; 7.8%	0.31	3.13	0.13; 75.53	0.48	Absolute difference in proportions and relative difference presented as risk ratio. 95% CI in absolute difference calculated. To calculate the risk ratio, we have applied the standard method and added 0.5 to all cells in the 2x2 table.
	Placebo	72	0 (0.0%) 95% CI: 0.0%; 0.0%							

Proportion of subjects who discontinue treatment due to lack of effect (week 12)	Filgotinib 200 mg	69	0 (0.0%) 95% CI: 0.0%; 0.0%	-2.8 percentage points	-9.6%; 2.9%	0.165	0.21	0.01; 4.27	0.31	Absolute difference in proportions and relative difference presented as risk ratio. 95% CI in absolute difference calculated. To calculate the risk ratio, we have applied the standard method and added 0.5 to all cells in the 2x2 table.
	Placebo	72	2 (2.8%) 95% CI: -1.0%; 6.6%							
Proportion of subjects without radiographic progression (defined as ≤0 change from baseline in mTSS)	Filgotinib 200 mg	NA		NA			NA			NA
	Placebo									
Proportion of subjects who achieved HAQ-DI response (defined as a reduction from baseline ≥0.22) (week 12)	Filgotinib 200 mg	69	55 (79.7%) 95% CI: 70.2%; 89.2%	28.3 percentage points	12.7%; 42.1%	<0.001	1.55	1.20; 2.00	<0.001	Absolute difference in proportions and relative difference presented as risk ratio. 95% CI in absolute difference calculated.
	Placebo	72	37 (51.4%) 95% CI: 39.8%; 62.9%							

TABLE 58: RESULTS ON THE OUTCOMES REQUESTED IN THE DMC PROTOCOL ON FILGOTINIB FROM THE MORELAND ET AL. 1999 STUDY

Trial name:	Moreland et al. 1999									
NCT number:	Not reported									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (%) 95% CI	Difference	95% CI	*P* value	Risk ratio	95% CI	*P* value	
Proportion of subjects who achieved ACR50 response (3 months)	Etanercept	78	32 (41%) 95% CI: 30%; 52%	33 percentage points	20%; 45%	<0.001	5.47	2.42; 12.35	<0.001	Absolute difference in proportions and relative difference presented as risk ratio. 95% CI in absolute difference calculated.
	Placebo	80	6 (8%) 95% CI: 2%; 14%							
Proportion of subjects who discontinue treatment due to an AEs (6 months)	Etanercept	78	2 (2.6%) 95% CI: -0.9%; 6.1%	-1.2 percentage points	-8.1%; 5.6%	0.67	0.68	0.12; 3.98	0.67	Absolute difference in proportions and relative difference presented as risk ratio. 95% CI in absolute difference calculated.
	Placebo	80	3 (3.8%) 95% CI: -0.4%; 7.9%							
Proportion of subjects who experienced a serious infection	Etanercept	NA		NA			NA			NA
	Placebo									
Proportion of subjects who discontinue treatment due to lack of effect (6 months)	Etanercept	78	12 (15.4%) 95% CI: 7.4%, 23.4%	-37.1 percentage points	-49.5%; -22.7%	<0.001	0.29	0.17; 0.51	<0.001	Absolute difference in proportions and relative difference presented as risk ratio. 95% CI in absolute difference calculated.
	Placebo	80	42 (52.5%) 95% CI: 41.6%; 63.4%							
Proportion of subjects without radiographic progression (defined as	Etanercept	NA		NA			NA			NA
	Placebo									

≤0 change from baseline in mTSS)					
Proportion of subjects who achieved HAQ-DI response (defined as a reduction from baseline ≥0.22)	Etanercept Placebo	NA	NA	NA	NA

TABLE 59: RESULTS ON THE OUTCOMES SPECIFIED IN THE DMC PROTOCOL ON FILGOTINIB FROM THE JERA TRIAL

Trial name:	JERA trial (post-hoc analysis)									
NCT number:	NCT00445770									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (%) 95% CI	Difference	95% CI	*P* value	Risk ratio	95% CI	*P* value	
Proportion of subjects who achieved ACR50 response (week 12)	Etanercept MTX	122 108	48 (39%) 95% CI: 30%; 48% 19 (18%) 95% CI: 11%; 25%	21 percentage points	9%; 32%	<0.001	2.24	1.41; 3.56	<0.001	Absolute difference in proportions and relative difference presented as risk ratio. 95% CI in absolute difference calculated.
Proportion of subjects who discontinue treatment due to an AEs (week 52)	Etanercept MTX	122 108	14 (11.5%) 95% CI: 5.8%; 17.1% 5 (4.6%) 95% CI: 0.7%; 8.6%	6.8% percentage points	-0.5%; 14.2%	0.06	2.48	0.92; 6.66	0.07	Absolute difference in proportions and relative difference presented as risk ratio. 95% CI in absolute difference calculated.
Proportion of subjects who experienced a serious infection (week 52)	Etanercept MTX	122 108	0 (0.0%) 95% CI: 0.0%; 0.0% 1 (0.9%) 95% CI: -0.9%; 2.7%	-0.9 percentage points	-5.1%; 2.2%	0.29	0.30	0.01; 7.17	0.45	Absolute difference in proportions and relative difference presented as risk ratio. 95% CI in absolute

									difference calculated. To calculate the risk ratio, we have applied the standard method and added 0.5 to all cells in the 2x2 table.
Proportion of subjects who discontinue treatment due to lack of effect (week 52)	Etanercept MTX	122 108	3 (2.5%) 95% CI: -0.3%; 5.2% 23 (21.3%) 95% CI: 13.6%; 29.0%	-18.8 percentage points	-27.6%; -10.8%	<0.001	0.12	0.04; 0.37	<0.001	Absolute difference in proportions and relative difference presented as risk ratio. 95% CI in absolute difference calculated.
Proportion of subjects without radiographic progression (defined as ≤0 change from baseline in mTSS) (week 52)	Etanercept MTX	121 103	50 (41.3%) 95% CI: 32.5%; 50.1% 26 (25.2%) 95% CI: 16.9%; 33.6%	16.1 percentage points	3.7%; 27.7%	0.01	1.64	1.10; 2.43	0.01	Absolute difference in proportions and relative difference presented as risk ratio. 95% CI in absolute difference calculated.
Proportion of subjects who achieved HAQ-DI response (defined as a reduction from baseline ≥0.22)	Etanercept MTX	NA		NA			NA			NA

7.4 Statistical methodology

7.4.1 Estimation of relative risks

In this appendix, we describe the applied method for conducting relative risk estimates and associated confidence intervals. Suppose that we are interested in the incidence or frequency of some outcome assessed in two groups defined by the presence or absence of some characteristics. For example, we are interested in assessing the frequency of patients who achieved ACR50 response in patients treated with filgotinib relative to patients receiving placebo. The data from such a study can be tabulated as follows:

2x2 TABLE OF STUDY OUTCOME

Intervention group	Outcome		
	Yes	No	Total
Filgotinib	A	C	=A+C
Placebo	B	D	=B+D

The outcome probabilities in the group of patients treated with filgotinib and in the group of patients receiving placebo can be estimated as $\frac{A}{A+C}$ and $\frac{B}{B+D}$. The estimate of the relative risk (or risk ratio), RR, from treatment with filgotanib is given by the ratio of these two outcome probabilities:

$$RR = \frac{A/_{A+C}}{B/_{B+D}}$$

The confidence interval for the estimate of RR can be calculated from a logarithmic transformation, where the standard error of $\ln RR$ is:

$$SE(\ln RR) = \sqrt{\frac{1}{A} - \frac{1}{A+C} + \frac{1}{B} - \frac{1}{B+D}}$$

A $100(1-\alpha)\%$ confidence interval for RR can be found by calculating the two quantiles:

$$I_{RR,\ \frac{\alpha}{2}} = \ln RR + N_{\frac{\alpha}{2}} * SE(\ln RR)$$

$$I_{RR,\ \frac{\alpha}{2}} = \ln RR + N_{1-\frac{\alpha}{2}} * SE(\ln RR)$$

Where N_{ϕ} is the appropriate value for the ϕ^{th} percentile of the standard normal distribution.

7.4.2 Random effects meta-analysis

In this appendix, we describe the applied method for conducting random effects meta-analyses (relevant for clinical question 3).

In a fixed effect meta-analysis, it is assumed that all studies are estimating the same (fixed) treatment effect, whereas a random effects meta-analysis allows for differences in the treatment effect from study to study. For that reason, the random effects meta-analysis has become the preferred method when conducting meta-analyses (23).

The overall estimate of the RR can be obtained as a weighted average of the individual estimates of the RR from each study included in the meta-analysis:

$$\ln \overline{RR_{RE}} = \frac{\sum_i w_i' * \ln RR_i}{\sum_i w_i'}$$

Resulting in:

$$\overline{RR_{RE}} = \exp(\ln \overline{RR_{RE}})$$

where the weights equal the inverse of the variance, but the variance is modified by the between-study variance.

Between-study variance refers to variation across study findings beyond random sampling error.

$$w_i' = \frac{1}{SE(\ln RR) + \tau^2}$$

In the above, τ^2 is a measure of the between-study variance and is calculated as:

$$\tau^2 = \frac{Q - df}{\gamma}$$

where

$$Q = \sum_i (w_i * \ln RR_i)^2 - \frac{(\sum_i w_i * \ln RR_i)^2}{\sum_i w_i}$$
$$df = k - 1$$

where k is the number of studies included in the analysis. Lastly,

$$\gamma = \sum_i w_i - \frac{\sum_i w_i^2}{\sum_i w_i}$$

In addition to the above, the standard error for $\overline{RR_{FE}}$ is calculated as:

$$SE(\overline{RR_{RE}}) = \sqrt{\frac{1}{\sum_i w_i + \tau^2}}$$

and the resulting confidence intervals as:

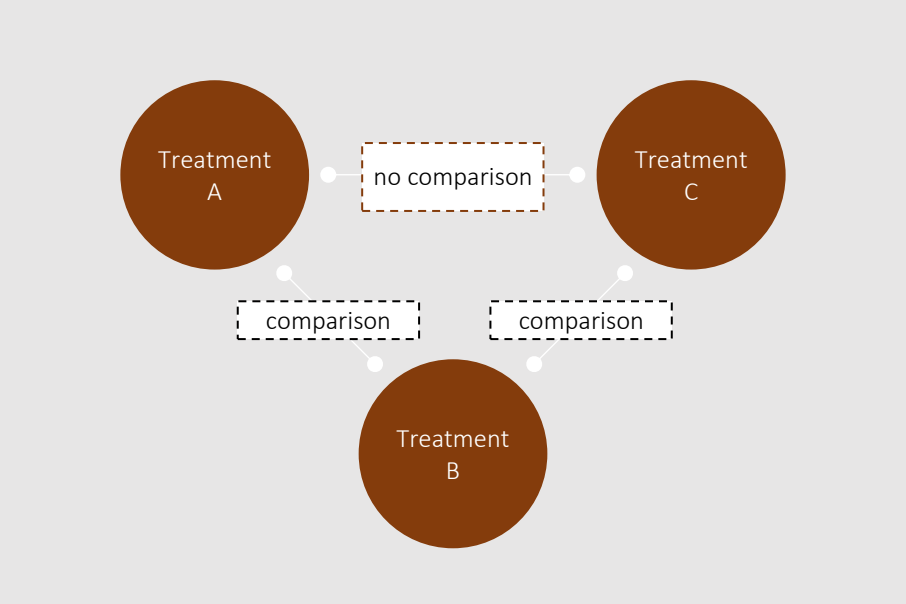
$$I_{\overline{RR_{RE}},\ \frac{\alpha}{2}} = \exp\left(\ln \overline{RR_{RE}} + N_{\frac{\alpha}{2}} * SE(\overline{RR_{RE}})\right)$$
$$I_{\overline{RR_{RE}},\ 1-\frac{\alpha}{2}} = \exp\left(\ln \overline{RR_{RE}} + N_{1-\frac{\alpha}{2}} * SE(\overline{RR_{RE}})\right)$$

7.4.3 Buchers' indirect comparison

In this appendix, we describe the applied method for conducting Buchers' indirect comparison (relevant for clinical question 3).

Buchers and co-authors suggested a simple method of adjusted indirect comparison, in which the indirect comparison of A and C is adjusted according to the results of their direct comparisons with a common intervention, B (17,18). This is illustrated below.

INDIRECT COMPARISON OF TREATMENT A AND TREATMENT B



Let $\ln RR_{\overline{AB}}$ denote log RR, estimated from a meta-analysis (as described above) of the studies that compares treatment A and treatment B. Similarly, we denote $\ln RR_{\overline{CB}}$ as the RR from a meta-analysis of the studies that compares treatment C and treatment B. The log RR of the adjusted indirect comparison of treatment A and C ($\ln RR'_{AB}$) can be estimated as:

$$\text{Ln}\, RR'_{AB} = \ln RR_{\overline{AC}} - \ln RR_{\overline{CB}}$$

$$RR'_{AB} = \exp(\ln RR_{\overline{AC}} - \ln RR_{\overline{CB}})$$

and since the estimates are derived from two independent populations, we must assume independence of the two estimates of $\ln RR_{\overline{AB}}$ and $\ln RR_{\overline{CB}}$, and the standard error of $\text{Ln}\, RR'_{AB}$ can be calculated as:

$$SE(\text{Ln}\, RR'_{AB}) = \sqrt{(SE(\ln RR_{\overline{AC}})^2 + SE(\ln RR_{\overline{BC}})^2}$$

When these two measures are calculated, we can construct the $100(1-\alpha)\%$ confidence interval as:

$$I_{RR'_{AB},\ \frac{\alpha}{2}} = \exp\left(\ln RR'_{AB} + N_{\frac{\alpha}{2}} * SE(RR'_{AB})\right)$$

$$I_{RR'_{AB},\ 1-\frac{\alpha}{2}} = \exp\left(\ln RR'_{AB} + N_{1-\frac{\alpha}{2}} * SE(RR'_{AB})\right)$$

Lastly, we can construct the t-statistic and the p-value of the test: H_0: $RR'_{AB} = 1$ as:

$$t = \frac{\text{Ln}\, RR'_{AB}}{SE(\text{Ln}\, RR'_{AB})}$$

The absolute differences (AD) were estimated using the following formula:

$$\text{AD} = \text{event rate for treatment C} * (RR'_{AB} - 1)$$

7.5 Forest plots from ReVman 5.3

In this appendix, we present forest plots conducted in ReVman 5.3 for the two etanercept studies (Moreland et al. 1999 and the JERA trial) on proportion of subjects who achieve ACR50 response (Figure 8) and the proportion of subjects who discontinue treatment due to AEs (Figure 9).

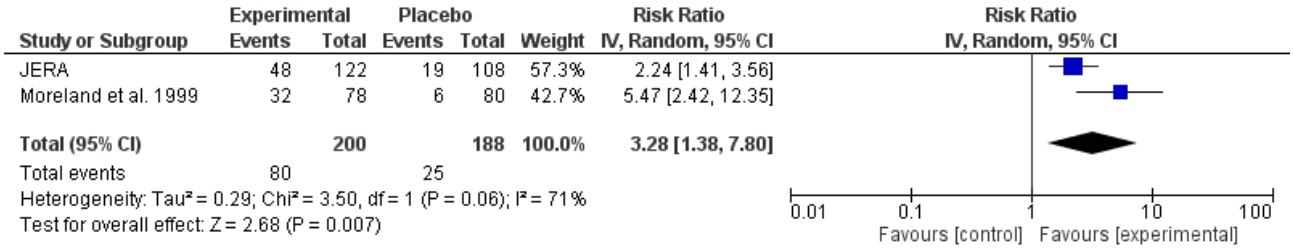


FIGURE 8: FOREST PLOTS FROM REVMAN 5.3 FOR ETANERCEPT ON PROPORTION OF SUBJECTS WHO ACHIEVE ACR50 RESPONSE

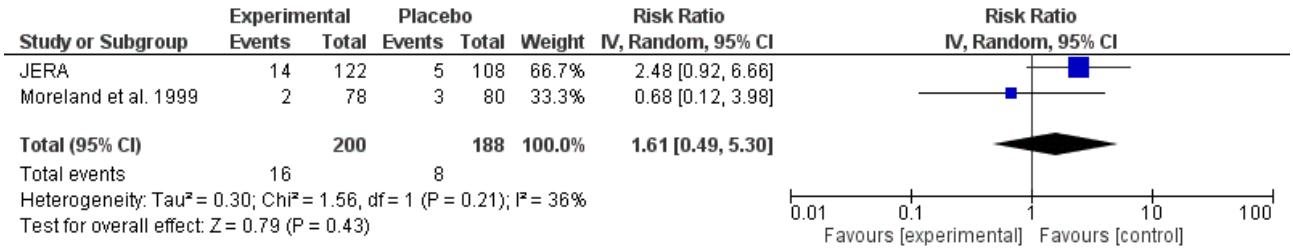


FIGURE 9: FOREST PLOTS FROM REVMAN 5.3 FOR ETANERCEPT ON PROPORTION OF SUBJECTS WHO DISCONTINUE TREATMENT DUE TO AES

7.6 Results per PICO (clinical question)

In this appendix, we present the PICO tables related to clinical question 1 and 3. We were not able to perform comparative analyses related to clinical question 2 and 4. Table 60 is the PICO table related to clinical question 1, and

Table 61 and Table 62 are the PICO tables related to clinical question 3.

TABLE 60: PICO RESULTS RELATED TO CLINICAL QUESTION 1. THE TABLE PROVIDES AN OVERVIEW OF THE COMPARATIVE ANALYSES OF FILGOTINIB AND ADALIMUMAB IN COMBINATION WITH MTX IN BDMARD/TSDMARD-NAÏVE PATIENTS.

Results per outcome	Studies included in the analysis	Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
		Difference	95% CI	*P* value	Risk ratio	95% CI	*P* value	
Proportion of subjects who achieved ACR50 response	FINCH 1	3.5 percentage points	-3.2%; 11.1%	NA	1.060	0.945; 1.188	0.320	Relative difference estimated based on OR from logistic regression. The absolute difference was calculated based on the relative difference. Formulas from the DMC guideline were used.
Proportion of subjects who discontinue treatment due to an AEs	FINCH 1	-0.1 percentage points	-3.6%; 3.1%	0.969	0.988	0.551; 1.773	0.969	Absolute difference in proportions and relative difference presented as risk ratio.
Proportion of subjects who experienced a serious infection	FINCH 1	-0.3 percentage points	-3.0%; 2.3%	0.777	0.889	0.395; 2.004	0.777	Absolute difference in proportions and relative difference presented as risk ratio.
Proportion of subjects who discontinue treatment due to lack of effect	FINCH 1	1.8 percentage points	-1.5%; 4.9%	0.268	1.417	0.761; 2.640	0.272	Absolute difference in proportions and relative difference presented as risk ratio.
Proportion of subjects without radiographic progression (defined as ≤0 change from baseline in mTSS)	FINCH 1	5.2 percentage points	-0.3%; 11.1%	NA	1.063	0.996; 1.135	0.068	Relative difference estimated based on OR from logistic regression. The absolute difference was calculated based on the relative difference. Formulas from the DMC guideline were used.
Proportion of subjects who achieved HAQ-DI response (defined as a	FINCH 1	5.7 percentage points	-0.7%; 12.7%	NA	1.081	0.990; 1.181	0.084	Relative difference estimated based on OR from logistic regression. The absolute difference was calculated based on the relative

reduction from baseline ≥0.22)								difference. Formulas from the DMC guideline were used.

TABLE 61: PICO RESULTS RELATED TO CLINICAL QUESTION 3, SHOWING THE COMPARATIVE ANALYSES OF FILGOTINIB COMPARED TO ETANERCEPT AS MONOTHERAPY IN BDMARD/TSDMARD TREATMENT-NAÏVE PATIENTS: DARWIN 2 VERSUS THE STUDY BY MORELAND ET AL. (1999)

Results per outcome	Studies included in the analysis	Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
		Difference	95% CI	*P* value	Risk ratio	95% CI	*P* value	
Proportion of subjects who achieved ACR50 response	DARWIN 2; The study by Moreland et al. (1999)	-11.67%	-31.02%; 45.20%	NA	0.72	0.24; 2.10	0.54	Absolute difference in effect is estimated assuming event rate for etanercept (the study by Moreland et al. 1999).
Proportion of subjects who discontinue treatment due to AEs	DARWIN 2; The study by Moreland et al. (1999)	-0.61%	-2.46%; 35.17%	NA	0.76	0.04; 14.71	0.86	Absolute difference in effect is estimated assuming event rate for etanercept (the study by Moreland et al. 1999).
Proportion of subjects who experienced a serious infection	DARWIN 2; The study by Moreland et al. (1999)	NA	NA	NA	NA	NA	NA	It is not possible to estimate the absolute or relative difference in effect. In the study by Moreland et al. (1999), this outcome measure was not reported.
Proportion of subjects who discontinue treatment due to lack of effect	DARWIN 2; The study by Moreland et al. (1999)	-4.43%	-14.88%; 84.62%	NA	0.71	0.03; 15.34	0.83	Absolute difference in effect is estimated assuming event rate for etanercept (the study by Moreland et al. 1999).
Proportion of subjects without radiographic progression (defined as ≤0 change in mTSS)	DARWIN 2; The study by Moreland et al. (1999)	NA	NA	NA	NA	NA	NA	It is not possible to estimate the absolute or relative difference in effect. In the DARWIN 2 trial and the study by Moreland et al. (1999), this outcome measure was not reported.
Proportion of subjects who achieved HAQ-	DARWIN 2; The study by	NA	NA	NA	NA	NA	NA	It is not possible to estimate the absolute or relative difference

DI response (defined as ≥0.22 change in HAQ-DI)	Moreland et al. (1999)							in effect. In the study by Moreland et al. (1999), this outcome was not reported.

TABLE 62: PICO RESULTS RELATED TO CLINICAL QUESTION 3, SHOWING THE COMPARATIVE ANALYSES OF FILGOTINIB COMPARED TO ETANERCEPT AS MONOTHERAPY IN BDMARD/TSDMARD TREATMENT-NAÏVE PATIENTS: DARWIN 2 VERSUS A META-ANALYSIS BETWEEN THE STUDY BY MORELAND ET AL. (1999) AND JERA

Results per outcome	Studies included in the analysis	Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
		Difference	95% CI	*P* value	Risk ratio	95% CI	*P* value	
Proportion of subjects who achieved ACR50 response	DARWIN 2; The study by Moreland et al. (1999); JERA	7.76%	-24.39%; 60.00%	NA	1.19	0.39; 3.65	0.76	Absolute difference in effect is estimated assuming event rate for etanercept (the study by Moreland et al. 1999 and JERA).
Proportion of subjects who discontinue treatment due to AEs	DARWIN 2; The study by Moreland et al. (1999); JERA	-5.41%	-7.82%; 28.92%	NA	0.32	0.02; 4.61	0.41	Absolute difference in effect is estimated assuming event rate for etanercept (the study by Moreland et al. 1999 and JERA).
Proportion of subjects who experienced a serious infection	DARWIN 2;JERA	1.31%	-10.95%; 1.45%	NA	10.60	0.12; 960.92	0.30	In the study by Moreland et al. (1999), this outcome measure was not reported. Thus, the estimates are based on the DARWIN 2 trial and the JERA trial. Absolute difference in effect is estimated assuming event rate for filgotinib (DARWIN 2).
Proportion of subjects who discontinue treatment due to lack of effect	DARWIN 2; The study by Moreland et al. (1999); JERA	-0.17%	-7.18%; 92.50%	NA	0.98	0.04; 22.58	0.99	Absolute difference in effect is estimated assuming event rate for etanercept (the study by Moreland et al. 1999 and JERA).
Proportion of subjects without radiographic progression (defined as ≤0 change in mTSS)	DARWIN 2; The study by Moreland et al. (1999); JERA	NA	NA	NA	NA	NA	NA	It is not possible to estimate the absolute or relative difference in effect. In the DARWIN 2 trial and the study by Moreland et al. (1999), this outcome measure was not reported.

Proportion of subjects who achieved HAQ-DI response (defined as ≥0.22 change in HAQ-DI)	DARWIN 2; The study by Moreland et al. (1999); JERA	NA	NA	NA	NA	NA	NA	It is not possible to estimate the absolute or relative difference in effect. In the study by Moreland et al. (1999) and the JERA trial, this outcome was not reported.

Cost per patient and budget impact analysis of filgotinib (Jyseleca®) for the treatment of rheumatoid arthritis

Application to the Danish Medicines Council

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List of abbreviations

AE	Adverse events
bDMARD	Biologic disease-modifying-anti-rheumatic drugs
csDMARD	Conventional synthetic disease-modifying-anti-rheumatic drugs
DANBIO	Danish rheumatologic database
DMC	Danish Medicines Council
MTX	Methotrexate
DMARD	Disease-modifying-anti-rheumatic drug
JAK	Janus Kinase
NSAID	Non-steroidal anti-inflammatory drug
RA	Rheumatoid arthritis
SmPC	Summary of product characteristics
STATs	Signal transducers and activators of transcription
TNF	Tumour Necrosis factor
tsDMARD	Targeted synthetic disease-modifying-anti-rheumatic drug

1 Background

Rheumatoid arthritis (RA) is a chronic, progressive, and systemic autoimmune disease. RA is characterised by inflammation, swelling and pain in and around the joint. RA usually affects the joints of the hands and feet but can occur in any joint. Progressed RA can lead to erosion and destruction of joints and extra-articular manifestations, such as arteriosclerosis and lung involvement. These extra-articular manifestations are associated with increased mortality in RA patients. Common symptoms include swelling, tenderness and stiffness of the joints, which can be present especially when patients get up in the morning and after rest. Patients with RA experience pain and fatigue, as well as a general feeling of discomfort (1).

There is no curative treatment for RA, but early treatment can slow down the disease progression and improve the prognosis. RA treatment is life-long and consists of various immunosuppressive treatment options including disease-modifying anti-rheumatic drugs (DMARDs). Different types of DMARDs exist. The first choice of DMARD is the conventional synthetic DMARD (csDMARD) methotrexate (MTX). If MTX does not have the desired effect, MTX can be combined with other csDMARDs. If low disease activity or remission is not reached with csDMARD combination treatment, the next treatment choice is biologic DMARDs (bDMARD) and targeted synthetic DMARDs (tsDMARD), possibly in combination with MTX (1).

1.1 Filgotinib (Jyseleca®) in a Danish setting

Filgotinib is a small-molecule Janus kinase (JAK) inhibitor and belongs to the tsDMARD drug class. JAKs are intracellular enzymes which transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to influence various cellular processes such as haematopoiesis, and immune cell function. Within the signalling pathway, JAKs phosphorylate and activate signal transducers and activators of transcription (STATs) which modulate intracellular activity, including gene expression. Filgotinib is a preferential inhibitor of JAK1, which is involved in the inflammatory signalling pathway that drives RA progression. It works by blocking the JAK/STAT pathway that mediates pro-inflammatory cytokine signalling and preferentially inhibits JAK1, with >5-fold higher potency for JAK1 over JAK2, JAK3 and TYK2.

Filgotinib is available as 100 mg and 200 mg film-coated tablets. According to the summary of product characteristics (SmPC), the recommended dose of filgotinib in treatment of RA in adults is 200 mg orally once daily, and treatment should be continued (AEs). A starting dose of 100 mg once daily is recommended for patients aged 75 years and older. Filgotinib can be administered as monotherapy or in combination with methotrexate. Information on filgotinib is provided in Table 1.

Table 1 **Filgotinib**

Name	Jyseleca®
Indication	Filgotinib is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs). Filgotinib may be used as monotherapy or in combination with methotrexate.
Strength and dosing	100 mg and 200 mg tablets
ATC-code	L04AA45
Packages	30 tablets
EC-date of approval	24 September 2020

Source: (2,3).

1.2 Patient population

The number of patients treated for RA in Denmark as of 2018 amounts to 22,274 patients according to the Danish rheumatologic database DANBIO (1). Of this population, 5,700 received treatment with bDMARDs/tsDMARDs, which means that most patients are treated with csDMARDs alone or in combination with bDMARDs/tsDMARDs. For some patients, bDMARDs/tsDMARDs as monotherapy is the only treatment option. The Danish Medicines Council's (DMC) protocol on filgotinib refers to a study by Jørgensen et al. 2015, who found that 19% of the 5,700 patients in bDMARD/tsDMARD treatment is treated with bDMARDs/tsDMARDs as monotherapy (approximately 1,100 patients) (4).

The average incidence of patients receiving treatment with bDMARDs/tsDMARDs (treatment-naïve patients) has been 250 patients per year since 2010, and approximately 500 treatment-naïve patients on average before 2010. Therefore, the expert committee assess that the real incidence of treatment-naïve patients is between 250-500.

It is estimated that approximately 10-15% of the 5,700 patients treated with bDMARDs/tsDMARDs will switch treatment within a year due to lack of effect or AEs. This means that approximately 700 patients will have switched treatment over the course of a year and be classified as treatment-experienced patients (1).

1.3 Clinical questions

The purpose of the cost per patient analysis is to estimate the incremental cost per patient for the intervention (filgotinib) compared with the comparators (adalimumab and etanercept) (1). In addition, the purpose of the budget impact analysis is to estimate the financial consequences for the healthcare budgets with and without the recommendation of filgotinib. To estimate both the cost per patient and the budget impact, the details of the clinical questions are used as input and parameters for the analyses. The DMC protocol on filgotinib for the treatment of RA lists the following four clinical questions:

1) **What is the value of filgotinib in combination with MTX compared with adalimumab in combination with MTX in treatment-naïve patients with moderate to severe chronic RA?**

   Population: Patients on MTX treatment who have moderate to severe disease activity despite the MTX treatment.

   Intervention: Filgotinib 200 mg administered orally once daily in combination with MTX.

   Comparator: Adalimumab 40 mg administered subcutaneously once every second week in combination with MTX.

2) **What is the value of filgotinib in combination with MTX compared with adalimumab in combination with MTX in treatment-experienced patients with moderate to severe chronic RA?**

   Population: Patients on MTX treatment who have moderate to severe disease activity despite treatment with bDMARDs/tsDMARDs.

   Intervention: Filgotinib 200 mg administered orally once daily in combination with MTX.

   Comparator: Adalimumab 40 mg administered subcutaneously once every second week in combination with MTX.

3) **What is the value of filgotinib as monotherapy compared with etanercept as monotherapy in treatment-naïve patients with moderate to severe chronic RA?**

   Population: Patients with moderate to severe disease activity who are bDMARD/tsDMARD-naïve and where treatment with csDMARDs is not possible.

   Intervention: Filgotinib 200 mg administered orally once daily.

   Comparator: Etanercept 50 mg administered subcutaneously once every week.

4) **What is the value of filgotinib as monotherapy compared with etanercept as monotherapy in treatment-experienced patients with moderate to severe chronic RA?**

   Population: Patients with moderate to severe disease activity despite treatment with bDMARDs/tsDMARDs and where treatment with csDMARDs is not possible.

   Intervention: Filgotinib 200 mg administered orally once daily.

   Comparator: Etanercept 50 mg administered subcutaneously once every week.

2 Method: Cost per patient analysis

As mentioned, the purpose of this analysis is to estimate the incremental cost of treating RA patients with filgotinib compared with adalimumab and etanercept (described further below). The comparison is informed primarily by the following sources: SmPCs on filgotinib and comparators, the DMC protocol on filgotinib and the DMC extended standard of reference (ESR) on RA (1,3,5).

The cost per patient analysis is performed by applying a simple cost model and has a limited societal perspective in accordance with the DMC guidelines (6). The analysis has a time horizon of 18 months, and the rationale for choosing a time horizon of 18 months is based on the DMC RA ESR, completed by Amgros on behalf of the DMC (5). The DMC RA ESR states that the RA expert committee has estimated an average treatment duration of 18 months.

2.1 Applied model

A simple Excel model was developed for the cost per patient and budget impact analyses. The Excel model is submitted along with this application. The rationale for choosing a simple cost model is the relatively simple disease and treatment pathway of RA, negating the need for more complex health state models.

2.2 Intervention

The intervention in the model is filgotinib 200 mg tablets in combination with MTX (clinical question 1 and 2) or as monotherapy (clinical question 3 and 4). According to the SmPC on filgotinib, filgotinib 200 mg should be administered once daily. Treatment should be continued until the patient stops responding effectively to treatment or undesired AEs emerge.

2.3 Comparators

The comparator in the cost per patient analysis in clinical question 1 and 2 is adalimumab in combination with MTX. In the cost per patient analysis of clinical question 3 and 4, the comparator is etanercept as monotherapy.

Adalimumab

Adalimumab is a recombinant human monoclonal antibody belonging to the bDMARDs that inhibits tumor necrosis factor. Adalimumab is available as pre-filled pens or syringes with 40 mg adalimumab for subcutaneous injection. Adalimumab is also available as a biosimilar (7).

Etanercept

Etanercept is a fusion protein that inhibits tumour necrosis factor (TNF) and belongs to the bDMARDs Etanercept is available in pre-filled syringes containing 25 mg etanercept and pre-filled syringes containing 50 mg etanercept for injection. It is also available in pre-filled pens with 25 mg or 50 mg etanercept for injection. Etanercept is available as a biosimilar medicinal product (8).

MTX

Methotrexate (4-amino-10-methylfolic acid) is a folic acid antagonist which inhibits the reduction of folic acid and increase of tissue cells (9). MTX is available in different forms; however, tablets with 2.5 mg of MTX for peroral treatment is included in this analysis.

2.4 Combination therapy

For clinical question 1 and 2, the treatment of patients consists of combination therapy. Filgotinib is administrated (200 mg) daily in combination with MTX, and adalimumab is administered (40 mg) every second week in combination with MTX. We assume an average MTX dosing of 15,3 mg per week based on the mean dose reported in FINCH 1 (10). This is in line with MTX dosing previously reported for combination therapy from the DANBIO registry (11–13).

2.5 Perspective of the analysis

The cost per patient analysis has a limited societal perspective, following the DMC guidelines (6). All costs and results are reported at 2020 price level.

2.6 Time horizon

The health economic model applies a time horizon of 18 months in the base case analysis. The time horizon is based on the DMC ESR for RA. We have chosen a time horizon of 18 months because the RA expert committee states in the ESR that an average treatment duration before an average patient switches treatment is 18 months. In addition, the model includes a 12-month time horizon option. The reason for including the 12 months' time horizon is because it is used in the budget impact model. The model is not flexible, since the relevant treatment period is 18 months, as stated in the ESR (5).

2.7 Discounting

Costs incurred after year 1 (months 13-18) is discounted with a 4% annual discount rate in accordance with the guidelines from the Danish Ministry of Finance (14). Because the cost per patient analysis applies a time horizon of 18 months, we could have discounted the costs incurred after year 1 (months 13-18) using a monthly discounting method. However, we chose not to do so, because this would have a minimal impact on the results.

2.8 Resource use and unit costs

The cost per patient analysis of filgotinib includes drug costs, hospital administration costs, patient costs and transportation costs. However, cross-sectorial costs, costs of background treatments, except for MTX, and adverse event (AE) costs are not included in the present analysis. These costs are excluded because we assume that there will be no cost difference between filgotinib and the comparators in these cost categories.

Drug costs

Drug costs of filgotinib, adalimumab, etanercept and MTX were based on pharmacy purchasing prices (PPP). The prices of adalimumab, etanercept and MTX were obtained from www.medicinpriser.dk (11 November 2020), and for the price of filgotinib we apply the same price per tablet as for the JAK inhibitor upadacitinib (RINVOQ) as of 11 November 2020. Information on drug costs are presented in Table 2.

Table 2 **Drug costs**

	Strength (mg)	Package size	Price AIP (DKK)
Filgotinib (Jyseleca®)	200	30 tablets	7,116
Adalimumab (Hyrimoz®)	40	2 injections	7,151
Etanercept (Benepali®)	50	4 injections	6,336
Methotrexate (Emthexate TEVA®)	2.5	100 tablets	68

Source: Medicinpriser.dk, 11 November 2020

Hyrimoz® and Benepali® are chosen based on the current DMC recommendations as of July 2020 (15)

Hospital administration costs

Hospital administration costs when treating RA patients with filgotinib, adalimumab and etanercept were estimated based on the DMC ESR for RA completed by Amgros on behalf of the DMC (5). The DMC RA ESR includes a detailed description of the resource use associated with treating RA patients with bDMARDs/tsDMARDs in a Danish hospital setting. The DMC ESR is based

on a micro-costing approach and was completed in June 2020, and costs were therefore presented in 2020 prices. We assume that the ESR provides an accurate estimate of the hospital costs associated with treating RA patients with the included alternatives, because it is completed based on the RA expert committee's description of the treatment pathway with bDMARDs/tsDMARDs.

Filgotinib is not included in the DMC ESR for RA. To estimate the hospital administration costs associated with filgotinib treatment, we used the hospital administration costs published in the DMC ESR for other JAK inhibitors, which are also administered orally. Information regarding hospital administration costs for filgotinib can be seen in Table 3.

Table 3 **Assumed hospital administration costs per patient, 18 months, filgotinib**

Resource	Costs (DKK)	Method
Doctor	2,753	Micro-costing
Nurse	1,852	Micro-costing
Rooms and wards	65	Micro-costing
Cost of utensils	0	Micro-costing
Diagnostic procedures	1,437	Micro-costing

Source: DMC ESR for RA.

To estimate the hospital administration costs for adalimumab and etanercept, the DMC ESR for RA were used, since both treatments are included. The hospital administration costs for adalimumab and etanercept are estimated to be identical in the DMC ESR for RA (5), as shown in Table 4.

Table 4 **Hospital administration costs per patient, 18 months, adalimumab and etanercept**

Resource	Costs (DKK)	Method
Doctor	2,550	Micro-costing
Nurse	2,114	Micro-costing
Rooms and wards	72	Micro-costing
Cost of utensils	78	Micro-costing
Diagnostic procedures	1,421	Micro-costing

Source: DMC ESR for RA.

Patient and transportation costs

Patient and transportation costs were included in accordance with the DMC guidelines (6). The estimation of patient and transportation costs associated with the drug alternatives was based on

the ESR for RA as well, with the same argument as stated for the hospital administration costs. The patient and transportation costs associated with filgotinib were based on these costs estimated for tofacitinib and baricitinib in the DMC ESR for RA, which are also orally administered JAK inhibitors. Information regarding patient and transportation costs for filgotinib can be seen in Table 5.

Table 5 **Patient and transportation costs per patient, 18 months, filgotinib**

Resource	Costs (DKK)	Method
Patient time	1,284	Micro-costing
Transport	1,651	Micro-costing

Source: DMC ESR for RA.

The patient and transportation costs associated with adalimumab were also based on the DMC ESR for RA. In Table 6, the information regarding adalimumab is illustrated.

Table 6 **Patient and transportation costs per patient, 18 months, adalimumab**

Resource	Costs (DKK)	Method
Patient time	2,256	Micro-costing
Transport	1,642	Micro-costing

Source: DMC ESR for RA.

The patient and transportation costs associated with etanercept were based on the DMC ESR for RA. In Table 7, the information regarding etanercept is presented.

Table 7 **Patient and transportation costs per patient, 18 months, etanercept**

Resource	Costs (DKK)	Method
Patient time	3,211	Micro-costing
Transport	1,642	Micro-costing

Source: DMC ESR for RA

Adverse events

As mentioned, AE costs were not included in the cost per patient analysis, because we assume there is no difference in the AEs requiring treatment between filgotinib, adalimumab and etanercept.

The assumption of no difference between filgotinib and adalimumab is based on the FINCH 1 trial, where filgotinib is compared directly with adalimumab. We focused on data on serious AEs and treatment emerged (TE) AEs leading to discontinuation of treatment, which was the AE outcomes requested in the protocol from the medicines council. In the FINCH 1 trial, TE serious AEs were experienced by 35 (7.4%) subjects in the filgotinib arm versus 22 (6.8%) subjects in the adalimumab arm. TE serious AEs that were related to study drug were experienced by 17 (3.6%) subjects in the filgotinib arm versus 10 (3.1%) subjects in the adalimumab arm. 26 (5.5%) subjects in the filgotinib arm and 18 (5.5%) subjects in the adalimumab arm discontinued treatment prematurely due to a treatment emerged AE.

No studies comparing filgotinib and etanercept directly exists, which makes it difficult to compare the safety profiles of filgotinib and etanercept. Therefore, the comparison of the safety profiles of filgotinib and etanercept is based on the SmPC on the two drugs with a presentation of the AE outcomes requested in the protocol from the medicines council. Many of the reported AEs in the SmPC for filgotinib are also reported in the SmPC for etanercept (e.g. nausea, infections such as upper respiratory tract infections and urinary infections, opportunistic infections such as tuberculosis, and severe infections). Furthermore, the management of these AEs described in the SmPC are similar for the two products. The most common serious infection reported for filgotinib is pneumonia. The serious infections reported in the SmPC on etanercept are sepsis, tuberculosis, opportunistic infections including invasive fungal infections, listeriosis and legionellosis. These infections were due to bacteria, mycobacteria, fungi, viruses, and parasites (including protozoa). Based on this, we find it acceptable to assume that there is no difference in the safety profiles, because neither of the two drugs have a safety profile that is more preferable than the other.

2.9 Sensitivity analyses

We have chosen not to include a sensitivity analysis in the cost per patient analysis, because the analysis is based on the DMC ESR (5).

2.10 Overview of base case settings in the model

Table 8 provides an overview of the base case settings in the cost per patient analysis and possible alternative settings in the model.

Table 8 **Overview of base case settings and possible alternative settings in the cost per patient model**

	Base-case	Alternative settings/comments
Applied model	Simple cost model	
Intervention	Filgotinib	
Comparator	Adalimumab and MTX, etanercept	None
Time horizon	18 months	12 months
Discount rate	4%	The discount rate can be varied.
Perspective	Limited societal	None
Included costs	Drug costs Hospital administration costs Patient and transportation cost	All included costs can be varied in the model.
Applied unit costs	Pharmacy purchasing price DMC estimated standard reference DMC unit prices	Other costs are assumed to be equal for filgotinib, adalimumab and etanercept.
Dose and number of treatments	200 mg tablet daily	None
Administration form	Peroral	None
Inclusion of waste	No	None
OS modelling	Not applied/not relevant	

3 Results: Cost per patient analysis

In this section, we present the results of the four parts of the cost per patient analyses. We have estimated the cost of treating an average RA patient with filgotinib in combination with MTX and as monotherapy compared with adalimumab in combination with MTX and etanercept as monotherapy.

3.1 Clinical question 1 and 2

The incremental cost of treating RA patients with filgotinib tablets compared with adalimumab injections is DKK – 10,915 over a time horizon of 18 months. Since both clinical question 1 and 2 relate to the comparison of filgotinib and adalimumab in combination therapy (with different populations), the cost per patient will be identical. The results of the cost per patient analysis of the comparison between filgotinib and adalimumab are presented in Table 9.

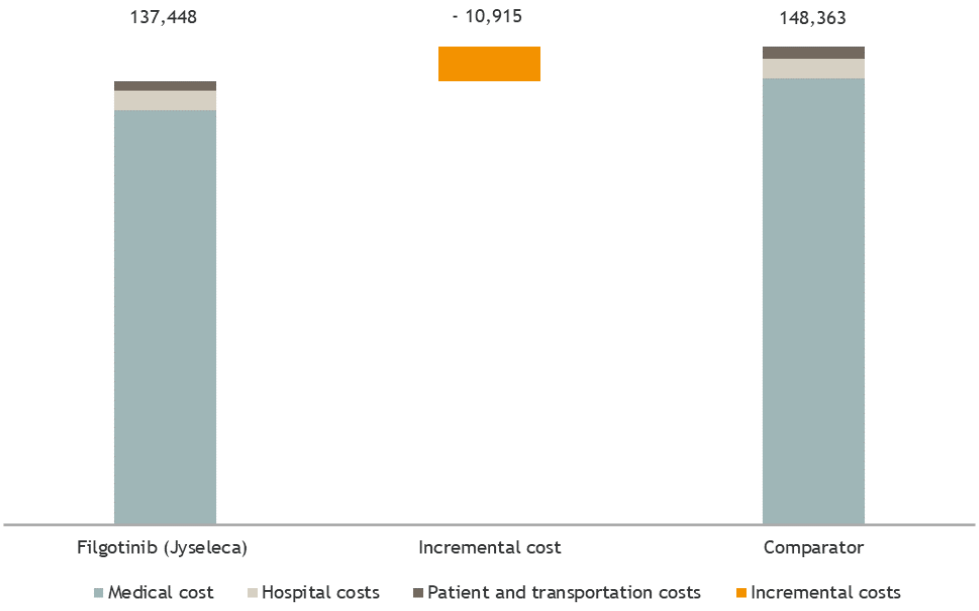
Table 9 **Costs per patient analysis, filgotinib/adalimumab, 18 months, discounted (DKK)**

	Filgotinib	Adalimumab	Incremental cost
Drug costs (including MTX)	128,522	138,360	- 9,838
Hospital costs	6,029	6,155	- 126
Patient and transportation costs	2,897	3,848	- 951
Total	**137,448**	**148,363**	**-10,915**

Source: Own calculations.

The incremental cost of treating RA patients with filgotinib compared with adalimumab is illustrated in Figure 1.

Figure 1 **Incremental cost per patient filgotinib/adalimumab**



3.2 Clinical question 3 and 4

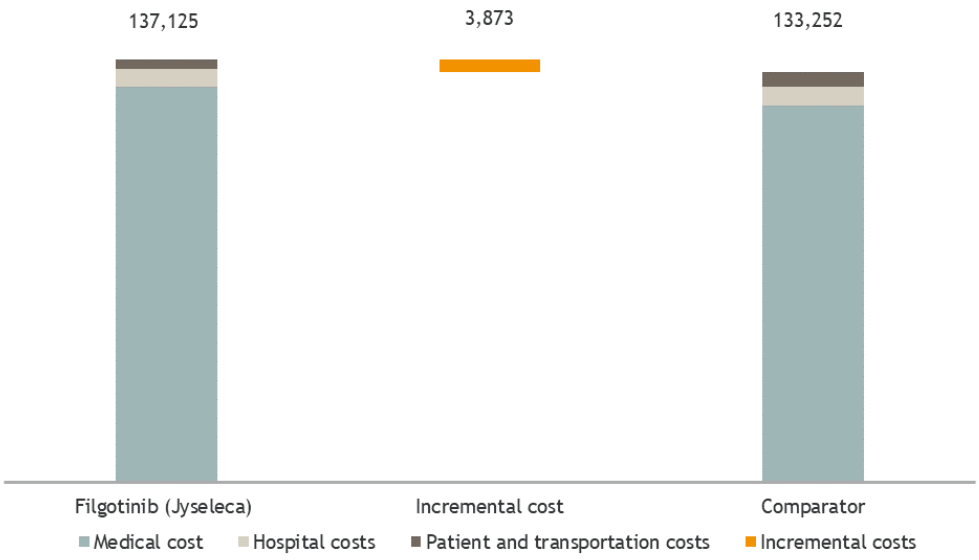
The incremental cost of treating RA patients with filgotinib tablets compared with etanercept injections is DKK 3,873 over a time horizon of 18 months. Since both clinical question 3 and 4 relate to the comparison of filgotinib and etanercept in monotherapy (with different populations), the cost per patient will be identical. The results of the cost per patient analysis of the comparison between filgotinib and etanercept are presented in Table 10.

Table 10 **Costs per patient analysis, filgotinib/etanercept, 18 months, discounted (DKK)**

	Filgotinib	Etanercept	Incremental cost
Drug costs	128,199	122,307	5,893
Hospital costs	6,029	6,155	- 126
Patient and transportation costs	2,897	4,791	- 1,893
Total	**137,125**	**133,252**	**3,873**

The incremental cost of treating RA patients with filgotinib compared to etanercept is illustrated in Figure 2.

Figure 2 **Incremental cost per patient filgotinib/etanercept**



4 Method: Budget impact analysis

The purpose of the budget impact analysis is to estimate the budgetary impact of recommending filgotinib as the standard treatment of moderate to severe RA at Danish hospitals. The budget impact is estimated per year in the first five years after the recommendation of filgotinib. The budget impact analysis compares the costs for the Danish regions in the scenario where filgotinib is recommended as a possible standard treatment and the scenario where filgotinib is not recommended as a possible standard treatment of RA. The total budget impact per year is the difference between the two scenarios. The costs in the budget impact are based on the cost per patient analysis (above) but exclude patient and transportation costs and are undiscounted costs.

The general methodology of the budget impact model is to multiply the cost per patient with the number of patients in the populations stated by the DMC protocol (1). The calculation of the budget impact is based specifically on the multiplication of the estimated 18 months cost per patient. To perform an accurate allocation of costs to each year: 12 months of costs are allocated to every new patient in the first year that they enter the model. In addition, 6 months of costs are allocated in the second year the patient is in the model.

4.1 Market share

If filgotinib is recommended as standard treatment, we assume an increasing uptake over the five years, starting with 2% in year 1 and ending with a market share (or patient uptake) of 10% in year 5 (see Table 11).

Table 11 **Market share each year in the budget impact analysis**

	Year 1	Year 2	Year 3	Year 4	Year 5
Recommended	2%	4%	6%	8%	10%
Not recommended	0%	0%	0%	0%	0%

Source: Assumption.

4.2 Patient numbers

The expert committee estimates that 700 treatment-experienced patients would be eligible for treatment with filgotinib and could be offered the therapy if it is approved as a standard treatment in Denmark. Additionally, the expert committee estimates that an average of 250 to 500 treatment-naïve patients each year would need treatment and could be offered filgotinib

therapy (1). Based on this, we include 700 treatment-experienced patients in the budget impact analysis. In addition, we include 250 treatment-naïve patients in the budget impact analysis. We assume 250, since these are the most recent numbers (2010-) compared to 500 treatment-naïve (before 2010). According to the DMC protocol on filgotinib, 19% of RA patients are treated with bDMARDs/tsDMARDs as monotherapy, and 81% are treated with bDMARDs/tsDMARDs in combination with csDMARDs. According to the ESR, the average treatment period is 18 months; hence, the patients will stay in the model for 18 months.

Clinical question 1

The number of patients eligible for treatment each year in the budget impact analysis varies between the different clinical questions. All patient numbers for each year are based on the DMC protocol on filgotinib (1). Hence, a constant number of new patients over the five years is assumed. Clinical question 1 relates to treatment-naïve patients in combination therapy. Of the treatment-naïve patients (250), we assume that 81% are in combination therapy and that 2% of these will start filgotinib treatment, based on the market shares seen in Table 11. All new patients will stay in the model for 18 months (costs are allocated for 18 months per new patient). The estimated number of new patients treated with filgotinib and adalimumab per year with recommendation is presented in Table 12.

Table 12 **Number of new patients treated with filgotinib and adalimumab with recommendation of filgotinib**

	Year 1	Year 2	Year 3	Year 4	Year 5
Filgotinib	4	8	12	16	20
Adalimumab	198	194	190	186	182

Source: Calculations based on the DMC protocol.
Please note that the number of new patients is rounded.

Given the number of new patients treated on filgotinib and adalimumab with recommendation of filgotinib, the number of patients treated with filgotinib and adalimumab is estimated in a scenario where filgotinib is not recommended. The estimates for both treatments are shown in Table 13.

Table 13 **Number of new patients treated with filgotinib and adalimumab without recommendation of filgotinib**

	Year 1	Year 2	Year 3	Year 4	Year 5
Filgotinib	0	0	0	0	0
Adalimumab	203	203	203	203	203

Source: Calculations based on the DMC protocol and assumptions.
Please note that the number of new patients is rounded.

Clinical question 2

Clinical question 2 relates to treatment-experienced patients in combination therapy. Of the applied treatment-experienced patients (700), we assume that 81% are in combination therapy, and based on the market share in Table 11, 2% of these will start filgotinib treatment. All other assumptions are similar to that of clinical question 1. The estimated number of patients relevant to clinical question 2 is presented in Table 14.

Table 14 **Number of new patients treated with filgotinib and adalimumab with recommendation of filgotinib**

	Year 1	Year 2	Year 3	Year 4	Year 5
Filgotinib	11	23	34	45	57
Adalimumab	556	544	533	522	510

Source: Calculations based on the DMC protocol.
Please note that the number of new patients is rounded.

Given the number of new patients treated on filgotinib and adalimumab with recommendation of filgotinib, the number of patients treated with filgotinib and adalimumab is estimated in a scenario where filgotinib is not recommended. The estimates for both treatments are shown in Table 15.

Table 15 **Number of new patients treated with filgotinib and adalimumab without recommendation of filgotinib**

	Year 1	Year 2	Year 3	Year 4	Year 5
Filgotinib	0	0	0	0	0
Adalimumab	567	567	567	567	567

Source: Calculations based on the DMC protocol and assumptions.
Please note that the number of new patients is rounded.

Clinical question 3

Clinical question 3 relates to treatment-naïve patients in monotherapy. Of the applied number of treatment-naïve patients (250), we assume that 19% are in monotherapy, and based on the assumed market share, 2% of these will be start filgotinib treatment. All other assumptions are similar to that of clinical question 1. The estimated number of new patients treated with filgotinib and etanercept per year with recommendation is presented in Table 16.

Table 16 **Number of new patients treated with filgotinib and etanercept with recommendation of filgotinib**

	Year 1	Year 2	Year 3	Year 4	Year 5
Filgotinib	1	2	3	4	5
Etanercept	47	46	45	44	43

Source: Calculations based on the DMC protocol.
Please note that the number of new patients is rounded.

Given the number of new patients treated on filgotinib and etanercept with recommendation of filgotinib, the number of patients treated with filgotinib and etanercept is estimated in a scenario where filgotinib is not recommended. The estimates for both treatments are shown in Table 17.

Table 17 **Number of new patients treated with filgotinib and etanercept without recommendation of filgotinib**

	Year 1	Year 2	Year 3	Year 4	Year 5
Filgotinib	0	0	0	0	0
Etanercept	48	48	48	48	48

Source: Calculations based on the DMC protocol and assumptions.
Please note that the number of new patients is rounded.

Clinical question 4

Clinical question 4 relates to treatment-experienced patients in monotherapy. From the applied number of treatment-experienced patients (700), we assume that 19% are in monotherapy and based on the assumed market share, 2% of these will start filgotinib treatment. All other assumptions are similar to that of clinical question 1. The estimated number of new patients treated with filgotinib and etanercept per year with recommendation of filgotinib is presented in Table 18.

Table 18 **Number of new patients treated with filgotinib and etanercept with recommendation of filgotinib**

	Year 1	Year 2	Year 3	Year 4	Year 5
Filgotinib	3	5	8	11	13
Etanercept	130	128	125	122	120

Source: Calculations based on the DMC protocol.
Please note that the number of new patients is rounded.

Given the number of new patients treated on filgotinib and etanercept with recommendation of filgotinib, the number of patients treated with filgotinib and etanercept is estimated in a scenario where filgotinib is not recommended. The estimates for both treatments are shown in Table 19.

Table 19 **Number of new patients treated with filgotinib and etanercept without recommendation of filgotinib**

	Year 1	Year 2	Year 3	Year 4	Year 5
Filgotinib	0	0	0	0	0
Etanercept	133	133	133	133	133

Source: Calculations based on the DMC protocol and assumptions.
Please note that the number of new patients is rounded.

4.3 Sensitivity analyses

For clinical questions 1 and 3, we performed sensitivity analyses on the number of patients. The reason for doing so is the range (250-500) of treatment-naïve patients stated in the DMC protocol (1).

5 Results: Budget impact analysis

In this section, we present the results of the budget impact analysis.

Clinical question 1

The budget impact in the scenario where filgotinib is recommended as standard of care (SoC) shows a budget impact of DKK - 190,763 in year 5. The budget impact in each year can be seen in Table 20.

Table 20 **The budget impact in each year in the scenario where filgotinib + MTX is recommended as SoC for the treatment of RA in treatment-naïve patients and the budget impact in the scenario where it is not recommended (DKK)**

	Year 1	Year 2	Year 3	Year 4	Year 5
With recommendation	19,735,644	29,576,214	29,535,336	29,494,459	29,453,581
Without recommendation	19,762,896	29,644,344	29,644,344	29,644,344	29,644,344
Budget impact	-27,252	-68,130	-109,007	-149,885	-190,763

Clinical question 2

The budget impact in the scenario where filgotinib is recommended as SoC shows a budget impact of DKK - 534,137 in year 5. The budget impact in each year can be seen in Table 21.

Table 21 **The budget impact in each year in the scenario where filgotinib + MTX is recommended as SoC for the treatment of RA in treatment-experienced patients and the budget impact in the scenario where it is not recommended as SoC (DKK)**

	Year 1	Year 2	Year 3	Year 4	Year 5
With recommendation	55,259,803	82,813,400	82,698,942	82,584,484	82,470,026
Without recommendation	55,336,109	83,004,163	83,004,163	83,004,163	83,004,163
Budget impact	-76,305	-190,763	-305,221	-419,679	-534,137

Clinical question 3

The budget impact in the scenario where filgotinib is recommended as SoC shows a budget impact of DKK 25,896 in year 5. The budget impact in each year can be seen in Table 22.

Table 22 **The budget impact in each year in the scenario where filgotinib as monotherapy is recommended as SoC for the treatment of RA in treatment-naïve patients and the budget impact in the scenario where it is not recommended as SoC (DKK)**

	Year 1	Year 2	Year 3	Year 4	Year 5
With recommendation	4,124,483	6,190,424	6,195,973	6,201,522	6,207,071
Without recommendation	4,120,783	6,181,175	6,181,175	6,181,175	6,181,175
Budget impact	3,699	9,248	14,798	20,347	25,896

Clinical question 4

The budget impact in the scenario where filgotinib is recommended shows a budget impact of DKK 72,508 in year 5. The budget impact in each year can be seen in Table 23.

Table 23 **The budget impact in each year in the scenario where filgotinib as monotherapy is recommended as SoC for the treatment of RA in treatment-experienced patients and the budget impact in the scenario where it is not recommended as SoC (DKK)**

	Year 1	Year 2	Year 3	Year 4	Year 5
With recommendation	11,548,552	17,333,186	17,348,723	17,364,261	17,379,798
Without recommendation	11,538,194	17,307,290	17,307,290	17,307,290	17,307,290
Budget impact	10,358	25,896	41,433	56,970	72,508

5.1 Sensitivity analyses

We have performed sensitivity analyses to test for uncertainties. In the DMC protocol, the estimated range of new treatment-naïve patients is between 250-500. In the base case model, we assume 250 patients, and to test this assumption, we have performed a sensitivity analysis by simply changing the number to 500 patients. The results can be seen in table Table 24.

Table 24 **Sensitivity analysis showing the budget impact (difference) in year 5 with 250 treatment-naïve patients and 500 treatment-naïve patients for each clinical question, DKK**

	Clinical question 1 - budget impact in year 5	Clinical question 3 - budget impact in year 5
Budget impact 250 patients	-190,763	25,896
Budget impact 500 patients	-381,526	51,791

Source: Own calculations.

The sensitivity analysis is only relevant for clinical question 1 and 3, since the DMC protocol states a range (250-500). For clinical question 2 and 4, the number of treatment-experienced patients is stated as exactly 700 in the DMC protocol (1).

6 Concluding remarks

In this analysis, we have estimated the cost per patient and budget impact of introducing filgotinib as standard treatment for patients diagnosed with RA in Denmark. We have applied a simple cost model, estimating the cost per patient and budget impact of filgotinib compared to adalimumab and etanercept.

Given these assumptions, the incremental cost per patient is estimated to DKK - 10,915 over a time horizon of 18 months for filgotinib compared with adalimumab, and the total budget impact is estimated to DKK - 190,763 after five years for clinical question 1 and DKK - 534,137 for clinical question 2.

Moreover, the incremental cost per patient is estimated to DKK 3,873 over a time horizon of 18 months for filgotinib compared with etanercept, and the total budget impact is estimated to DKK 25,896 after five years for clinical question 3 and DKK 72,508 for clinical question 4.

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Medicinrådet

Medicinrådets protokol for vurdering af filgotinib til behandling af kronisk leddegigt

Versionsnr.: 1.0

Medicinrådet

Om Medicinrådet

Medicinrådet er et uafhængigt råd etableret af Danske Regioner.

Medicinrådet vurderer, om nye lægemidler og indikationsudvidelser skal anbefales som mulig standardbehandling. Medicinrådet udarbejder også behandlingsvejledninger og rekommandationer for anvendelse af medicin på sygehusene. Derudover kan Medicinrådet tage andre typer sager op, der handler om medicinanvendelse.

Om protokollen

Protokollen beskriver, hvordan Medicinrådet vil foretage vurderingen af lægemidlets værdi for patienterne. Den indeholder ét eller flere kliniske spørgsmål, som den ansøgende virksomhed skal besvare i sin endelige ansøgning. Til hvert spørgsmål knytter sig en definition af patientgruppen, det lægemiddel, vi undersøger, den behandling, vi sammenligner med, og effektmålene. Udover de(t) kliniske spørgsmål indeholder protokollen også en beskrivelse af, hvordan litteratursøgning, -selektion og databehandling skal foregå.

Protokollen er udarbejdet med udgangspunkt i *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*, som du kan finde på Medicinrådets hjemmeside under siden Metoder, og den ansøgende virksomheds foreløbige ansøgning, der fortæller, hvilke data der findes for lægemidlet.

Fremkommer der nye og væsentlige oplysninger i sagen af betydning for protokollens indhold, kan Medicinrådet tage protokollen op til fornyet behandling. Det samme gælder, hvis der er begået væsentlige fejl i forbindelse med sagsbehandlingen vedrørende protokollen. Hvis Medicinrådet foretager ændringer i protokollen, vil ansøgende virksomhed få besked.

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1 Begreber og forkortelser

ACR50	*American College of Rheumatology 50 % response*
bDMARD:	Biologisk *Disease Modifying Anti-Rheumatic Drug*
CRP	C-reaktivt protein
csDMARD	Konventionelt syntetisk *Disease Modifiying Anti-Rheumatic Drug*
DANBIO	Dansk Reumatologisk Database
DMARD	*Disease Modifying Anti-Rheumatic Drug*
EMA	Det Europæiske Lægemiddelagentur (*European Medicines Agency)*
EPAR	*European Public Assessment Report*
EULAR	*European League Against Rheumatism*
GRADE	System til at vurdere evidens (*Grading of Recommendations, Assessment, Development and Evaluation*)
HAQ-DI	*Health Assessment Questionnaire Disability Index*
ITT	*Intention to treat*
JAK	Janus kinase
MTX	Methotrexat
PICO	Population, intervention, komparator og effektmål (*Population, Intervention, Comparison and Outcome)*
SAE	Alvorlig uønsket hændelse (*Serious Adverse Event)*
SMD	*Standardized Mean Difference*
TNF	Tumor nekrosis faktor
tsDMARD	Targeteret syntetisk *Disease Modifying Anti-Rheumatic Drug*
TSS	*Total Sharp Score*

2 Introduktion

Protokollen er udarbejdet, fordi Medicinrådet har modtaget en foreløbig ansøgning fra Gilead Sciences, som ønsker, at Medicinrådet vurderer filgotinib til behandling af patienter med kronisk leddegigt. Vi modtog den foreløbige ansøgning den 13. juli 2020.

2.1 Kronisk leddegigt

Kronisk leddegigt er en systemisk og fremadskridende sygdom [1], der er karakteriseret ved betændelse i led og lednære strukturer, hvilket kan medføre leddestruktion. De vigtigste symptomer er ledhævelser og ledsmerter, der medfører nedsat funktionsevne. For en betydelig del af patienterne er funktionsevnen nedsat i en sådan grad, at de bliver helt eller delvist uarbejdsdygtige. Udover leddestruktion kan sygdommen medføre symptomer fra andet end led, bl.a. hjerte-kar-sygdomme. Kronisk leddegigt er forbundet med øget dødelighed, især pga. hjerte-kar-sygdomme, åreforsnævring og lungeinvolvering. Der er mange forskellige årsager, som spiller sammen ved udvikling af kronisk leddegigt, hvor genetik (visse vævstyper) og miljøfaktorer (fx tobaksrygning) spiller en rolle.

Sygdommen klassificeres efter 2010 ACR/EULAR, hvilket er kriterier, som er defineret af American College of Rheumatology (ACR) og European League Against Rheumatism (EULAR) [2]. Klassifikationen er baseret på antal involverede led, blodprøver (autoimmun serologi og akutfase respons), og hvor længe symptomerne har varet.

Kronisk leddegigt forekommer globalt, men med geografisk og etnisk variation. I DANBIO (Dansk Reumatologisk Database) var der ved udgangen af 2019 registreret ca. 24.800 patienter i behandling for kronisk leddegigt, og i 2018 var der ca. 1.300 nye patienter i behandling [3,4]. Sygdommen kan debutere i alle aldre, men typisk mellem 50 og 70 år [5].

2.2 Filgotinib

Filgotinib er en selektiv Janus kinase (JAK) inhibitor, der primært hæmmer JAK1. JAK spiller en vigtig rolle i betændelsesprocessen og i den beskadigelse af leddene, som finder sted ved kronisk leddegigt.

Filgotinib administreres oralt 200 mg én gang dagligt.

EMA-indikationen er: *Filgotinib is indicated as monotherapy or in combination with methotrexate (MTX) for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to, or who are intolerant to, one or more disease modifying antirheumatic drugs (DMARDs).*

Filgotinib har ikke andre indikationer.

2.3 Nuværende behandling

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

Methotrexat (MTX), en konventionel syntetisk DMARD (csDMARD), er førstevalg ved opstart af behandling med DMARDs. Hvis MTX ikke har tilfredsstillende effekt, bliver det kombineret med andre csDMARDs, typisk Salazopyrin og hydroxychloroquin (triplebehandling). Hvis patienten heller ikke her

opnår lav sygdomsaktivitet/remission, er næste behandlingsmulighed biologisk behandling med antistoffer (bDMARDs) eller targeteret syntetisk behandling med små molekyler (tsDMARDs), enten i kombination med MTX (kombinationsbehandling) eller som monoterapi. De biologiske DMARDs kan opdeles i tumor nekrosis faktor (TNF)-hæmmere (adalimumab, certolizumab, etanercept, golimumab og infliximab) og biologiske lægemidler med andre virkningsmekanismer (rituximab, tocilizumab, sarilumab, abatacept og anakinra). Dertil kommer de targeterede syntetiske DMARDs (tsDMARDs) (baricitinib og tofacitinib).

I DANBIO var der ved udgangen af 2018 registreret 22.724 patienter i behandling for kronisk leddegigt, hvoraf ca. 5.700 var i behandling med bDMARDs/tsDMARDs [3]. De fleste patienter vil blive behandlet med csDMARDs alene eller i kombination med bDMARDs/tsDMARDs. For nogle patienter er behandling med csDMARDs ikke en mulighed pga. toksicitet og intolerans. Her vil bDMARDs/tsDMARDs monoterapi være eneste mulige behandling. Et studie fra 2015 baseret på data fra DANBIO [6] viser, at 19 % af patienter med kronisk leddegigt var i bDMARDS/tsDMARDS monoterapi (ca. 1.100 patienter). Af disse var 70 % (ca. 770 patienter) initieret på monoterapi med bDMARDs, og ca. 30 % (ca. 330 patienter) havde tidligere været i kombinationsterapi med MTX.

Antallet af patienter med kronisk leddegigt i behandling med bDMARDs/tsDMARDs er stigende. Således er antallet vokset med ca. 1.500 patienter siden 2010 [7–10], hvilket svarer til en gennemsnitlig stigning på ca. 250 patienter pr. år siden 2010. Der er før 2010 beskrevet en stigning på ca. 500 behandlingsnaive patienter pr. år [11], og det skønnes, at det egentlige tal ligger et sted imellem 250 og 500. Fagudvalget anslår, at 10-15 % af patienter i behandling med bDMARDs/tsDMARDs vil skifte præparat i løbet af et år, hvilket hovedsageligt skyldes mangel på effekt eller uacceptable bivirkninger. Det vil sige, at omkring 700 patienter i behandling med bDMARDs/tsDMARDs i 2018 vil have skiftet lægemiddel i løbet af et år.

3 Kliniske spørgsmål

Medicinrådet bruger kliniske spørgsmål til at vurdere lægemidlers værdi for patienterne. Til hvert spørgsmål knytter sig en definition af patientgruppen (population), af det lægemiddel, vi undersøger (interventionen), af den behandling, vi sammenligner med (komparator(er)), og af effektmålene.

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

3.1 Klinisk spørgsmål 1

Hvilken værdi har filgotinib i kombination med MTX sammenlignet med adalimumab i kombination med MTX for behandlingsnaive patienter med moderat til svær kronisk leddegigt?

Population
Patienter i MTX-behandling med fortsat moderat til svær sygdomsaktivitet på trods af behandlingen.

Intervention
Filgotinib, oralt 200 mg dagligt i kombination med MTX.

Komparator
Adalimumab, subkutant 40 mg hver anden uge i kombination med MTX.

Adalimumab er førstevalg i den gældende lægemiddelrekommandation for kombinationsbehandling af behandlingsnaive patienter [12].

Effektmål
De valgte effektmål står i tabel 1.

3.2 Klinisk spørgsmål 2

Hvilken værdi har filgotinib i kombination med MTX sammenlignet med adalimumab i kombination med MTX for behandlingserfarne patienter med moderat til svær kronisk leddegigt?

Population
Patienter i MTX-behandling med fortsat moderat til svær sygdomsaktivitet trods behandling med bDMARDs/tsDMARDS.

Intervention
Filgotinib, oralt 200 mg dagligt i kombination med MTX.

Komparator
Adalimumab, subkutant 40 mg hver anden uge i kombination med MTX.

Adalimumab er førstevalg i den gældende lægemiddelrekommandation for kombinationsbehandling af behandlingserfarne patienter [12].

Effektmål
De valgte effektmål fremgår af tabel 1.

3.3 Klinisk spørgsmål 3

Hvilken værdi har filgotinib som monoterapi sammenlignet med etanercept som monoterapi for behandlingsnaive patienter med moderat til svær kronisk leddegigt?

Population
Patienter med fortsat moderat til svær sygdomsaktivitet, som endnu ikke har modtaget bDMARDs/tsDMARDs, og hvor behandling med csDMARDs ikke er en mulighed.

Intervention
Filgotinib, oralt 200 mg dagligt.

Komparator
Etanercept, subkutant 50 mg hver uge. Komparator er førstevalg i den gældende lægemiddelrekommandation for monoterapi af behandlingsnaive patienter [12].

Effektmål
De valgte effektmål fremgår af tabel 1.

3.4 Klinisk spørgsmål 4

Hvilken værdi har filgotinib som monoterapi sammenlignet med etanercept som monoterapi for behandlingserfarne patienter med moderat til svær kronisk leddegigt?

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

Intervention
Filgotinib, oralt 200 mg dagligt.

Komparator
Etanercept, subkutant 50 mg hver uge. Komparator er førstevalg i den gældende lægemiddelrekommandation for monoterapi af behandlingserfarne patienter [12].

Effektmål
De valgte effektmål fremgår af tabel 1.

3.5 Effektmål

Medicinrådet mener, at vurderingen af lægemidlets værdi bliver bedst understøttet af de effektmål, som fremgår af tabel 1. For hvert effektmål har Medicinrådet fastsat en mindste klinisk relevant forskel (MKRF). I det følgende afsnit argumenterer vi for valget af effektmål og de mindste klinisk relevante forskelle.

Tabel 1. Effektmål

Effektmål	Vigtighed	Effektmålsgruppe	Måleenhed	Mindste klinisk relevante forskel
American College of Rheumatology 50 % response (ACR50)	Kritisk	Livskvalitet, alvorlige symptomer og bivirkninger	Andel patienter, der oplever respons	15 %-point
Bivirkninger	Kritisk	Livskvalitet, alvorlige symptomer og bivirkninger	Andel patienter, der ophører behandling pga. uønskede hændelser	5 %-point
			Andel patienter, der oplever alvorlige infektioner	5 %-point
			Gennemgang af bivirkningsprofil	Narrativ vurdering
Behandlingsophør grundet manglende effekt	Vigtigt	Livskvalitet, alvorlige symptomer og bivirkninger	Andel patienter, der ophører behandling	10 %-point
Total Sharp Score (TSS) efter minimum 12 måneder	Vigtigt	Livskvalitet, alvorlige symptomer og bivirkninger	Andel patienter uden progression	10 %-point
Health Assessment Questionnaire Disability Index (HAQ-DI)	Vigtigt	Livskvalitet, alvorlige symptomer og bivirkninger	Andel patienter, der oplever respons	15 %-point

For alle effektmål ønsker vi data med længst mulig opfølgningstid, medmindre andet er angivet.

3.5.1 Kritiske effektmål

ACR50

Fagudvalgets primære mål for effekt er ACR50. Dette er defineret som 50 % forbedring i både ømme og hævede led samt 50 % forbedring inden for mindst tre ud af følgende fem kategorier: patientens overordnede vurdering, lægens overordnede vurdering, patientens vurdering af smerter, HAQ-DI-score og C-reaktivt protein (CRP). Fagudvalget vurderer, at en 50 %'s forbedring hos den enkelte patient er tilstrækkeligt for at definere respons, hvorimod en 20 %'s forbedring (ACR20) i fagudvalgets optik ikke er et tilstrækkelig klinisk respons. ACR50 indgår desuden som kritisk effektmål i behandlingsvejledningen fra 2018 [12]. Fagudvalget har ikke kendskab til en defineret klinisk relevant forskel for effektmålet, men vurderer, at en forskel på 15 %-point i andelen af patienter, der opnår ACR50, er klinisk relevant, hvilket er i overensstemmelse med behandlingsvejledningen fra 2018 [12].

Bivirkninger

Behandlingsophør grundet uønskede hændelser: Det er fagudvalgets vurdering, at uønskede hændelser, der fører til ophør af behandlingen, er et brugbart mål for bivirkninger. Dette mål bliver ofte rapporteret i kliniske studier. Der findes ikke studier, der beskriver, hvor stor en andel patienter der skal ophøre med behandling grundet uønskede hændelser, før det er klinisk relevant. Fagudvalget vurderer, at den mindste klinisk relevante forskel er 5 %-point mellem grupperne, hvilket er i overensstemmelse med behandlingsvejledningen fra 2018 [12].

Alvorlige infektioner: Udover behandlingsophør grundet uønskede hændelser ønskes antallet af alvorlige infektioner (som defineret i de kliniske studier) opgjort selvstændigt, da disse særligt frygtes af patienter og klinikere, siden de kan forårsage pauser i behandlingen med risiko for forværring af symptomer/sygdomsprogression. Fagudvalget vurderer, at den mindste klinisk relevante forskel er 5 %-point, hvilket er i overensstemmelse med behandlingsvejledningen fra 2018 [12].

Gennemgang af bivirkningsprofil: Fagudvalget ønsker en gennemgang af filgotinib og komparatorernes bivirkningsprofiler med henblik på at vurdere bivirkningernes type, håndtérbarhed og reversibilitet. Ansøger bedes derfor levere bivirkningsdata fra lægemidlernes produktresuméer.

3.5.2 Vigtige effektmål

Behandlingsophør grundet manglende effekt

Fagudvalget mener, at dette er et vigtigt effektmål, da det er relevant at afdække forskelle i manglende effekt af lægemidler med potentielle bivirkninger. 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 den mindste klinisk relevante forskel mellem grupperne er 10 %-point, hvilket er i overensstemmelse med behandlingsvejledningen fra 2018 [12].

Total Sharp Score (TSS)

Fagudvalget mener, at dette er et relevant radiologisk effektmål efter minimum 12 måneders opfølgning, da det kan tolkes som et udtryk for sygdomsprogression [13]. Den mindste klinisk relevante forskel i TSS er defineret ved antal patienter uden progression, dvs. fravær af radiologiske ændringer [14]. Der er dog ikke konsensus om, hvor stor en andel af patienterne der skal undgå progression, før det er klinisk relevant. For patienter i standardbehandling forventes ca. 80 % at være uden progression i løbet af et år [15], og fagudvalget finder derfor, at en forskel på 10 %-point mellem to behandlinger efter minimum 12 måneders opfølgning er klinisk relevant. Dette er i overensstemmelse med behandlingsvejledningen fra 2018 [12].

HAQ-DI

HAQ-DI er et mål for patienternes invaliditet/funktionstab og afspejler i denne sammenhæng livskvalitet. Det er et domænespecifikt instrument, der er pålideligt, velundersøgt og valideret til leddegigt [16]. HAQ-DI er valgt fremfor et generisk instrument, idet fagudvalget vurderer, at det er af større relevans for patienter med kronisk leddegigt, 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 %-point i andel patienter, der oplever en klinisk signifikant ændring, hvilket er i overensstemmelse med behandlingsvejledningen fra 2018 [12]. En klinisk signifikant ændring er defineret som et fald eller forbedring i HAQ-DI-score på ≥ 0,22 fra baseline [17].

4 Litteratursøgning

Medicinrådet har på baggrund af den foreløbige ansøgning undersøgt, om der findes en eller flere fuldtekstartikler publiceret i videnskabelige, fagfællebedømte tidsskrifter, hvor filgotinib er sammenlignet direkte med adalimumab (klinisk spørgsmål 1 og 2) og etanercept (klinisk spørgsmål 3 og 4).

Klinisk spørgsmål 1

Medicinrådet har fundet følgende studie, som indeholder en direkte sammenligning mellem filgotinib og adalimumab:

- FINCH 1 (NCT02889796)

Det er tilstrækkeligt datagrundlag til at besvare det kliniske spørgsmål. Ansøger skal derfor ikke søge efter yderligere fuldtekstartikler, men skal konsultere Det Europæiske Lægemiddelagenturs (EMA) European public assessment reports (EPAR) for både det aktuelle lægemiddel og dets komparator(er).

Klinisk spørgsmål 2, 3 og 4

Medicinrådet har ikke fundet fuldtekstartikler, der indeholder en direkte sammenligning mellem filgotinib og hhv. adalimumab (klinisk spørgsmål 2) og etanercept (klinisk spørgsmål 3 og 4). Derfor skal ansøger søge efter artikler til indirekte sammenligninger. Søgestrengene fremgår af bilag 1. Derudover skal ansøger konsultere Det Europæiske Lægemiddelagenturs (EMA) European public assessment reports (EPAR) for både det aktuelle lægemiddel og dets komparatorer.

Ansøger skal ekskludere artikler med andre populationer end de, der er specificeret i protokollen, og artikler, der ikke rapporterer mindst ét af de kritiske eller vigtige effektmål.

Kriterier for litteratursøgning

Ansøger skal søge relevant litteratur i databaserne PubMed og CENTRAL (via Cochrane Library). Ansøger skal dokumentere søgningen for hver af de to databaser, fx i form af et skærmklip eller en downloadet søgestrategi. Eventuelle ændringer/tilføjelser til søgestrategien skal fremgå af dokumentationen.

Kriterier for udvælgelse af litteratur

Ansøger skal screene de artikler, der identificeres ved databasesøgningerne, for overensstemmelse med de i protokollen definerede kliniske spørgsmål samt kriterier for studie- og publikationstype(r). Det vil sige, at ansøger skal ekskludere artikler med andre populationer end de i protokollen specificerede. Dette gælder ligeledes for artikler, som ikke rapporterer mindst ét af de kritiske eller vigtige effektmål.

Den ansøgende virksomhed skal ved screening af artikler ekskludere først på titel- og abstractniveau, dernæst ved gennemlæsning af fuldtekstartikler. Artikler, der ekskluderes ved fuldtekstlæsning, skal fremgå af en eksklusionsliste, hvor eksklusionen begrundes kort. Den samlede udvælgelsesproces skal afrapporteres ved brug af et flowdiagram som beskrevet i PRISMA-Statement (http://prisma-statement.org/PRISMAStatement/FlowDiagram.aspx).

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

5 Databehandling og -analyse

Ansøger skal bruge Medicinrådets ansøgningsskema til sin endelige ansøgning. Vær opmærksom på følgende:

Studier og resultater

- Beskriv de inkluderede studier og baselinekarakteristikken af studiepopulationerne.
- Angiv, hvilke studier/referencer der er benyttet til at besvare hvilke kliniske spørgsmål.
- Brug som udgangspunkt ansøgningsskemaet til ekstraktion af al relevant data.
- Krydstjek de ekstraherede data med de resultater, der fremgår af de relevante EPARs.
- Angiv årsager, hvis der er uoverensstemmelser mellem resultaterne fra artikler og EPARs.
- Angiv årsager, hvis der er uoverensstemmelser i forhold til PICO mellem protokollen og studierne.
- Vurdér, hvordan uoverensstemmelserne påvirker estimaterne.

Statistiske analyser

- Begrund valget af syntesemetode (metaanalyse eller narrativ beskrivelse), og lad specifikke analysevalg fremgå tydeligt.
- Udfør en komparativ analyse for hvert enkelt effektmål på baggrund af de ekstraherede data.
- Hvis data for et effektmål ikke er baseret på alle deltagere i et studie, skal ansøger ikke gøre forsøg på at erstatte manglende data med en meningsfuld værdi.
- Angiv for hvert effektmål og studie, hvilken analysepopulation (fx intention to treat (ITT), per-protocol) der er anvendt.
- Angiv en sensitivitetsanalyse baseret på ITT-populationen, hvis den komparative analyse ikke er baseret herpå.
- Angiv for hvert effektmål og studie, hvilken statistisk analysemetode der er anvendt.
- Basér de statistiske analyser for dikotome effektmål på den relative forskel.
- Beregn den absolutte forskel med udgangspunkt i den estimerede relative forskel for et antaget niveau på hændelsesraten i komparatorgruppen (jf. appendiks 5 i *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*).
- Foretag eventuelt en indirekte analyse, hvis der ikke foreligger direkte sammenlignende studier, og hvis intervention og komparator er sammenlignet med samme alternative komparator i separate studier. Anvend eventuelt Buchers metode for indirekte justeret sammenligning.

Metaanalyser

- Foretag en metaanalyse for de effektmål, hvor det er metodemæssigt forsvarligt, hvis der er mere end ét sammenlignende studie.
- Basér metaanalyser vedr. effektmål, hvor forskellige måleinstrumenter er brugt på tværs af de inkluderede studier, på standardized mean difference (SMD). Omregn den estimerede SMD til den

foretrukne skala for effektmålet (jf. appendiks 7 i *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*).
- Udfør alene netværksmetaanalyse i de undtagelsesvise situationer, hvor Medicinrådet specifikt beder om det i protokollen. Redegør i disse tilfælde for, i hvilken grad antagelserne om transitivitet og konsistens er opfyldt (gerne ved hjælp af passende statistiske metoder).
- Begrund for alle statistiske analyser valget mellem 'fixed effects'- og 'random effects'-modeller.
- Beskriv den anvendte metode detaljeret.

Narrative analyser

- Begrund valget af syntesemetode (metaanalyse eller narrativ beskrivelse), og lad specifikke analysevalg fremgå tydeligt.
- Syntetisér data narrativt, hvis det ikke er en mulighed at udarbejde komparative analyser baseret på statistiske metoder.
- Beskriv studie- og patientkarakteristika samt resultater fra de inkluderede studier narrativt og i tabelform med angivelse af resultater pr. effektmål for både intervention og komparator(er).
- Beskriv forskelle mellem studier og vurdér, hvorvidt resultaterne er sammenlignelige.

Særlige forhold i denne protokol

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

Vær opmærksom på, at Medicinrådets sekretariat forbeholder sig retten til at foretage sensitivitets- og subgruppeanalyser på baggrund af studiernes validitet og relevans, uanset valg af analysemetode.

6 Evidensens kvalitet

Medicinrådet anvender GRADE (Grading of Recommendations, Assessments, Development and Evaluation) til at foretage en systematisk og transparent vurdering af kvaliteten af evidensen. Evidensens kvalitet fortæller, i hvor høj grad vi kan have tiltro til den evidens, vi baserer vurderingen af lægemidlets værdi på.

7 Andre overvejelser

Fagudvalget er opmærksom på, at der for nogle af populationerne i de kliniske spørgsmål kan være problemer med at fremskaffe data. I disse tilfælde vil fagudvalget forholde sig til, om det er muligt at ekstrapolere fra de populationer, hvor der er data.

Fagudvalget er bekendt med, at FDA ikke har godkendt filgotinib til behandling af kronisk leddegigt pga. af et sikkerhedssignal ved behandling med 200 mg filgotinib. FDA efterspørger data fra to igangværende studier, MANTA og MANTA-Ray, som undersøger påvirkning af behandling med 200 mg filgotinib på mænds sædkvalitet. De to studier bliver først afsluttet i 2021. Derudover har FDA udtrykt generel bekymring for balancen mellem effekt og bivirkninger ved behandling med 200 mg filgotinib. Fagudvalget vil bede virksomheden om at sende en nærmere beskrivelse af FDAs årsager til manglende godkendelse

8 Relation til behandlingsvejledning

Fagudvalget vil i forbindelse med vurderingen af filgotinib tage stilling til, hvor det foreløbigt kan placeres i Medicinrådets behandlingsvejledning for kronisk leddegigt.

9 Referencer

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10 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende gigtsygdomme

Formand	**Indstillet af**
Ulrik Tarp Ledende overlæge, dr.med.	Lægevidenskabelige Selskaber og Dansk Reumatologisk Selskab
Medlemmer	**Udpeget af**
Salome Kristensen Overlæge, ph.d.	Region Nordjylland
Lars Erik Bartels Afdelingslæge, ph.d.	Region Midtjylland
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Annemarie Lyng Svensson Overlæge, ph.d.	Region Hovedstaden
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Thomas Loof Hedegård Farmaceut	Dansk Selskab for Sygehusapoteksledelse
Dorte Vendelbo Jensen Overlæge, sekretariatsleder	DANBIO
Udpegning i gang	Dansk Reumatologisk Selskab
Connie Ziegler Patient/patientrepræsentant	Danske Patienter
En patient/patientrepræsentant	Danske Patienter

Medicinrådets sekretariat

Medicinrådet
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11 Versionslog

Version	Dato	Ændring
1.0	29. september 2020	Godkendt af Medicinrådet.

12 Bilag 1

Søgestreng til PubMed:

PUBMED https://www.ncbi.nlm.nih.gov/pubmed/advanced

#	Søgetermer	Kommentarer
1	Arthritis, Rheumatoid[majr]	Termer for indikation
2	rheumatoid arthriti*[ti] OR reumatoid arthriti*[ti] OR RA[ti]	
3	#1 OR #2	
4	GLPG0634[nm]	Termer for lægemidler
5	filgotinib[tiab] OR GLPG0634[tiab]	
6	Adalimumab[majr]	
7	adalimumab[tiab] OR Humira*[tiab] OR "ABP 501"[tiab]	
8	Etanercept[majr]	
9	etanercept[tiab] or enbrel[tiab] or ((TNFR*[tiab] OR TNF[tiab] OR TNT[tiab]) AND fusion[tiab] AND protein[tiab]) or TNR-001[tiab]	
10	#4 OR #5 OR #6 OR #7 OR #8 OR #9	
11	("Randomized Controlled Trial"[pt] OR "Controlled Clinical Trial"[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR "Clinical Trials as Topic"[mh:noexp] OR randomly[tiab] OR trial[ti]) NOT ("Animals"[mh] NOT "Humans"[mh])	Filter til identifikation af randomiserede, kontrollerede forsøg
12	#3 AND #10 AND #11	Kombination af indikation, lægemidler og RCT filter
13	Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Guideline[pt] OR Letter[pt] OR Review[pt] OR Systematic Review[pt] OR Meta-Analysis[pt]	Irrelevante publikationstyper til eksklusion
14	case report[ti] OR review[ti] OR meta-analysis[ti] OR animal[ti]	
15	**#12 NOT (#13 OR #14)**	**Endeligt resultat**

Feltkoder: majr = MeSH Major Topic, mh = MeSH Terms, nm = Supplementary Concept/Substance, pt = publication type, ti = title, tiab = title/abstract, inkl. forfatterkeywords

Søgestreng til CENTRAL:

CENTRAL Cochrane Library https://www.cochranelibrary.com/advanced-search/search-manager

#	Søgetermer	Kommentarer
1	MeSH descriptor: [Arthritis, Rheumatoid] this term only	Termer for indikation
2	((rheumatoid OR reumatoid) NEXT arthritis):ti OR RA:ti	
3	#1 OR #2	
4	(filgotinib OR GLPG0634):ti,ab,kw	Termer for lægemidler
5	(adalimumab OR Humira*):ti,ab,kw	
6	MeSH descriptor: [Adalimumab] explode all trees	
7	(etanercept or enbrel* or TNR-001):ti,ab,kw	
8	((TNFR* OR TNF OR TNT) AND fusion AND protein):ti,ab,kw	
9	MeSH descriptor: [Etanercept] explode all trees	
10	#4 OR #5 OR #6 OR #7 OR #8 OR #9	
11	#3 AND #10	Kombination af indikation og lægemidler
12	conference abstract:pt OR review:pt OR meta-analysis:pt	Irrelevante publikationstyper til eksklusion
13	("clinicaltrials gov" OR trialsearch):so	
14	NCT*:au	
15	#12 OR #13 OR #14	
16	#11 NOT #15	

17	Embase:an NOT Pubmed:an	Identifikation af poster, der kommer fra Embase
18	#16 AND #17	Endeligt resultat

Feltkoder: ti: title, ab: abstract, so: source, kw: keywords, her kontrollerede/indekserede termer fra databaserne Medline og/eller Embase. pt = publication type