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Medicinrådet

Baggrund for Medicinrådets anbefaling vedrørende tofacitinib som mulig standard-behandling til colitis ulcerosa

Versionsnr.: 2.1

Medicinrådet

Om Medicinrådet

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

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

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

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

Om anbefalingen

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

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

Dokumentoplysninger	
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Indhold

1 Lægemiddelinformationer

Lægemidlets oplysninger	
Handelsnavn	Xeljanz
Generisk navn	Tofacitinib
Firma	Pfizer ApS
ATC-kode	L04AA29
Virkningsmekanisme	Janus kinase inhibitor
Administration/dosis	Tabletter 10 mg to gange dagligt i otte uger efterfulgt af 5 mg to gange dagligt.
EMA-indikation	Tofacitinib er indiceret til behandling af voksne patienter med moderat til alvorlig aktiv ulcerativ colitis (UC), der har haft et utilstrækkeligt respons, ophørt respons eller har været intolerante over for enten konventionel behandling eller et biologisk lægemiddel.

2 Medicinrådets anbefaling

Medicinrådet **anbefaler ikke** tofacitinib som mulig standardbehandling til bionaive patienter med moderat til svær aktiv colitis ulcerosa.

Medicinrådet **anbefaler** tofacitinib som mulig standardbehandling til bioerfarne patienter med moderat til svær aktiv colitis ulcerosa.

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

1. *Hvad er den kliniske merværdi af tofacitinib til bionaive patienter med moderat til svær colitis ulcerosa sammenlignet med henholdsvis infliximab og vedolizumab?*

2. *Hvad er den kliniske merværdi af tofacitinib til bioerfarne patienter med moderat til svær colitis ulcerosa sammenlignet med henholdsvis infliximab og vedolizumab?*

3 Formål

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

4 Baggrund

Colitis ulcerosa er en kronisk, inflammatorisk tarmsygdom med uspecifik inflammation i ende- og tyktarmens slimhinde.

4.1 Sagsbehandlingstid og proces for Medicinrådets vurdering

Medicinrådet modtog den foreløbige ansøgning den 22. juni 2018, og protokollen blev sendt til Pfizer den 24. oktober 2018.

Materialet til den endelige ansøgning blev modtaget den 4. marts 2019. Ansøger kunne ikke levere publicerede data for flere effektmål for de angivne subpopulationer (bionaive og -erfarne), og fagudvalget efterspurgte derfor data på den samlede population for disse effektmål den 19. marts 2019. Sekretariatet modtog de supplerende analyser den 9. april 2019, hvor ansøgningen blev betragtet som endelig. Medicinrådet har gennemført vurderingen af tofacitinib på 20 uger og én dag.

Ansøger indsendte supplerende oplysninger til sekretariatet den 18. november 2019 angående EMAs undersøgelse om øget risiko for blodpropper ved brug af tofacitinib. Fagudvalget har på baggrund af de nye data og anbefalinger fra EMA revurderet den kliniske merværdi af tofacitinib til behandling af colitis ulcerosa. Medicinrådet har revurderet den kliniske merværdi samt anbefaling af tofacitinib som mulig standardbehandling den 19. februar 2020.

5 Medicinrådets vurdering af samlet klinisk merværdi

Medicinrådet vurderer, at tofacitinib giver:

- **negativ klinisk merværdi** hos bionaive patienter med moderat til svær colitis ulcerosa sammenlignet med infliximab og vedolizumab (meget lav evidenskvalitet).
- **ingen klinisk merværdi** sammenlignet med vedolizumab (meget lav evidenskvalitet) og **ikkedokumenterbar merværdi** sammenlignet med infliximab (evidensens kvalitet kan ikke vurderes) hos bioerfarne patienter med moderat til svær colitis ulcerosa.

Medicinrådets vurdering af tofacitinib giver anledning til ovenstående merværdier. Dette skyldes primært, at tofacitinib stadig har en forholdsvis uafklaret bivirkningsprofil, hvilket er illustreret af nye bivirkningsdata for tofacitinib som omtalt i vurderingsrapportens afsnit 9.1.2 (øget risiko for blodpropper i lungerne samt dybe venetromboser hos patienter med kronisk leddegigt med høj risiko for blodpropper, samt øget risiko for alvorlige og fatale infektioner hos patienter over 65 år behandlet med tofacitinib 10 mg 2 x dagligt).

6 Høring

Ansøger indsendte den 25. februar 2020 høringssvar til Medicinrådets revurdering af tofacitinib. Høringssvaret gav ikke anledning til ændring af kategoriseringen af klinisk merværdi (bilag 2).

7 Resumé af økonomisk beslutningsgrundlag

Amgros har vurderet de gennemsnitlige meromkostninger per patient og budgetkonsekvenserne for regionerne ved brug af tofacitinib hos henholdsvis bionaive og -erfarne patienter. Amgros har indgået aftale med Pfizer om indkøb af tofacitinib til en pris, der er lavere end listeprisen (AIP). Omkostningerne ved behandling med tofacitinib til bionaive og -erfarne patienter er på niveau med infliximab men er lavere sammenlignet med vedolizumab.

Medicinrådet vurderer på denne baggrund, at forholdet mellem omkostninger og den kliniske merværdi for bioerfarne patienter er rimeligt. Da behandling med tofacitinib har en negativ klinisk merværdi for bionaive patienter sammenlignet med standardbehandling, er der for denne patientpopulation ikke taget stilling til sundhedsøkonomi.

Amgros fremhæver, at infliximab er vægtafhængigt, og resultatet af tofacitinib sammenlignet med infliximab derfor i høj grad afhænger af, hvilken gennemsnitsvægt det antages, en patient med colitis ulcerosa har.

Amgros' sundhedsøkonomiske analyse er vedlagt som bilag 1.

Amgros' dokumenter er baseret på de kliniske spørgsmål og merværdikategorierne.

8 Overvejelser omkring alvorlighed/forsigtighed

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

9 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende inflammatoriske tarmsygdomme

Forvaltningslovens § 3 stk. 2, har været anvendt i forbindelse med udpegning af medlemmer til dette fagudvalg.

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Medicinrådets sekretariat

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10 Versionslog

Version	Dato	Ændring
1.0	28. august 2019	Godkendt af Medicinrådet.
2.0	24. marts 2020	Ændret anbefaling godkendt af Medicinrådet på baggrund af revurdering af klinisk merværdi foretaget den 19. februar 2020.
2.1	25. marts 2020	Afsnit 7 er rettet, så det korrekt fremgår, at omkostningerne for tofacitinib er på niveau med infliximab men lavere end for vedolizumab.

11 Bilag

Bilagsliste:

- Amgros' sundhedsøkonomiske analyse
- Høringssvar fra ansøger
- Vurdering af den kliniske merværdi af tofacitinib til colitis ulcerosa - vers. 2.0
- Ansøgers endelige ansøgning
- Protokol for vurdering af den kliniske merværdi af tofacitinib til colitis ulcerosa – vers. 1.0

XELJANZ (TOFACITINIB)

COLITIS ULCEROSA

AMGROS 9. juli 2019

AMGROS

OPSUMMERING

Baggrund

Tofacitinib (Xeljanz) er indiceret til behandling af voksne patienter med moderat til alvorlig aktiv ulcerativ colitis (UC), der har haft et utilstrækkeligt respons, ophørt respons, eller har været intolerante over for enten konventionel behandling eller et biologisk lægemiddel. Amgros' vurdering tager udgangspunkt i dokumentation indsendt af Pfizer.

Analyse

I analysen estimeres de inkrementelle omkostninger forbundet med behandling med tofacitinib (Xeljanz) sammenlignet med infliximab og vedolizumab.

Inkrementelle omkostninger og budgetkonsekvenser

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

I scenariet Amgros mener er mest sandsynligt, er de gennemsnitlige meromkostninger for tofacitinib (Xeljanz) ca. [redacted] sammenlignet med infliximab og [redacted] sammenlignet med vedolizumab. Hvis analysen udføres med AIP bliver de inkrementelle omkostninger til sammenligning ca. 7.600 DKK per patient sammenlignet med infliximab og -94.000 DKK sammenlignet med vedolizumab.

Amgros vurderer, at budgetkonsekvenserne for regionerne per år ved anbefaling af tofacitinib (Xeljanz) som standardbehandling vil være ca. [redacted] for bionaive patienter og [redacted] for bioerfarne patienter. Hvis analysen udføres med AIP, er budgetkonsekvenserne hhv. ca. -1,5 mio. DKK og -17 mio. DKK om året.

Konklusion

Behandling med tofacitinib (Xeljanz) er forbundet med besparelser sammenlignet med behandling med infliximab og vedolizumab. Omkostningerne for tofacitinib (Xeljanz) er drevet af lægemiddelomkostningerne.

Resultatet er følsomt over for ændringer i gennemsnitsvægten for en UC-patient.

Liste over forkortelser

AIP	Apotekernes indkøbspris
DKK	Danske kroner
DRG	Diagnose Relaterede Grupper
SAIP	Sygehusapotekernes indkøbspriser
UC	Ulcerativ colitis
SmPC	Summary of Product Characteristics
RADS	Rådet for anvendelse af dyr sygehusmedicin

INDHOLD

LOG

Ansøgning	
Lægemiddelfirma:	Pfizer ApS
Handelsnavn:	Xeljanz
Generisk navn:	Tofacitinib
Indikation:	Behandling af voksne patienter med moderat til alvorlig aktiv ulcerativ colitis, der har haft et utilstrækkeligt respons, ophørt respons, eller har været intolerante over for enten konventionel behandling eller et biologisk lægemiddel.
ATC-kode:	L04AA29

Proces	
Ansøgning modtaget hos Amgros:	20-02-2019
Endelig rapport færdig:	09-07-2019
Sagsbehandlingstid fra endelig ansøgning:	140 dage
Arbejdsgruppe:	**Lianna Geertsen** Pernille Winther Johansen Line Brøns Jensen Louise Greve Dal Mark Friborg

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

1 BAGGRUND

Tofacitinib (Xeljanz) er indiceret til behandling af voksne patienter med moderat til alvorlig aktiv ulcerativ colitis (UC), der har haft et utilstrækkeligt respons, ophørt respons, eller har været intolerante over for enten konventionel behandling eller et biologisk lægemiddel. Pfizer ApS (herefter omtalt som ansøger) er markedsføringstilladelsesindehaver af tofacitinib (Xeljanz) og har den 20.02.2019 indsendt en ansøgning til Medicinrådet om anbefaling af tofacitinib (Xeljanz) som standardbehandling på danske hospitaler af den nævnte indikation. Som et led i denne ansøgning vurderer Amgros, på vegne af Medicinrådet de økonomiske analyser, ansøger har sendt som en del af den samlede ansøgning til Medicinrådet. Denne rapport er Amgros' vurdering af de fremsendte økonomiske analyser (herefter omtalt som analysen).

1.1 Problemstilling

Formålet med analysen er at estimere de gennemsnitlige inkrementelle omkostninger per patient og de samlede budgetkonsekvenser for regionerne ved anbefaling af tofacitinib (Xeljanz) som standardbehandling på danske hospitaler med den nævnte indikation. I analyserne sammenlignes behandling med tofacitinib (Xeljanz) med behandling med infliximab og vedolizumab.

1.2 Patientpopulation

UC er en kronisk, inflammatorisk tarmsygdom med uspecifik inflammation i ende- og tyktarmens slimhinde. Sygdommen påvirker oftest/altid endetarmen og nedre dele af tyktarmen. Efter den første episode af UC oplever patienten ofte skiftende perioder med henholdsvis spontan remission, hvor sygdommen ikke giver symptomer, og tilbagefald. Patienter med moderat til svær UC har symptomer i form af blodige diarréer og/eller afgang af blodigt slim per rektum ved/imellem defækationer (1,2).
Prævalensen af UC i Danmark er estimeret til ca. 35.000 personer, og incidensen er ca. 18,6 pr. år pr. 100.000 personer. Incidensen i Danmark er blandt den højeste i verden og er stigende (3,4).

1.3 Nuværende behandling

Ved kronisk aktiv UC kan biologisk behandling initieres, hvis sygdommen ikke bliver bragt i remission under steroidbehandling, hvis sygdommen recidiverer under aftrapning af steroidbehandling, hvis sygdommen ikke bliver holdt i remission med immunosuppressiv behandling (azathioprin, 6-mercaptopurin), og hvis kirurgi ikke er at foretrække (2).
Hos cirka en tredjedel af patienterne aftager effekten af den biologiske behandling, hvorefter dosis kan øges, eller intervallerne mellem behandling må afkortes. Ved ophør af behandlingsrespons kan patienterne i 25-35 % af tilfældene opnå en effekt ved at skifte til en anden biologisk behandling (2).
RADS har i 2016 ligestillet de biologiske lægemidler infliximab, golimumab og vedolizumab som 1. og 2. linjebehandling af UC ved bionaive og bioerfarne patienter, mens adalimumab kan overvejes som 3. linjebehandling (5).

1.4 Behandling med tofacitinib (Xeljanz)

Indikation

Tofacitinib (Xeljanz) er indiceret til behandling af voksne patienter med moderat til alvorlig aktiv ulcerativ colitis (UC), der har haft et utilstrækkeligt respons, ophørt respons, eller har været intolerante over for enten konventionel behandling eller et biologisk lægemiddel.

Virkningsmekanisme

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

Dosering
Den anbefalede dosis er 10 mg to gange dagligt i otte uger efterfulgt af 5 mg to gange dagligt. Tofacitinib (Xeljanz) gives som en tablet, og patienten kan dermed selv administrere behandlingen.

1.4.1 Komparator

Medicinrådet har defineret infliximab og vedolizumab som komparatorer for både P1 og P2, se tabel 1.

Tabel 1: Definerede populationer og komparatorer.

Population	Komparator
P1: Bionaive patienter med moderat til svær UC, der er bionaive og opfylder kriterierne for biologisk behandling.	Infliximab intravenøs (i.v.) infusion 5 mg/kg uge 0, 2 og 6, herefter hver 8. uge. Vedolizumab i.v. infusion 300 mg uge 0, 2 og 6, herefter 8. uge
P2: Bioerfarne patienter med moderat til svær UC, der opfylder kriterierne for biologisk behandling.	Infliximab intravenøs (i.v.) infusion 5 mg/kg uge 0, 2 og 6, herefter hver 8. uge. Vedolizumab i.v. infusion 300 mg uge 0, 2 og 6, herefter 8. uge Placebo

1.5 Medicinrådets kliniske spørgsmål

Medicinrådet har vurderet den kliniske merværdi af tofacitinib (Xeljanz) som vedligeholdelsesbehandling for følgende populationer:

- **P1:** Hvad er den kliniske merværdi af tofacitinib til bionaive patienter med moderat til svær UC sammenlignet med henholdsvis infliximab og vedolizumab?
- **P2:** Hvad er den kliniske merværdi af tofacitinib til bioerfarne patienter med moderat til svær UC sammenlignet med henholdsvis infliximab og vedolizumab?

2 VURDERING AF INDSENDT ØKONOMISK ANALYSE

I omkostningsanalysen af gennemsnitlige behandlingsomkostninger per patient sammenlignes behandling med tofacitinib (Xeljanz) med behandling med infliximab og vedolizumab til hhv. bionaive og bioerfarne patienter med UC.

2.1 Model, metode og forudsætninger

2.1.1 Modelbeskrivelse

Ansøger har indsendt en omkostningsanalyse, der estimerer de gennemsnitlige omkostninger for behandling med tofacitinib (Xeljanz) og komparatorerne. Analysen anvender et begrænset samfundsperspektiv, hvor lægemiddelomkostninger, administrationsomkostninger og transportomkostninger inkluderes.

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

Analysen inkluderer lægemiddelomkostninger, forskelle i administrationsomkostninger (peroral og intravenøs) samt omkostninger forbundet med patienttid og transport. Analysen inkluderer ikke monitorerings eller bivirkningsrelaterede omkostninger, da disse antages at være ens på tværs af lægemidlerne.

Amgros' vurdering

Amgros vurderer, at det anvendte analyseperspektiv, tidshorisont og overordnede modeltilgang er acceptabelt.

Efter udarbejdelsen af denne afrapportering er Amgros blevet gjort opmærksom på at EMA på baggrund af nye bivirkningsdata nu anbefaler at alle patienter, der får tofacitinib (Xeljanz) 10 mg to gange dagligt, uanset indikation, monitoreres for symptomer på blodpropper i lungerne. Disse monitoreringsomkostninger er ikke opgjort i afrapporteringen, men det må forventes at implementeringen af ovenstående vil øge omkostningerne for behandling med tofacitinib (Xeljanz).

2.1.2 Analyseperspektiv

Ansøger har indsendt en omkostningsanalyse med et begrænset samfundsperspektiv. Analysen har en tidshorisont på 18 måneder. Dette valg har ansøger argumenteret ud fra at samme tidshorisont gør sig gældende i en RADS behandlingsvejledning for inflammatoriske tarmsygdomme fra 2016. Desuden finder ansøger at alle forskelle i relevante omkostninger er ligger inden for en tidshorisont på 18 måneder. Omkostninger der ligger efter det første år, er diskonteret med en rate på 4 %.

Amgros' vurdering

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

2.1.3 Omkostninger

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

Lægemiddelomkostninger

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

Doseringen af infliximab og vedolizumab er vægtbaseret og ansøger antager at gennemsnitsvægten for en UC-patient ligger på 77 kg. Dette er baseret på et publiceret studie af Madsen et al 2018 (6). Beregning af den samlede dosering af lægemidlerne og de heraf følgende omkostninger over 18 uger, er illustreret i tabellen nedenfor. Ansøger antager at der ikke er noget spild forbundet med brugen af lægemidlerne.

Tabel 2: Anvendte lægemiddelpriser, SAIP.

	Tofacitinib		Infliximab	Vedolizumab
Styrke	5 mg	10 mg	100 mg	300 mg
Pakningsstørrelse	56 tabletter	56 tabletter	1 hætteglas	1 hætteglas
Dosis per administration	1	1	3,85	1
Pris (SAIP)	[redacted]	[redacted]	[redacted]	[redacted]
Antal doser (18 måneder)	980	112	42,35	11
Lægemiddelomkostninger, gns. Patient (18 måneder)	[redacted]		[redacted]	[redacted]

Amgros' vurdering

Doseringen er i tråd med lægemidlernes SmPC og seneste behandlingsvejledning fra RADS. Amgros vurderer derfor at doseringen og beregningen af lægemiddelomkostningerne er acceptabelt. Amgros har været i dialog med klinikere omkring gennemsnitsvægten for en UC-patient og denne findes acceptabel.

Administrationsomkostninger

Ansøger har anvendt Amgros' udvidet sammenligningsgrundlag på reumatoid artritis som kilde for administrationsomkostningerne for de tre lægemidler (7). Vedolizumab er ikke en del af det udvidede sammenligningsgrundlag for reumatoid artritis og ansøger har derfor antaget, at administrationsomkostningerne sammenlignelige med infliximab, da lægemidlerne gives på samme måde (11 behandlinger over 18 måneder).

Tabel 3: Administrationsomkostninger, 18 måneder, DKK.

	Tofacitinib	Infliximab	Vedolizumab
Læge (tid)	2.753	2.550	2.550
Sygeplejerske (tid)	1.852	13.587	13.587
Blodprøver	1.437	1.421	1.421
Lokale	65	416	416
Utensilier	0	1.037	1.037
Total	**6.107**	**19.011**	**19.011**

Amgros' vurdering

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

Patientomkostninger

Ansøger har valgt at inkludere omkostninger til patienttid og transport. På samme måde som for administrationsomkostningerne er dette gjort på baggrund Amgros's udvidet sammenligningsgrundlag på reumatoid artritis. Ansøger antager at omkostningerne er ens for infliximab og vedolizumab. Den estimerede patienttid kan ses i tabel 4.

Tabel 4: Ansøgers estimat af patienttid og transport, 18 måneder

	Tofacitinib	Infliximab	Vedolizumab
Patient- og pårørendetid	1.284	5.275	5.275
Transport	1.651	1.680	1.680
Total	**2.935**	**6.955**	**6.955**

Amgros' vurdering

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

2.2 Følsomhedsanalyser

Ansøger har udarbejdet følsomhedsanalyser for de parametre, der antages at have stor betydning for resultatet. Det drejer sig om følgende parametre:

- Gennemsnitsvægt for en UC-patient
- Vial sharing
- Administrationsomkostningerne

Amgros' vurdering

Amgros vurderer at ansøgers følsomhedsanalyser er relevante og afspejler de relevante usikkerheder, der er i analysen.

3 RESULTATER

3.1 Ansøgers hovedanalyse

Resultaterne fra ansøgers hovedanalyse præsenteres i tabel 5 og 6.

Ansøger estimerer i analysen de inkrementelle omkostninger per patient for tofacitinib (Xeljanz) sammenlignet med infliximab til en meromkostning på ca. [redacted]. Sammenlignes tofacitinib (Xeljanz) med vedolizumab estimeres en meromkostning på ca. [redacted]

Tabel 5: Resultatet af ansøgers hovedanalyse ved sammenligning med infliximab, DKK.

	Tofacitinib (Xeljanz)	Infliximab	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Administrationsomkostninger	6.029	18.767	-12.738
Patientomkostninger	2.897	6.866	-3.969
Totale omkostninger	[redacted]	[redacted]	[redacted]

Tabel 6: Resultatet af ansøgers hovedanalyse ved sammenligning med vedolizumab, DKK.

	Tofacitinib (Xeljanz)	Vedolizumab	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Administrationsomkostninger	6.029	18.767	-12.738
Patientomkostninger	2.897	6.866	-3.969
Totale omkostninger	[redacted]	[redacted]	[redacted]

Amgros' vurdering

Ansøger har i deres hovedanalyse anvendt sammenligning med billigste infliximab på det tidspunkt, hvor ansøgningen blev indsendt. Da der efterfølgende er sket ændringer i priserne, anvender Amgros den på nuværende tidspunkt billigste version af infliximab i Amgros' hovedanalyse.

3.1.1 Ansøgers følsomhedsanalyser

Der er udarbejdet en-vejs og multivariate følsomhedsanalyser. Ansøger finder, at de parametre, der har størst betydning for analysen, er gennemsnitsvægten for en UC-patient, spild ved brug af infliximab og administrationsomkostningerne. Nedenfor præsenteres de væsentligste resultater fra følsomhedsanalyserne.

Infliximab har en vægtafhængig dosering. Gennemsnitsvægten har stor betydning for lægemiddelomkostningerne for infliximab og ansøger har derfor udarbejdet en følsomhedsanalyse, hvor gennemsnitsvægten varieres fra 50 kg til 110 kg. Ansøger har undersøgt hvilken betydning vægten har på omkostningerne pr. patient. Analysen viser en besparelse ved anvendelse af tofacitinib (Xeljanz), når en gennemsnitspatient vejer over 75 kg. Vejer patienten mindre end 75 kg er behandling med tofacitinib (Xeljanz) forbundet med meromkostninger.

I ansøgers hovedanalyse antages det, at der ikke er noget spild forbundet med behandlingen. Ansøger har derfor udarbejdet en følsomhedsanalyse, hvor det antages at det ikke er muligt, at dele hætteglas og at den gennemsnitlige dosis infliximab øges fra 3,85 hætteglas til 4 hætteglas. De totale omkostninger for infliximab vil da stige og de inkrementelle omkostninger øges dermed til fordel for tofacitinib (Xeljanz).

Ansøger har udarbejdet en følsomhedsanalyse, hvor administrationsomkostningerne på tofacitinib, infliximab og vedolizumab er varieret med 20%-50% i op- og nedadgående retning. Følsomhedsanalysen viser at ændringer i administrationsomkostningerne har begrænset indflydelse på det samlede resultat.

3.2 Amgros' hovedanalyse

Amgros´ hovedanalyse bygger på samme antagelser som ansøgers hovedanalyse, med undtagelse af:

- Amgros anvender billigste version af infliximab

Resultaterne fra Amgros' hovedanalyse præsenteres tabel 7 og 8.

Amgros' hovedanalyse resulterer i gennemsnitlige meromkostninger per patient for tofacitinib (Xeljanz) på ca. [redacted] sammenlignet med infliximab og på ca. [redacted] sammenlignet med vedolizumab.

Hvis analysen udføres på baggrund af AIP, bliver lægemiddelomkostningerne for tofacitinib (Xeljanz) ca. 126.600 DKK, mens de totale inkrementelle omkostninger bliver ca. 7.600 DKK sammenlignet med infliximab og -94.000 sammenlignet med vedolizumab.

Tabel 7: Resultatet af Amgros' hovedanalyse ved sammenligning med infliximab, DKK.

	Tofacitinib (Xeljanz)	Infliximab	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Administrationsomkostninger	6.029	18.767	-12.738
Patientomkostninger	2.897	6.866	-3.969
Totale omkostninger	[redacted]	[redacted]	[redacted]

Tabel 8: Resultatet af Amgros' hovedanalyse ved sammenligning med vedolizumab, DKK.

	Tofacitinib (Xeljanz)	Vedolizumab	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Administrationsomkostninger	6.029	18.767	-12.738
Patientomkostninger	2.897	6.866	-3.969
Totale omkostninger	[redacted]	[redacted]	[redacted]

4 BUDGETKONSEKVENSER

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

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

Budgetkonsekvenserne bliver differencen mellem budgetkonsekvenserne i de to scenarier.

4.1 Ansøgers estimater

4.1.1 Patientpopulation og markedsandel

Medicinrådet har i protokollen ikke angivet deres vurdering over antallet af patienter. Ansøger har derfor selv udarbejdet et estimat. Ansøger antager at der er 175 bionaive patienter og 175 bioerfarne patienter om året. Dette estimat er fra RADS behandlingsvejledning 2016. Heraf antager ansøger at en del patienter vil falde ud af behandling over tid. Således antages 100% af nyopstartede patienter at være i behandling i år 1, men kun 15 % i år 5. Frafaldet er estimeret ud fra et dansk publiceret studie (Madsen et al 2018) (6). Desuden antager ansøger, at ikke alle patienter begynder behandling år 1. Fordelingen af patienter på de enkelte lægemidler er estimeret ud fra tal fra databasen for biologisk behandling af inflammatoriske tarmsygdomme (BioIBD).

Tabel 9 og 10 viser ansøgers estimat af antal patienter årligt.

Tabel 91: Ansøgers estimat af antal nye patienter per år, bionaive patienter.

	Anbefales som standardbehandling						Anbefales ikke som standardbehandling				
	År 1	År 2	År 3	År 4	År 5		År 1	År 2	År 3	År 4	År 5
Tofacitinib (Xeljanz)	5	11	15	18	19		0	0	0	0	0
Infliximab	79	178	250	298	322		79	178	250	298	322
Vedolizumab	0	0	0	0	0		5	11	15	18	19

Tabel 102: Ansøgers estimat af antal nye patienter per år, bioerfarne patienter.

	Anbefales som standardbehandling						Anbefales ikke som standardbehandling				
	År 1	År 2	År 3	År 4	År 5		År 1	År 2	År 3	År 4	År 5
Tofacitinib (Xeljanz)	70	157	220	262	283		0	0	0	0	0
Infliximab	0	0	0	0	0		9	20	28	33	35
Vedolizumab	9	20	28	33	35		70	157	220	262	283

Amgros' vurdering af estimeret antal patienter
Amgros vurderer at antallet af estimerede patienter på baggrund af RADS behandlingsvejledning virker rimeligt, men har dog fundet en fejl i ansøgers fordeling af patienter over tid.
Amgros tilretter dette i egen budgetkonsekvensanalyse.

4.1.2 Estimat af budgetkonsekvenser

Ansøger har inkluderet de samme omkostninger i budgetkonsekvensanalysen, som der er inkluderet i omkostningsanalysen. Med de indlagte antagelser estimerer ansøger, at anvendelse af tofacitinib (Xeljanz) vil resultere i budgetkonsekvenser på ca. [redacted] per år for bionaive patienter og [redacted] per år for bioerfarne patienter.
Ansøgers estimat af budgetkonsekvenserne fremgår af tabel 11 og 12.

Tabel 11: Ansøgers hovedanalyse for totale budgetkonsekvenser (bionaive patienter), mio. DKK, ikke-diskonterede tal.

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

Tabel 12: Ansøgers hovedanalyse for totale budgetkonsekvenser (bioerfarne patienter), mio. DKK, ikke-diskonterede tal.

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

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

4.1.3 Følsomhed af budgetkonsekvenserne

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

4.2 Amgros' estimater af budgetkonsekvenser

Amgros har korrigeret følgende estimater i forhold til ansøgers analyse:

- Omkostninger til patienttid og transport ekskluderes
- Patientantal tilrettes

Med de indlagte antagelser estimerer Amgros, at anvendelse af tofacitinib (Xeljanz) vil resultere i budgetkonsekvenser på ca. [redacted] per år for de bionaive patienter og [redacted] for de bioerfarne patienter. Se tabel.

Hvis analysen udføres med AIP bliver budgetkonsekvenserne ca. -1,5 mio. per år for de bionaive patienter og -17 mio. DKK for de bioerfarne patienter.

Tabel 13: Amgros' analyse af totale budgetkonsekvenser (bionaive patienter), mio. DKK, ikke-diskonterede tal.

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

Tabel 3: Amgros' analyse af totale budgetkonsekvenser (bioerfarne patienter), mio. DKK, ikke-diskonterede tal.

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

5 DISKUSSION

Behandling med Tofacitinib (Xeljanz) er forbundet med besparelser sammenlignet med behandling med infliximab og vedolizumab. Omkostningerne for Tofacitinib (Xeljanz) er drevet af lægemiddelomkostningerne.
Da tofacititnib (Xeljanz) er et peroralt lægemiddel er administrationsomkostningerne forbundet med brugen af lægemidlet lavere end ved henholdsvis infliximab og vedolizumab som begge gives intravenøst.

Infliximab er vægtafhængig og resultatet af sammenligningen med dette lægemiddel afhænger derfor i høj grad af hvilken gennemsnitsvægt det antages en UC-patient har.

Efter udarbejdelsen af denne afrapportering er Amgros blevet gjort opmærksom på at EMA på baggrund af nye bivirkningsdata nu anbefaler at alle patienter, der får tofacitinib (Xeljanz) 10 mg to gange dagligt, uanset indikation, monitoreres for symptomer på blodpropper i lungerne. Disse monitoreringsomkostninger er ikke opgjort i afrapporteringen, men det forventes at implementeringen af ovenstående vil øge omkostningerne for behandling med tofacitinib (Xeljanz).

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Mette Hollensted

Fra: Sciera, Lucca <Lucca.Sciera@pfizer.com>
Sendt: 25. februar 2020 09:13
Til: Mette Hollensted
Cc: Dahl, Palle; Pilgaard, Trine; Julie Breinholm Svarrer Jakobsen
Emne: Høring over udkast til vurdering af klinisk merværdi for tofacitinib

Opfølgningsflag: Opfølgning
Flagstatus: Fuldført

Kære Mette Hollensted, Medicinrådet

Tak for Medicinrådets endelige vurdering af klinisk merværdi for tofacitinib til behandling af colitis ulcerosa som modtaget pr e-mail den 19. februar 2020, samt vores mulighed for at læse og kommentere vurderingen.

Pfizer accepterer vurderingen som fremsendt.

Vi ønsker at kommentere følgende:

- Vi er enige i, at der i dag er knyttet en vis usikkerhed til sikkerhedsprofilen for tofacitinib ved colitis ulcerosa. Vi ønsker imidlertid at påpege, at usikkerheden i stor udstrækning er relateret til lang tids brug af tofacitinib 10 mg BID som vedligeholdelses-behandling. Vi understreger i den forbindelse, at der for nuværende ikke er noget, som tyder på, at der skulle være en særlig risiko forbundet med brug af tofacitinib 10 mg BID som induktionsbehandling (8 uger) eller forlænget induktionsbehandling (8+8 uger), herunder risiko for alvorlige infektioner eller tromboemboliske hændelser, jvn.f. OCTAVE Induction-studierne(1, 2).
- Med henblik på klinisk merværdi ønsker vi desuden at anføre, at en nyligt publiceret netværks-metaanalyse (3) helt klart viser, at induktionsbehandling med tofacitinib 10 mg BID sammenlignet med placebo i bio-erfarne patienter med colitis ulcerosa medfører en klar klinisk merværdi i forhold til vedolizumab, hvor vedolizumab ikke var signifikant bedre sammenlignet med placebo både som opgjort ved 'mucosal healing' ("endoscopic improvement") samt ved 'klinisk remission'. I bio-naïve patienter var resultaterne mere sammenlignelige.
- Resultater fra Pfizers "long term extension" studie (OCTAVE Open) har vist, at lungeemboli og DVT i patienter med veldefinerede risikofaktorer for sådanne hændelser forekom tidligst efter 7 måneders behandling med tofacitinib 10 mg BID (4). Anbefalingen fra PRAC, og det nyligt opdaterede SmPC, er tydelig omkring anbefalingen af tofacitinib 5 mg BID som standard vedligeholdelses-behandling ved colitis ulcerosa. Tofacitinib 10 mg BID er alene anbefalet til patienter med utilstrækkelig klinisk effekt af tofacitinib 5 mg BID, og hvis patienterne tidligere har haft utilstrækkelig respons af anden avanceret behandling (for eksempel anti-TNF), samt hvis patienterne ikke har kendte risikofaktorer for tromboemboliske hændelser (forudsat at anden behandling ikke er tilgængelig). Det synes i dag usikkert, hvor stor en andel af patienterne, der har behov for tofacitinib 10 mg BID for at opretholde klinisk remission. Pfizer vil fortsat monitorere anvendelsen af tofacitinib til behandling af colitis ulcerosa. Dette inkluderer en evaluering af andelen af patienter, som behandles med tofacitinib 10 mg BID som vedligeholdelses-behandling, samt hvor længe denne dosis af tofacitinib anvendes.

Vi ser frem til en mulig reevaluering af tofacitinib, når dennes sikkerhedsprofil ved colitis ulcerosa findes yderligere klarlagt, herunder viden om forekomst af pulmonær emboli og DVT.

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Med venlig hilsen,
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Medicinrådet

Medicinrådets vurdering af klinisk merværdi for tofacitinib til behandling af colitis ulcerosa

Versionsnr.: 2.0

Medicinrådet

Om Medicinrådet

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

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

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

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

Om vurderingen af klinisk merværdi

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

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

Se Medicinrådets metodehåndbog for yderligere information.

Dokumentoplysninger	
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Indhold

1 Lægemiddelinformationer

Lægemidlets oplysninger	
Handelsnavn	Xeljanz
Generisk navn	Tofacitinib
Firma	Pfizer ApS
ATC-kode	L04AA29
Virkningsmekanisme	Janus kinase inhibitor
Administration/dosis	Tabletter 10 mg to gange dagligt i otte uger efterfulgt af 5 mg to gange dagligt.
EMA-indikation	Tofacitinib er indiceret til behandling af voksne patienter med moderat til alvorlig aktiv colitis ulcerosa, der har haft et utilstrækkeligt respons, ophørt respons eller har været intolerante over for enten konventionel behandling eller et biologisk lægemiddel.

2 Medicinrådets konklusion vedrørende klinisk merværdi

EMA har i november 2019 ændret anbefalingen for anvendelsen af tofacitinib til patienter med moderat til svær colitis ulcerosa. Medicinrådet har på den baggrund revurderet den kliniske merværdi. Denne vurdering af klinisk merværdi erstatter derfor den tidligere vurdering af tofacitinib, som er udgivet af Medicinrådet den 1. juli 2019.

Medicinrådet finder, at tofacitinib giver:

- **negativ klinisk merværdi** hos bionaive patienter med moderat til svær aktiv colitis ulcerosa sammenlignet med infliximab og vedolizumab (meget lav evidenskvalitet)
- **ingen klinisk merværdi** sammenlignet med vedolizumab (meget lav evidenskvalitet) og **ikkedokumenterbar merværdi** sammenlignet med infliximab (evidensens kvalitet kan ikke vurderes) hos bioerfarne patienter med moderat til svær UC.

Medicinrådet kategoriserer lægemidlers kliniske merværdi i en af følgende kategorier:

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

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

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

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

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

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

3 Forkortelser

DVT:	Dybe venetromboser
EMA:	Det Europæiske Lægemiddelagentur (*European Medicines Agency)*
EPAR:	*European public assessment report*
GRADE:	System til vurdering af evidens (*Grading of Recommendations Assessment, Development and Evaluation*)
HR:	*Hazard ratio*
IBDQ:	*Inflammatory Bowel Disease Questionnaire*
ITT:	*Intention-to-treat*
LE:	Lungeemboli
OR:	*Odds ratio*
RADS:	Rådet for Anvendelse af Dyr Sygehusmedicin
RR:	Relativ risiko
SAE:	Alvorlig uønsket hændelse (*Serious Adverse Event)*
s.c.:	Subkutan
SD:	Standardafvigelse (*Standard Deviation)*
TNF:	*Tumor Necrosis Factor*
UC:	Colitis ulcerosa (*Ulcerative Colitis)*

4 Formål

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

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

5 Baggrund

Colitis ulcerosa

Colitis ulcerosa (UC) er en kronisk, inflammatorisk tarmsygdom med uspecifik inflammation i ende- og tyktarmens slimhinde. Sygdommen påvirker oftest/altid endetarmen og nedre dele af tyktarmen. Efter den første episode af UC oplever patienten ofte skiftende perioder med henholdsvis spontan remission, hvor sygdommen ikke giver symptomer, og tilbagefald hvor sygdommen kræver vedligeholdelsesbehandling.

Patienter med moderat til svær UC har symptomer i form af blodige diarréer og/eller afgang af blodigt slim per rektum ved/imellem defækationer [1,2].

Prævalensen af UC i Danmark er estimeret til ca. 35.000 personer, og incidensen er ca. 18,6 pr. år pr. 100.000 personer. Incidensen i Danmark er blandt den højeste i verden og er stigende [3,4].

Nuværende behandling

Ved kronisk aktiv UC kan biologisk behandling initieres, hvis sygdommen ikke bliver bragt i remission under steroidbehandling, hvis sygdommen recidiverer under aftrapning af steroidbehandling, hvis sygdommen ikke bliver holdt i remission med immunsuppressiv behandling (azathioprin, 6-mercaptopurin), og hvis kirurgi ikke er at foretrække [2].

Hos cirka en tredjedel af patienterne aftager effekten af den biologiske behandling, hvorefter dosis kan øges, eller intervallerne mellem behandling må afkortes. Ved ophør af behandlingseffekt kan patienterne i 25-35 % af tilfældene opnå en effekt ved at skifte til en anden biologisk behandling [2].

RADS har i 2016 ligestillet de biologiske lægemidler infliximab, golimumab og vedolizumab som første- og andenlinjebehandling af UC ved bionaive og bioerfarne patienter, mens adalimumab kan overvejes som tredjelinjebehandling [5]. Adalimumab, golimumab og infliximab er TNF-alfa-hæmmere, og vedolizumab er en integrinhæmmer.

Anvendelse af det nye lægemiddel

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

Den anbefalede dosis er 10 mg to gange dagligt i otte uger efterfulgt af 5 mg to gange dagligt. Tofacitinib gives peroralt som tablet, og patienten kan dermed selv administrere behandlingen i modsætning til infliximab og vedolizumab, der gives intravenøst.

Det Europæiske Lægemiddelagentur (EMA) offentliggjorde i 2019 bivirkningsdata vedrørende tofacitinib. På baggrund heraf igangsatte EMA den 16. maj 2019 en undersøgelse af fordele og risici ved brug af tofacitinib til alle godkendte indikationer. På baggrund af undersøgelsen har EMA i november 2019 anbefalet, at tofacitinib 10 mg 2 x dagligt ikke bør anvendes til vedligeholdelsesbehandling, og at patienter over 65 år ikke bør behandles med tofacitinib, medmindre der ikke er andre behandlingsalternativer. Nærmere informationer vedr. anvendelse kan ses på EMAs hjemmeside og i produktresuméet for tofacitinib. Beskrivelse af bivirkninger og konklusioner fra EMAs undersøgelser kan ses i afsnit 9.1.2.

6 Metode

De præspecificerede metoder i protokollen er udarbejdet af Medicinrådet. Ansøger har anvendt og fulgt den præspecificerede metode, jf. protokol, som blev godkendt i Medicinrådet den 24. oktober 2018.

Jf. protokollen har fagudvalget opstillet følgende kliniske spørgsmål, som vil blive besvaret i denne rapport:

1. *Hvad er den kliniske merværdi af tofacitinib til bionaive patienter med moderat til svær UC sammenlignet med henholdsvis infliximab og vedolizumab?*
2. *Hvad er den kliniske merværdi af tofacitinib til bioerfarne patienter med moderat til svær UC sammenlignet med henholdsvis infliximab og vedolizumab?*

Fagudvalget ønskede at sammenligne tofacitinib med to biologiske standardbehandlinger med forskellige virkningsmekanismer (en TNF-alfa-hæmmer og en integrinhæmmer).

Ansøger har indsendt indirekte sammenligninger af tofacitinib og hhv. infliximab og vedolizumab til at besvare klinisk spørgsmål 1. Da ansøger ikke har kunnet identificere data for infliximab i en bioerfaren population, har ansøger kun indsendt en indirekte sammenligning af tofacitinib og vedolizumab til at besvare klinisk spørgsmål 2.

Ansøger har lavet de indirekte sammenligninger ved Buchers metode [6].

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

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

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

7 Litteratursøgning

Ansøger har gennemført en systematisk søgning som efterspurgt i protokollen.

Litteratursøgningen resulterede i identifikationen af 10 publikationer af ni kliniske studier til at besvare klinisk spørgsmål 1. Af disse 10 publikationer er fem publikationer af fire kliniske studier også anvendt til at besvare klinisk spørgsmål 2. De 10 publikationer er beskrevet i tabel 1.

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

Publikationer	Klinisk forsøg	NCT-nummer	Klinisk spørgsmål
Tofacitinib as Induction and Maintenance Therapy for Ulcerative Colitis. **Sandborn et al. 2017. NEJM.** [7]	OCTAVE induction 1 OCTAVE induction 2 OCTAVE SUSTAIN	NCT01465763 NCT01458951 NCT01458574	1 + 2
Tofacitinib in Patients with Ulcerative Colitis: Health-Related Quality of Life in Phase 3 Randomised Controlled Induction and Maintenance Studies. **Panes et al. 2018. JCC.** [8]	OCTAVE induction 1 OCTAVE induction 2 OCTAVE SUSTAIN	NCT01465763 NCT01458951 NCT01458574	1 + 2
Vedolizumab as induction and maintenance therapy for ulcerative colitis. **Feagan et al. 2013. NEJM.** [9]	GEMINI 1	NCT00783718	1 + 2
Efficacy of Vedolizumab Induction and Maintenance Therapy in Patients With Ulcerative Colitis, Regardless of Prior Exposure to Tumor Necrosis Factor Antagonists. **Feagan et al. 2017. Clin Gastroenterol Hepatol.** [10]	GEMINI 1	NCT00783718	1 + 2
Effects of vedolizumab on health-related quality of life in patients with ulcerative colitis: results from the randomised GEMINI 1 trial. **Feagan et al. 2017. Aliment Pharmacol Ther.** [11]	GEMINI 1	NCT00783718	1 + 2
Infliximab for induction and maintenance therapy for ulcerative colitis. **Rutgeerts et al. 2005. NEJM.** [12]	ACT 1 ACT 2	NCT00036439 NCT00096655	1
The effects of infliximab therapy on health-related quality of life in ulcerative colitis patients. **Feagan et al. 2007. Am J Gastroenterol.** [13]	ACT 1 ACT 2	NCT00036439 NCT00096655	1
Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis. **Panaccione et al. 2014. Gastroenterology.** [14]	UC-SUCCES	NCT00537316	Anvendes ikke
First trough level of infliximab at week 2 predicts future outcomes of induction therapy in ulcerative colitis-results from a multicenter prospective randomized controlled trial and its post hoc analysis. **Kobayashi et al. 2016. J. Gastroenterol.** [15]	Kobayashi et al.	Japic CTI-060298	Anvendes ikke
Low-dose Infliximab for Induction and Maintenance Treatment in Chinese Patients With Moderate to Severe Active Ulcerative Colitis. **Jian et al. 2015. J Clin Gastroenterol.** [16]	Jiang et al.	NA	Anvendes ikke

Ansøger har udover ovenstående indsendt data fra tofacitinib, infliximab og vedolizumabs European Public Assessment Report (EPAR) [17–19].

8 Databehandling

De statistiske analyser er udført af ansøger og valideret af Medicinrådets sekretariat. Ansøger har anvendt Buchers metode til indirekte sammenligninger [6]. Medicinrådet har ikke fundet anledning til at foretage ændringer af beregninger foretaget af ansøger eller supplere med yderligere beregninger.

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

- Forskelle i placeboarmene har stor betydning for den indirekte sammenligning for både de absolutte og relative forskelle, da Buchers metode baseres på de relative effekter af lægemidlerne i forhold til placebo. I resultatgennemgangen er det fremhævet, hvor forskellene i effekt i placeboarmene ifølge fagudvalget antyder, at sammenligningerne er behæftet med særlig usikkerhed. Det data, der ligger til grund for ansøgers anvendelse af Buchers metode og dermed for effektresultaterne, fremgår af bilag 1.
- Ansøger har medsendt en sensitivitetsanalyse med data fra studierne af Kobyashi et al, Jiang et al. og UC-SUCCES. Fagudvalget vil dog ikke anvende disse sensitivitetsanalyser af følgende årsager:
    - Studierne af Kobayashi et al. og Jiang et al. undersøger udelukkende infliximab i asiatiske patienter. Fagudvalget vurderer, at forskellen i etnicitet kan få betydning for effektestimaterne.
    - Baselinekarakteristika i Jiang et al.-studiet er forskellige fra de andre studier, da patienterne eksempelvis er yngre og har været syge i kortere tid.
    - UC-SUCCES inkluderer ikke en placeboarm som i de andre studier af tofacitinib, infliximab og vedolizumab.
- I studierne af infliximab og vedolizumab er effektmål, der er baseret på endoskopiske vurderinger, foretaget lokalt, mens de endoskopiske vurderinger i studierne af tofacitinib er foretaget centralt. Det drejer sig om effektmålene *klinisk remission, steroidfri remission* og *mukosal heling*. Ansøger har indsendt data for lokale vurderinger af effektmålene for tofacitinib, men da data er upublicerede, kan fagudvalget ikke basere sine vurderinger herpå. Fagudvalget har derfor baseret vurderingerne af disse effektmål på en central vurdering i tofacitinibstudierne og en lokal vurdering i infliximab- og vedolizumabstudierne.
- Studierne af infliximab og vedolizumab definerer ikke remission som efterspurgt i protokollen og som opgjort i studierne af tofacitinib, dvs. total Mayo-score ≤ 2, ingen subscore > 1 og rektal blødning subscore = 0. Remission er i studierne af vedolizumab og infliximab defineret som en total Mayo-score ≤ 2, ingen subscore > 1 og rektal blødning subscore ≤ 1. På trods af denne forskel i definitionen finder fagudvalget, at effektmålene kan anvendes i sammenligningen med tofacitinib.
- Ansøger har ikke kunnet levere publicerede data for effektmålene *steroidfri remission* og *alvorlige uønskede hændelser* fordelt på bionaive og -erfarne patienter, der fik tofacitinib. I stedet vil fagudvalgets vurdering for disse effektmål være baseret på data for den samlede population.
- Effektmålene *klinisk remission* og *mukosal heling* er i GEMINI 1-studiet opgjort efter 6 uger og ikke efter 8 uger som efterspurgt i protokollen. På trods af denne forskel finder fagudvalget, at effektmålene kan anvendes i vurderingen af tofacitinib.
- Effektmålene *steroidfri remission, alvorlige uønskede hændelser, mukosal heling* og *IBDQ* er i ACT 1-studiet opgjort efter 54 uger og i ACT 2-studiet opgjort efter 30 uger. Det er således ikke opgjort efter 52 uger som efterspurgt i protokollen. På trods af denne forskel finder fagudvalget, at effektmålene kan anvendes i vurderingen af tofacitinib.
- Ansøger har udelukkende leveret IBDQ-data ved 8 ugers opfølgning vedr. tofacitinib og sammenlignet disse med IBDQ opgjort efter ca. 1 år for hhv. infliximab og vedolizumab.

- Ansøger har, udover at levere data på subpopulationerne, også leveret data for alle effektmål for den samlede population af bionaive og bioerfarne patienter vedr. tofacitinib og vedolizumab. Fagudvalget vil ved alle analyser, der er opdelt på bionaive og bioerfarne patienter, sammenholde resultaterne med analyser for den samlede population.

9 Klinisk merværdi

Som det er beskrevet i protokollen, vurderer fagudvalget den kliniske merværdi af tofacitinib i to populationer:

1) **Bionaive** patienter med moderat til svær UC, der opfylder kriterierne for biologisk behandling (jf. afsnit 5 *Nuværende behandling*)
2) **Bioerfarne** patienter med moderat til svær UC, der opfylder kriterierne for biologisk behandling (jf. afsnit 5 *Nuværende behandling*).

Dette er afspejlet i de to kliniske spørgsmål. Besvarelserne af de kliniske spørgsmål følger nedenfor. For hvert klinisk spørgsmål er der 1) en konklusion samt en gennemgang af 2) studier, 3) resultater og vurdering for hvert effektmål, 4) evidensens kvalitet og 5) argumentation og konklusion for det kliniske spørgsmål.

9.1 Konklusion klinisk spørgsmål 1

Hvad er den kliniske merværdi af tofacitinib til bionaive patienter med moderat til svær UC sammenlignet med henholdsvis infliximab og vedolizumab?

Fagudvalget har på baggrund af EMAs ændrede anbefalinger revurderet den kliniske merværdi af tofacitinib til bionaive patienter med moderat til svær UC.

Fagudvalget vurderer, at tofacitinib til bionaive patienter med UC giver **negativ klinisk merværdi** sammenlignet med henholdsvis infliximab og vedolizumab (meget lav evidenskvalitet).

9.1.1 Gennemgang af studier

Ansøger identificerede tre studier af tofacitinib, ét studie af vedolizumab og fem studier af infliximab. Studiernes karakteristika og populationer er beskrevet nedenfor.

Karakteristika

Studier af tofacitinib
OCTAVE induction 1 og OCTAVE induction 2 [7,8]: De to studier har samme studiedesign og er randomiserede, kontrollerede, dobbeltblindede 8-ugers induktionsstudier. Studierne undersøger dermed tofacitinib som induktionsbehandling hos patienter med moderat til svær UC. Patienterne var randomiseret 4:1 til tofacitinib 10 mg to gange dagligt (samlet n = 905) eller placebo (samlet n = 234). Randomiseringen blev blandt andet stratificeret efter tidligere behandling med en TNF-alfa-hæmmer. Effektanalyser er baseret

på alle randomiserede patienter (samlet = 1.139)[1], og sikkerhedsanalyser er baseret på alle randomiserede patienter, der modtog mindst én studiedosis (samlet n = 1.139). Studiernes primære effektmål er remission ved uge 8, og studiernes sekundære effektmål af relevans for vurderingen her er mukosal heling ved uge 8.

OCTAVE SUSTAIN [7,8]: Dette studie er en forlængelse af OCTAVE induction 1 og 2 og undersøger fastholdelsesbehandling med tofacitinib. Patienterne, der ved afslutningen af de to induktionsstudier havde klinisk respons[2], blev re-randomiseret 1:1:1 til tofacitinib 5 mg to gange dagligt (n = 198), 10 mg to gange dagligt (n = 197) eller placebo (n = 198). Randomiseringen blev stratificeret efter gruppetildeling i induktionsstudiet og remissionsstatus, men ikke for tidligere behandling med en TNF-alfa-hæmmer. 88 % af patienterne var behandlet med tofacitinib i induktionsstudiet, og 30 % var i remission, da de indgik i OCTAVE SUSTAIN-studiet. Effektanalyser er baseret på alle randomiserede patienter (n = 593), og sikkerhedsanalyser er baseret på alle randomiserede patienter, der modtog mindst én studiedosis (n = 592). Studiets primære effektmål er remission ved uge 52, og studiets sekundære effektmål af relevans for vurderingen her er mukosal heling ved uge 52, steroidfri remission ved uge 52, livskvalitet målt ved *Inflammatory Bowel Disease Questionnaire* (IBDQ) og sikkerhed.

Studier af vedolizumab

GEMINI 1 [9–11]: GEMINI 1 består af to integrerede randomiserede, kontrollerede, dobbeltblindede 6- og 52-ugers studier, der henholdsvis undersøger induktions- og fastholdelsesbehandling med vedolizumab hos patienter med aktiv UC. I induktionsdelen var patienterne randomiseret 3:2 til vedolizumab 300 mg dag 1 og 15 (n = 225) eller placebo (n = 149). Randomiseringen blev blandt andet stratificeret efter tidligere behandling med en TNF-alfa-hæmmer. Patienterne, der ved afslutningen af induktionsdelen havde klinisk respons, blev re-randomiseret 1:1:1 til vedolizumab hver 8. uge, vedolizumab hver 4. uge eller placebo. Randomiseringen blev blandt andet stratificeret efter gruppetildeling i induktionsdelen og tidligere behandling med en TNF-alfa-hæmmer. Effektanalyser er baseret på intention to treat (ITT)-populationen, dvs. alle randomiserede patienter (n = 374) og sikkerhedsanalyser er baseret på alle randomiserede patienter, der modtog mindst én studiedosis (n = 895)[3]. I induktionsdelen er studiets primære effektmål klinisk respons ved uge 6, og studiets sekundære effektmål af relevans for vurderingen her er klinisk remission ved uge 6. I fastholdelsesdelen er studiets primære effektmål klinisk remission ved uge 52, og studiets sekundære effektmål af relevans for vurderingen her er mukosal heling ved uge 52, steroidfri remission ved uge 52, livskvalitet målt ved IBDQ og sikkerhed.

Studier af infliximab

ACT 1 og ACT 2 [12,13]: De to studier har samme studiedesign og er randomiserede, kontrollerede, dobbeltblindede studier. Studierne undersøger induktions- og fastholdelsesbehandling med infliximab hos patienter med moderat til svær UC, der ikke tidligere har fået behandling med en TNF-alfa-hæmmer. ACT 1 følger patienterne i 54 uger, og ACT 2 følger dem i 30 uger. Patienterne var i begge studier randomiseret 1:1:1 til infliximab 5 mg pr. kg (n = 121 og n = 121), infliximab 10 mg pr. kg (n = 122 og n = 120) eller placebo (n = 121 og n = 123). Effekt- og sikkerhedsanalyser er baseret på alle randomiserede patienter (n = 364 og n = 364). Studiernes primære effektmål er klinisk respons ved uge 8. Studiernes sekundære effektmål

[1] 22 patienter blev randomiseret til tofacitinib 15 mg., da studierne i begyndelsen inkluderede denne behandlingsarm. Pfizer besluttede ikke at undersøge denne dosis nærmere og ændrede derfor protokollen undervejs i randomiseringen. De 22 patienter, der nåede at blive randomiseret til tofacitinib 15 mg., indgår ikke i effekt- og sikkerhedsanalyserne og er derfor ikke inkluderet her.
[2] Klinisk respons var defineret som en reduktion på mindst 3 point (og mindst 30 %) på patientens Mayo-score. Derudover skulle patienten have reduktion på mindst 1 point på subscoren for rektal blødning, eller score 0-1 på denne.
[3] Heraf indgår 521 patienter, der fik open-label vedolizumab.

af relevans for vurderingen her er klinisk remission ved uge 8, mukosal heling ved uge 8, mukosal heling ved uge 54, steroidfri remission ved uge 54, livskvalitet målt ved IBDQ og sikkerhed.

Population

Af nedenstående tabel fremgår baselinekarakteristika for de aktive studiearme i de inkluderede studier. Baselinekarakteristikaene er ikke fordelt på bionaive og -erfarne patienter, men for den samlede population hvad angår tofacitinib og vedolizumab. For infliximab er der kun data på bionaive patienter.

Tabel 2. Baselinekarakteristika for populationerne i de aktive studiearme

	OCTAVE 1	OCTAVE 2	OCTAVE Sustain	GEMINI 1	ACT 1	ACT 2
Mænd (%)	58,2	60,4*	52,0	58,7	64,5	62,8
Alder, år (gns. ± SD)	41,3 (14,1)	41,1 (13,5)	41,9 (13,7)**	40,1 (13,1)	42,4 (14,3)	40,5 (13,1)
Sygdoms-varighed, år median (range) (gns. ± SD)	6,5 (0,3-42,5)	6,0 (0,4-39,4)	6,5 (0,6-40,3)**	6,1 (5,1)	5,9 (5,4)	6,7 (5,3)
Sværhedsgrad, Mayo-score (gns. ± SD)***	9,0 (1,4)	9,0 (1,5)	3,3 (1,8)**	8,5 (1,8)	8,5 (1,7)	8,3 (1,5)
Tidligere behandling med TNF-alfa hæmmer (%)	53,4	54,5	45,5	42,2	0	0
Samtidig behandling (%) - Steroid - Immunosuppressiva	 45,0 0	 46,2 0	 51,0 0	 56 36,3	 57,9 54,5	 49,6 43

SD = Standardafvigelse *(Standard Deviation).*

* Der er signifikant forskel i andelen af mænd i tofacitinib- og placeboarmen (49,1 % mænd i placeboarmen).

** Målt ved start af OCTAVE Sustain, dvs. efter de 8 ugers induktionsbehandling i OCTAVE 1 og 2.

*** Total Mayo-score går fra 0-12, hvor en højere score indikerer svær UC.

Som tabel 2 viser, er der stor forskel i andelen af patienter, der tidligere har fået TNF-alfa- hæmmer, da infliximabstudierne ikke inkluderer bioerfarne patienter. Der er ligeledes en vis forskel i andelen af patienter, der sideløbende får anden medicinsk behandling, blandt andet fordi tofacitinibstudierne ikke tillader, at patienterne får samtidig behandling med immunsuppressiva.

Med ovenstående forskelle fremhævet finder fagudvalget, at der derudover ikke er betydende forskelle i baselinekarakteristika mellem studiearmene. Fagudvalget vurderer, at patientkarakteristika i studiet ikke afviger væsentligt fra den danske patientpopulation.

9.1.2 Resultater og vurdering

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

Som beskrevet i protokollen baserer fagudvalget den samlede kliniske merværdi af tofacitinib på en tidshorisont på 52 uger, men vurderer også enkelte effektmål efter 8 uger. For effektmål omhandlende sikkerhed vurderer fagudvalget data med en så lang opfølgningstid som muligt.

Klinisk remission, uge 8 (kritisk)

Klinisk remission er defineret ved en total Mayo-score ≤ 2, ingen subscore > 1 og rektal blødning-score = 0. Mayo-score er det mest anvendte scoringssystem i kliniske studier til at vurdere sygdomsaktivitet i UC. Mayo-score indeholder en samlet vurdering af følgende fire subscores: afføringsmønster, rektal blødning, endoskopiske fund og en samlet vurdering af sygdomsaktiviteten foretaget af en kliniker. For hvert område er der fire svarmuligheder (0 til 3 point), og den samlede score går således fra 0 til 12 point, hvor en høj score indikerer værre sværhedsgrad af UC [20].

Fagudvalget har vurderet, at en forskel på 10 procentpoint i andelen af patienter, der oplever klinisk remission ved uge 8, er klinisk relevant.

Som fremhævet i afsnit 8 'Databehandling' er der forskellige årsager til, at fagudvalget har forbehold for analyserne af dette effektmål:

- Studierne af infliximab og vedolizumab definerer ikke klinisk remission som efterspurgt i protokollen, men som en total Mayo-score ≤ 2, ingen subscore > 1 og rektal blødning-score ≤ 1.
- Effektmålet er i GEMINI 1-studiet opgjort efter 6 uger og ikke efter 8 uger som efterspurgt i protokollen.
- I studierne af infliximab og vedolizumab er vurderingen af effektmålet foretaget lokalt (hvad angår den endoskopiske vurdering), mens det i studiet af tofacitinib er foretaget centralt.

På trods af disse forskelle finder fagudvalget, at de sammenlignende analyser kan benyttes.

Tabel 3. Vurdering af klinisk merværdi: Klinisk remission, uge 8. Klinisk spørgsmål 1 (bionaive patienter).

	Forhåndsdefineret grundlag for vurdering		Resultater	
			Tofacitinib vs. infliximab	Tofacitinib vs. vedolizumab
Absolutte forskelle	10 procentpoint		-18,3 procentpoint [-29,5;10,9]	-10,9 procentpoint [-18,8;11,7]
Relative forskelle	Stor merværdi	Nedre konf.gr. > 1,33		
	Vigtig merværdi	Nedre konf.gr. > 1,11		
	Lille merværdi	Nedre konf.gr. > 1,00		
	Ingen merværdi	Nedre konf.gr. < 1,00	RR = 0,50 [0,19;1,30]	RR = 0,53 [0,18;1,51]
	Negativ merværdi	Øvre konf.gr. < 1,00		
Evidensens kvalitet	Meget lav			

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

De absolutte effektforskelle på hhv. -18,3 og -10,9 procentpoint er større end den forhåndsdefinerede mindste klinisk relevante forskel for en negativ forskel, dvs. i infliximabs og vedolizumabs favør. Disse resultater kan skyldes, at effekterne i placebogrupperne varierer på tværs af de inkluderede studier. I tofacitinibstudierne opnår 12,5 % af patienterne i placeboarmene effekt, mens kun 10,3 % og 6,6 % af patienterne i placeboarmene opnår effekt i henholdsvis infliximab- og vedolizumabstudierne (se bilag 1). Som beskrevet i afsnit 8 Databehandling kan dette medføre, at sammenligningerne er behæftet med usikkerhed.

De relative effektforskelle er hhv. 0,50 og 0,53 for tofacitinib sammenlignet med hhv. infliximab og vedolizumab. Begge effektestimaters nedre grænse af konfidensintervallet er mindre end 1,0 og indikerer dermed ingen merværdi.

For den samlede population af bionaive og -erfarne patienter er den absolutte forskel for sammenligningen med infliximab -8,0 procentpoint [-26,4; 44,4] og den relative forskel er 0,78 [0,27; 2,22]. Sammenlignet med vedolizumab er den absolutte forskel -1,3 procentpoint [-11,1; 25,5] og den relative forskel 0,93 [0,34; 2,51]. Fagudvalget finder, at disse data for den samlede population understøtter vurderingen af, at der ikke er klinisk merværdi vedr. effektmålet i den bionaive population alene.

Samlet vurderer fagudvalget, at tofacitinib har **ingen klinisk merværdi** sammenlignet med infliximab og vedolizumab vurderet på effektmålet *klinisk remission, uge 8*.

Steroidfri remission, uge 52 (kritisk)

Steroidfri remission er defineret ved, at patienterne ikke er i steroidbehandling efter 52 uger og har en total Mayo-score ≤ 2, ingen subscore > 1 og rektal blødning-score = 0. Mayo-scoresystemet er beskrevet ovenfor (afsnit vedr. klinisk remission).

Fagudvalget har vurderet, at en forskel på 10 procentpoint i andelen af patienter, der oplever steroidfri remission ved uge 52, er klinisk relevant.

Som fremhævet i afsnit 8 'Databehandling' har ansøger ikke kunnet levere publicerede data for effektmålet fordelt på bionaive og -erfarne patienter, der fik tofacitinib. I stedet anvendes derfor data for den samlede population til vurderingen.

Tabel 4. Vurdering af klinisk merværdi: Steroidfri remission, uge 52. Klinisk spørgsmål 1 (bionaive og -erfarne patienter).

	Forhåndsdefineret grundlag for vurdering		Resultater	
			Tofacitinib vs. infliximab	Tofacitinib vs. vedolizumab
Absolutte forskelle	10 procentpoint		-5,5 [-15,8; 21,5]	3,9 [-17,4; 58,0]
Relative forskelle	Stor merværdi	Nedre konf.gr. > 1,33		
	Vigtig merværdi	Nedre konf.gr. > 1,11		
	Lille merværdi	Nedre konf.gr. > 1,00		
	Ingen merværdi	Nedre konf.gr. < 1,00	RR = 0,76 [0,29; 1,96]	RR = 1,12 [0,45; 2,85]
	Negativ merværdi	Øvre konf.gr. < 1,00		
Evidensens kvalitet	Meget lav			

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

De absolutte effektforskelle på hhv. -5,5 og 3,9 procentpoint er mindre end den forhåndsdefinerede mindste klinisk relevante forskel.

De relative effektforskelle er opgjort som en relativ risiko på hhv. 0,76 og 1,12 for tofacitinib sammenlignet med hhv. infliximab og vedolizumab. Begge effektestimaters nedre grænse af konfidensintervallet er mindre end 1,0 og indikerer dermed ingen merværdi.

Samlet vurderer fagudvalget, at tofacitinib har **ingen klinisk merværdi** sammenlignet med infliximab og vedolizumab vurderet på effektmålet *steroidfri remission, uge 52.*

Alvorlige uønskede hændelser (kritisk)

Fagudvalget finder, at andelen af patienter, som oplever en eller flere alvorlige uønskede hændelser, er særligt relevant for vurderingen, da tofacitinib er et nyt lægemiddel med en ny virkningsmekanisme.

Fagudvalget har vurderet, at en forskel på 5 procentpoint i andelen af patienter, der oplever alvorlige uønskede hændelser, er klinisk relevant.

Som fremhævet i afsnit 8 'Databehandling' har ansøger ikke kunnet levere publicerede data for effektmålet fordelt på bionaive og -erfarne patienter, der fik tofacitinib. I stedet anvendes derfor data for den samlede population til vurderingen.

Tabel 5. Vurdering af klinisk merværdi: Alvorlige uønskede hændelser. Klinisk spørgsmål 1 (bionaive og -erfarne patienter).

	Forhåndsdefineret grundlag for vurdering		Resultater	
			Tofacitinib vs. infliximab	Tofacitinib vs. vedolizumab
Absolutte forskelle	5 procentpoint		1,1 [-9,1; 26,0]	4,0 [-4,0;27,6]
Relative forskelle	Stor merværdi	Øvre konf.gr. < 0,75		
	Vigtig merværdi	Øvre konf.gr. < 0,90		
	Lille merværdi	Øvre konf.gr. < 1,00		
	Ingen merværdi	Øvre konf.gr. > 1,00	RR = 1,07 [0,44; 2,62]	RR = 1,49 [0,51; 4,36]
	Negativ merværdi	Nedre konf.gr. > 1,00		
Evidensens kvalitet	Meget lav			

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

De absolutte effektforskelle på hhv. 1,1 og 4,0 procentpoint er mindre end den forhåndsdefinerede mindste klinisk relevante forskel.

De relative effektforskelle er opgjort som en relativ risiko på hhv. 1,07 og 1,49 for tofacitinib sammenlignet med hhv. infliximab og vedolizumab. Begge effektestimaters øvre grænse af konfidensintervallet er større end 1,0 og indikerer dermed ingen merværdi.

Ifølge fagudvalget indikerer ovenstående, at tofacitinib har ingen klinisk merværdi sammenlignet med infliximab og vedolizumab vurderet på effektmålet *alvorlige uønskede hændelser*.

Kvalitativ gennemgang – revurdering af effektmål på baggrund af ændret anbefaling fra EMA
Overordnet set har tofacitinib, infliximab og vedolizumab sammenlignelige sikkerhedsprofiler. Patienter behandlet med induktionsdosis af tofacitinib (2 x 10 mg dagligt) havde dog en højere forekomst af herpes zoster [17–19]. Stigninger i lipidkoncentrationerne i blodet er blevet rapporteret i forbindelse med anvendelse af tofacitinib, og monitorering af lipidkoncentrationerne otte uger efter behandlingsstart er anbefalet [18].

Fagudvalget er opmærksom på de af EMA nyligt offentliggjorte bivirkningsdata vedrørende tofacitinib til patienter med kronisk leddegigt [21]. Patienter, der fik tofacitinib i en daglig dosis på 20 mg (2 x 10 mg dagligt) i et fase 4 sikkerhedsstudie (NCT02092467), havde øget risiko for at få blodpropper i lungerne og dø. Dosis i studiet svarer til induktionsdosis for patienter behandlet for UC, og fagudvalget er derfor særligt opmærksomme på studiets bivirkningsdata. Patienterne i fase 4-studiet har kronisk leddegigt, er over 50 år og har i forvejen mindst en risikofaktor for hjerte-kar-sygdom.

EMA har på baggrund af de nye bivirkningsdata igangsat en undersøgelse af fordele og risici ved brug af tofacitinib til alle godkendte indikationer. Mens evalueringen foretages, har EMA besluttet, at tofacitinib 10 mg to gange dagligt er kontraindiceret til patienter, som er bedømt at have samtidig høj risiko for lungeemboli. EMA anbefaler desuden, at alle patienter, der får tofacitinib, uanset indikationen, monitoreres for symptomer på blodpropper i lungerne.

Fagudvalget vurderer, at der er betydelige forskelle mellem populationen i fase 4-studiet med kronisk leddegigt og populationen med UC, der potentielt vil få tofacitinib. Fagudvalget mener dog, at disse data viser, at tofacitinib fortsat har en forholdsvis uafklaret bivirkningsprofil for patienter med UC sammenlignet med de biologiske lægemidler, der anvendes som førstelinje i Danmark i dag.

EMA har den 15. november 2019 udsendt en opdateret anbefaling vedr. brug af tofacitinib på baggrund af det igangværende fase 4-studie (NCT02092467), som er beskrevet ovenfor. EMA konkluderer, at tofacitinib kan øge risikoen for lungeembolier samt dybe venetromboser (DVT) hos patienter, som i forvejen har øget risiko for blodpropper [22]. EMA anbefaler derfor, at tofacitinib bruges med forsigtighed til patienter med høj risiko for blodpropper og ikke anvendes til patienter over 65 år, med mindre der ikke er andre behandlingsalternativer. Yderligere anbefaler EMA, at tofacitinib 10 mg 2 x dagligt ikke anvendes til patienter med colitis ulcerosa som vedligeholdelsesbehandling, med mindre der ikke er andre behandlingsalternativer. Foreløbige data fra fase 4-studiet (NCT02092467) med patienter med kronisk leddegigt viser en dosisafhængig øget risiko for blodpropper ved behandling med tofacitinib sammenlignet med TNF-hæmmere.

Incidensraterne (95 % KI) for lungeembolier var 0,54 (0,32-0,87), 0,27 (0,12-0,52) og 0,09 (0,02-0,26) patienter med events per 100 patient-år for hhv. tofacitinib 10 mg 2 x dagligt, 5 mg 2 x dagligt og TNF-hæmmere. Hazard ratioen (HR) var 5,96 (1,75-20,33) for tofacitinib 10 mg 2 x dagligt og 2,99 (0,81-11,06) for tofacitinib 5 mg 2 x dagligt sammenlignet med TNF-hæmmere. Incidensraterne (95 % KI) for dybe venetromboser var for tofacitinib 10 mg 2 x dagligt, 5 mg 2 x dagligt og TNF-hæmmere hhv. 0,38 (0,20-0,67), 0,30 (0,14-0,55) og 0,18 (0,07-0,39) patienter med events per 100 patient-år. HR for dybe venetromboser var 2,13 (0,80-5,69) for tofacitinib 10 mg 2 x dagligt og 1,66 (0,60-4,57) for tofacitinib 5 mg 2 x dagligt sammenlignet med TNF-hæmmere [23].

En samlet opgørelse over forekomsten af DVT og lungeembolier i patienter med colitis ulcerosa i det kliniske udviklingsprogram for tofacitinib understøtter EMAs konklusion af studiet for patienter med leddegigt. I opgørelsen rapporteres én forekomst af DTV og 4 tilfælde af lungeembolier i patienter, som modtog tofacitinib 10 mg 2 x dagligt i vedligeholdelsesbehandling. Alle tilfælde blev rapporteret i et ekstensionsstudie. Til sammenligning blev der i placebogruppen rapporteret ét tilfælde af DVT og ét tilfælde af lungeemboli i induktionsperioden samt ét tilfælde af DTV og 2 tilfælde (i samme patient) af

lungeembolier i vedligeholdelsesperioden. I alle tilfælde havde patienterne kendte risikofaktorer for blodpropper [24].

Fagudvalget vurderer, på baggrund af de nye anbefalinger fra EMA, at tofacitinib fortsat har en uafklaret bivirkningsprofil. Selvom fagudvalget finder, at bivirkningsprofilerne overordnet set er sammenlignelige for den generelle population af patienter med colitis ulcerosa, vurderer fagudvalget dog, at bivirkningsprofilerne for infliximab og vedolizumab er bedre belyst, og vægter dette i vurderingen af effektmålet.

Samlet vurdering

Samlet vurderer fagudvalget, at tofacitinib har **negativ klinisk merværdi** sammenlignet med infliximab og vedolizumab vurderet på effektmålet *alvorlige uønskede hændelser*, grundet usikkerhed omkring bivirkningsprofilen. Derudover er anvendelse af tofacitinib forbundet med øget forekomst af herpes zoster og lipidstigninger.

Mukosal heling, uge 8 (vigtig)

Mukosal heling er defineret ved en endoskopisk subscore ≤ 1 (subscoren indgår i den samlede Mayo-score). Subscoren afspejler slimhindeudseendet ved en endoskopi, og scoren går fra 0-4, hvor en høj score indikerer værre sværhedsgrad af slimhindens udseende [20]. Mukosal heling er et vigtigt klinisk behandlingsmål, da det er prædiktor for behandlingseffekt og en prognostisk markør for langtidseffekt af behandlingen. Fagudvalget finder, at tidlig mukosal heling er vigtigt for patienterne.

Fagudvalget har vurderet, at en forskel på 10 procentpoint i andelen af patienter, der oplever mukosal heling ved uge 8, er klinisk relevant.

Som fremhævet i afsnit 8 'Databehandling' er der forskellige årsager til, at fagudvalget har visse forbehold for analyserne af dette effektmål:

- Effektmålet *mukosal heling* er i GEMINI 1-studiet opgjort efter 6 uger og ikke efter 8 uger som efterspurgt i protokollen.
- I studierne af infliximab og vedolizumab er vurderingen af effektmålet foretaget lokalt (hvad angår den endoskopiske vurdering), mens det i studiet af tofacitinib er foretaget centralt.

På trods af disse forskelle finder fagudvalget, at de sammenlignende analyser kan benyttes.

Tabel 6. Vurdering af klinisk merværdi: Mukosal heling, uge 8. Klinisk spørgsmål 1 (bionaive patienter).

	Forhåndsdefineret grundlag for vurdering		Resultater	
			Tofacitinib vs. infliximab	Tofacitinib vs. vedolizumab
Absolutte forskelle	10 procentpoint		-8,1 procentpoint [-26,5;20,0]	-8,2 procentpoint [-25,9;22,9]
Relative forskelle	Stor merværdi	Nedre konf.gr. > 1,33		
	Vigtig merværdi	Nedre konf.gr. > 1,11		
	Lille merværdi	Nedre konf.gr. > 1,00		
	Ingen merværdi	Nedre konf.gr. < 1,00	RR = 0,87 [0,57;1,33]	RR = 0,83 [0,47;1,47]
	Negativ merværdi	Øvre konf.gr. < 1,00		

Evidensens kvalitet	Lav for sammenligningen med infliximab Meget lav for sammenligningen med vedolizumab

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

De absolutte effektforskelle på hhv. -8,1 og -8,2 procentpoint er ikke større end den forhåndsdefinerede mindste klinisk relevante forskel, men er i infliximabs og vedolizumabs favør. Effektestimaterne er dog ikke statistisk signifikante.

De relative effektforskelle er opgjort som en relativ risiko på hhv. 0,87 og 0,83 for tofacitinib sammenlignet med hhv. infliximab og vedolizumab. Begge effektestimaters nedre grænse for konfidensintervallet er mindre end 1,0 og indikerer dermed ingen merværdi.

For den samlede population af bionaive og -erfarne patienter er den absolutte forskel for sammenligningen med infliximab 9,4 procentpoint [-13,7; 43,8] (til tofacitinibs fordel) og den relative forskel er 1,15 [0,78; 1,72]. Sammenlignet med vedolizumab er den absolutte forskel 13,2 procentpoint [-6,6; 45,4] og den relative forskel 1,32 [0,83; 2,11]. Resultaterne kan indikere, at de bioerfarne patienter muligvis har større effekt af tofacitinib, hvad angår dette effektmål (se tabel 15), men resultaterne er behæftet med stor usikkerhed og giver ikke fagudvalget anledning til at ændre merværdikategorien for den bionaive population.

Samlet vurderer fagudvalget, at tofacitinib har **ingen klinisk merværdi** sammenlignet med infliximab og vedolizumab vurderet på effektmålet *mukosal heling, uge 8*.

Mukosal heling, uge 52 (vigtig)

Mukosal heling er defineret ovenfor. Fagudvalget finder, at langtidseffekten af behandlingen er betydningsfuld for patienterne.

Fagudvalget har vurderet, at en forskel på 10 procentpoint i andelen af patienter, der opnår mukosal heling ved uge 52, er klinisk relevant.

Som fremhævet i afsnit 8 'Databehandling' bliver effektmålet i studierne af infliximab og vedolizumab vurderet lokalt, mens det i studiet af tofacitinib er foretaget centralt. På trods af dette finder fagudvalget, at de sammenlignende analyser kan benyttes.

Tabel 7. Vurdering af klinisk merværdi: Mukosal heling, uge 52. Klinisk spørgsmål 1 (bionaive patienter).

	Forhåndsdefineret grundlag for vurdering		Resultater	
			Tofacitinib vs. infliximab	Tofacitinib vs. vedolizumab
Absolutte forskelle	10 procentpoint		33,1 procentpoint [-9,2;124,3]	22,9 procentpoint [-20,4;114,2]
Relative forskelle	Stor merværdi	Nedre konf.gr. > 1,33		
	Vigtig merværdi	Nedre konf.gr. > 1,11		
	Lille merværdi	Nedre konf.gr. > 1,00		
	Ingen merværdi	Nedre konf.gr. < 1,00	RR = 1,72 [0,80;3,71]	RR = 1,38 [0,66;2,91]
	Negativ merværdi	Øvre konf.gr. < 1,00		

Evidensens kvalitet	Meget lav for sammenligningen med infliximab Lav for sammenligningen med vedolizumab

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

De absolutte effektforskelle på hhv. 33,1 og 22,9 procentpoint er større end den forhåndsdefinerede mindste klinisk relevante forskel i tofacitinibs favør. Estimaterne er dog behæftet med stor usikkerhed.

De relative effektforskelle er opgjort som en relativ risiko på hhv. 1,72 og 1,38 for tofacitinib sammenlignet med hhv. infliximab og vedolizumab. Begge effektestimaters nedre grænse for konfidensintervallet er mindre end 1,0 og indikerer dermed ingen merværdi.

For den samlede population af bionaive og -erfarne patienter er den absolutte forskel for sammenligningen med infliximab 21,8 procentpoint [-10,4; 83,0] og den relative forskel er 1,47 [0,77; 2,81]. Sammenlignet med vedolizumab er den absolutte forskel 4,5 procentpoint [-20,4; 49,4] og den relative forskel 1,09 [0,61; 1,96]. Usikkerheden i resultaterne gør, at fagudvalget ikke finder anledning til at ændre merværdikategorien for den bionaive population.

Samlet vurderer fagudvalget, at tofacitinib har **ingen klinisk merværdi** sammenlignet med infliximab og vedolizumab vurderet på effektmålet *mukosal heling, uge 52*.

Inflammatory Bowel Disease Questionnaire (IBDQ) (vigtig)

IBDQ er et velvalideret, sygdomsspecifikt livskvalitetsinstrument, der vægter symptomer og problemer, der er særlige for patienter med inflammatoriske tarmsygdomme [20,25]. Spørgeskemaet består af 32 spørgsmål fordelt på fire dimensioner: afføringssymptomer, emotionel sundhed, systemiske symptomer og social funktion. Skalaen går fra 32 til 224, hvor en højere værdi indikerer bedre livskvalitet.

Fagudvalget har vurderet, at en gennemsnitlig ændring fra baseline på 16 point eller mere er klinisk relevant.

Som fremhævet i afsnit 8 'Databehandling' er der forskellige årsager til, at fagudvalget har visse forbehold for analyserne af dette effektmål:

- Data vedr. tofacitinib er opsamlet ved uge 8 og sammenlignes med data efter ca. 1 års opfølgningstid vedr. infliximab og vedolizumab.
- Data vedr. infliximab er aflæst fra en graf.

Fagudvalget mener derfor, at resultaterne vedr. IBDQ skal tolkes meget varsomt.

Tabel 8. Vurdering af klinisk merværdi: IBDQ. Klinisk spørgsmål 1 (bionaive patienter).

	Forhåndsdefineret grundlag for vurdering	Resultater	
		Tofacitinib vs. infliximab	Tofacitinib vs. vedolizumab
Absolutte forskelle	Gennemsnitlig ændring fra baseline på 16 point eller mere	0,2 point [-9,3;9,6]	-8,6 point [-22,1;5,0]
Evidensens kvalitet	Meget lav		

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

De absolutte effektforskelle på hhv. 0,2 point og -8,6 point på IBDQ-skalaen er ikke større end den forhåndsdefinerede mindste klinisk relevante forskel. Derudover er estimaterne behæftet med stor usikkerhed.

For den samlede population af bionaive og -erfarne patienter er den absolutte forskel for sammenligningen med infliximab 2,5 point [-5,2; 10,2]. Sammenlignet med vedolizumab er den absolutte forskel -1,5 point [-11,9; 9,0].

Grundet fagudvalgets forbehold for data, der er af ringe kvalitet, og at estimaterne er behæftet med stor usikkerhed, vurderer fagudvalget, at merværdien for dette effektmål er **ikkedokumenterbar.**

9.1.3 Evidensens kvalitet

Evidensens kvalitet for klinisk spørgsmål 1 (bionaive patienter) er samlet set vurderet at være **meget lav,** da evidensens kvalitet for det laveste vurderede kritiske effektmål, er **meget lav**.

Indledningsvist blev lægemidlernes direkte sammenligninger med placebo vurderet. Overordnet var alle studier af høj kvalitet, og der blev ikke nedgraderet for risiko for bias (se bilag 2). Der er nedgraderet for *"inconsistency"* og *"imprecision"* for flere af effektmålene.

Derudover er der for alle effektmål nedgraderet for *"indirectness"*, da alle sammenligninger mellem tofacitinib og henholdsvis infliximab og vedolizumab er indirekte. Yderligere overvejelser vedrørende evidensens kvalitet kan ses i bilag 2.

9.1.4 Konklusion for klinisk spørgsmål 1 (bionaive patienter)

Fagudvalget vurderer, at tofacitinib til bionaive patienter med moderat til svær UC giver **negativ klinisk merværdi** (meget lav evidenskvalitet) sammenlignet med infliximab og vedolizumab.

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

Tabel 9. Samlet vurdering af klinisk merværdi. Klinisk spørgsmål 1 (bionaive patienter)

Effektmål	Vigtighed	Merværdi	Evidenskvalitet
Klinisk remission, uge 8	Kritisk	Ingen	Meget lav
Steroidfri remission, uge 52	Kritisk	Ingen	Meget lav
Alvorlige uønskede hændelser	Kritisk	Negativ	Meget lav
Mukosal heling, uge 8	Vigtig	Ingen	Lav til meget lav
Mukosal heling, uge 52	Vigtig	Ingen	Lav til meget lav
IBDQ	Vigtig	Ikkedokumenterbar	Meget lav
Samlet		**Negativ**	**Meget lav**

Fagudvalget lægger i den samlede vurdering vægt på, at der for de to kritiske effektmål (*klinisk remission uge 8* og *steroidfri remission uge 52*) ikke er vist en klinisk merværdi for tofacitinib sammenlignet med infliximab og vedolizumab. På baggrund af EMAs opdaterede anbefalinger vedr. brugen af tofacitinib vurderer fagudvalget, at det kritiske effektmål *alvorlige uønskede hændelser* giver negativ klinisk merværdi, grundet usikkerhed omkring bivirkningsprofilen. For bionaive patienter vægter fagudvalget sikkerheden højere end effekt, da der findes andre behandlingsalternativer, og finder, at tofacitinib derfor ikke bør være første behandlingsvalg.

9.2 Konklusion klinisk spørgsmål 2

Hvad er den kliniske merværdi af tofacitinib til bioerfarne patienter med moderat til svær UC sammenlignet med henholdsvis infliximab og vedolizumab?

Fagudvalget har på baggrund af EMAs ændrede anbefalinger revurderet den kliniske merværdi af tofacitinib til bioerfarne patienter med moderat til svær UC.

Fagudvalget vurderer, at tofacitinib giver **ingen klinisk merværdi** (meget lav evidenskvalitet) sammenlignet med vedolizumab og **ikkedokumenterbar merværdi** sammenlignet med infliximab (evidensens kvalitet kan ikke vurderes) hos bioerfarne patienter med moderat til svær UC.

9.2.1 Gennemgang af studier

Ansøger identificerede tre studier vedr. tofacitinib hos bioerfarne patienter, ingen studier vedr. infliximab hos bioerfarne og ét studie vedr. vedolizumab hos bioerfarne. Studiernes karakteristika og populationer er beskrevet i afsnit 9.1.1.

Karakteristika

Studierne, der indgår i analysen af klinisk spørgsmål 2, er beskrevet i afsnit 9.1.1. For tofacitinib omhandler det OCTAVE induction 1 og 2 samt OCTAVE SUSTAIN, og for vedolizumab er det GEMINI 1.

Population

Gennemgangen af baselinekarakteristika for de aktive studiearme i de inkluderede studier er beskrevet i afsnit 9.1.1.

Som tabel 2 i afsnit 9.1.1 viser, er der en vis forskel i andelen af patienter, der sideløbende får medicinsk behandling, blandt andet fordi tofacitinibstudierne ikke tillader, at patienterne får samtidig behandling med immunosuppressiva.

Med ovenstående forskelle fremhævet finder fagudvalget, at der derudover ikke er betydende forskelle i baselinekarakteristika mellem studiearmene. Fagudvalget vurderer, at patientkarakteristika i studiet ikke afviger væsentligt fra den danske patientpopulation.

9.2.2 Resultater og vurdering

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

Da der ikke foreligger data for bioerfarne patienter, der modtager infliximab, kan sammenligningen af tofacitinib med infliximab ikke foretages. For alle effektmål er kategorien derfor ikkedokumenterbar merværdi. Nedenstående gennemgang af resultater er derfor udelukkende baseret på sammenligninger af tofacitinib med vedolizumab.

Klinisk remission, uge 8 (kritisk)

Klinisk remission er defineret ved en total Mayo-score ≤ 2, ingen subscore > 1 og rektal blødning-score = 0. Mayo-score er det mest anvendte scoringssystem i kliniske studier til at vurdere sygdomsaktivitet i UC. Mayo-score indeholder en samlet vurdering af følgende fire subscores: afføringsmønster, rektal blødning, endoskopiske fund og en samlet vurdering af sygdomsaktiviteten foretaget af en kliniker. For hvert område

er der fire svarmuligheder (0 til 3 point), og den samlede score går således fra 0 til 12 point, hvor en høj score indikerer værre sværhedsgrad af UC [20].

Som fremhævet i afsnit 8 Databehandling er der forskellige årsager til, at fagudvalget har forbehold for analyserne af dette effektmål:

- Studiet af vedolizumab definerer ikke klinisk remission som efterspurgt i protokollen, men som en total Mayo-score ≤ 2, ingen subscore > 1 og rektal blødning subscore ≤ 1.
- Effektmålet er i GEMINI 1-studiet (vedolizumab) opgjort efter 6 uger og ikke efter 8 uger som efterspurgt i protokollen
- I GEMINI 1-studiet er vurderingen af effektmålet foretaget lokalt (hvad angår den endoskopiske vurdering), mens det i studiet af tofacitinib er foretaget centralt.

På trods af disse forskelle finder fagudvalget, at de sammenlignende analyser kan benyttes.

Fagudvalget har vurderet, at en forskel på 10 procentpoint i andelen af patienter, der oplever klinisk remission ved uge 8, er klinisk relevant.

Tabel 10. Vurdering af klinisk merværdi: Klinisk remission, uge 8. Klinisk spørgsmål 2 (bioerfarne patienter).

	Forhåndsdefineret grundlag for vurdering		Medicinrådets vurdering (tofacitinib vs. vedolizumab)
Absolutte forskelle	10 procentpoint		22,8 procentpoint [-6,2;286,7]
Relative forskelle	Stor merværdi	Nedre konf.gr. > 1,33	
	Vigtig merværdi	Nedre konf.gr. > 1,11	
	Lille merværdi	Nedre konf.gr. > 1,00	
	Ingen merværdi	Nedre konf.gr. < 1,00	RR = 3,34 [0,37;30,39]
	Negativ merværdi	Øvre konf.gr. < 1,00	
Evidensens kvalitet	Meget lav		

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

Den absolutte effektforskel på 22,8 procentpoint er større end den forhåndsdefinerede mindste klinisk relevante forskel. Estimatet er dog ikke statistisk signifikant.

Den relative effektforskel er opgjort som en relativ risiko på 3,34 for tofacitinib sammenlignet med vedolizumab. Effektestimatets nedre grænse for konfidensintervallet er mindre end 1,0 og indikerer dermed ingen merværdi.

For den samlede population af bionaive og -erfarne patienter er den absolutte forskel for sammenligningen med vedolizumab -1,3 procentpoint [-11,1;25,5] og den relative forskel 0,93 [0,34;2,51]. Usikkerheden i resultaterne gør, at fagudvalget ikke finder anledning til at ændre merværdikategorien for den bioerfarne population.

Samlet vurderer fagudvalget, at tofacitinib har **ingen klinisk merværdi** sammenlignet med vedolizumab vurderet på effektmålet *klinisk remission, uge 8*.

Steroidfri remission, uge 52 (kritisk)

Steroidfri remission er defineret ved, at patienterne ikke er i steroidbehandling efter 52 uger og har en total Mayo-score ≤ 2, ingen subscore > 1 og rektal blødning-score = 0. Mayo-scoresystemet er beskrevet ovenfor.

Fagudvalget har vurderet, at en forskel på 10 procentpoint i andelen af patienter, der oplever steroidfri remission ved uge 52, er klinisk relevant.

Som fremhævet i afsnit 8 'Databehandling' har ansøger ikke kunnet levere data for effektmålet *steroidfri remission* fordelt på bionaive og -erfarne patienter, der fik tofacitinib. I stedet anvendes derfor data for den samlede population til vurderingen. På trods af dette finder fagudvalget, at de sammenlignende analyser kan benyttes.

Tabel 11. Vurdering af klinisk merværdi: Steroidfri remission, uge 52. Klinisk spørgsmål 2 (bionaive og -erfarne patienter).

	Forhåndsdefineret grundlag for vurdering		Medicinrådets vurdering (tofacitinib vs. vedolizumab)
Absolutte forskelle	10 procentpoint		3,9 procentpoint [-17,4;58,0]
Relative forskelle	Stor merværdi	Nedre konf.gr. > 1,33	
	Vigtig merværdi	Nedre konf.gr. > 1,11	
	Lille merværdi	Nedre konf.gr. > 1,00	
	Ingen merværdi	Nedre konf.gr. < 1,00	RR = 1,12 [0,45;2,85]
	Negativ merværdi	Øvre konf.gr. < 1,00	
Evidensens kvalitet	Meget lav		

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

Den absolutte effektforskel på 3,9 procentpoint er mindre end den forhåndsdefinerede mindste klinisk relevante forskel.

De relative effektforskelle er opgjort som en relativ risiko på 1,12 for tofacitinib sammenlignet med vedolizumab. Effektestimatets nedre grænse af konfidensintervallet er mindre end 1,0 og indikerer dermed ingen merværdi.

Samlet vurderer fagudvalget, at tofacitinib har **ingen klinisk merværdi** sammenlignet med vedolizumab vurderet på effektmålet *steroidfri remission, uge 52.*

Alvorlige uønskede hændelser (kritisk)

Fagudvalget finder, at andelen af patienter, som oplever en eller flere alvorlige uønskede hændelser, er særligt relevant for vurderingen, da tofacitinib er et nyt lægemiddel med en ny virkningsmekanisme.

Fagudvalget har vurderet, at en forskel på 5 procentpoint i andelen af patienter, der oplever alvorlige uønskede hændelser, er klinisk relevant.

Som fremhævet i afsnit 8 'Databehandling' har ansøger har ikke kunnet levere publicerede data for effektmålet fordelt på bionaive og -erfarne patienter, der fik tofacitinib. I stedet vil fagudvalget vurdere effektmålet for den samlede population. På trods af dette finder fagudvalget, at de sammenlignende analyser kan benyttes.

Tabel 12. Vurdering af klinisk merværdi: Alvorlige uønskede hændelser. Klinisk spørgsmål 2 (bionaive og -erfarne patienter).

	Forhåndsdefineret grundlag for vurdering		Medicinrådets vurdering (tofacitinib vs. vedolizumab)
Absolutte forskelle	5 procentpoint		4,0 [-4,0;27,6]
Relative forskelle	Stor merværdi	Øvre konf.gr. < 0,75	
	Vigtig merværdi	Øvre konf.gr. < 0,90	
	Lille merværdi	Øvre konf.gr. < 1,00	
	Ingen merværdi	Øvre konf.gr. > 1,00	RR = 1,49 [0,51; 4,36]
	Negativ merværdi	Nedre konf.gr. > 1,00	
Evidensens kvalitet	Meget lav		

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

Den absolutte effektforskel på 4,0 procentpoint er mindre end den forhåndsdefinerede mindste klinisk relevante forskel.

Den relative effektforskel er opgjort som en relativ risiko på 1,49 for tofacitinib sammenlignet med vedolizumab. Begge effektestimaters øvre grænse af konfidensintervallet er større end 1,0 og indikerer dermed ingen merværdi.

Fagudvalget vurderer, at tofacitinib har ingen klinisk merværdi sammenlignet med vedolizumab for effektmålet *alvorlige uønskede hændelser*.

Kvalitativ gennemgang – revurdering af effektmål på baggrund af ændret anbefaling fra EMA
Se afsnit 9.1.2 for en kvalitativ gennemgang af tofacitinibs og vedolizumabs bivirkningsprofiler.

Fagudvalget vurderer, som for bionaive patienter, at tofacitinib har negativ klinisk merværdi sammenlignet med vedolizumab, grundet usikkerheden omkring tofacitinibs bivirkningsprofil.

Samlet vurdering
Samlet vurderer fagudvalget, at tofacitinib har en **negativ klinisk merværdi** sammenlignet med vedolizumab, grundet usikkerhed omkring bivirkningsprofilen.

Mukosal heling, uge 8 (vigtig)

Mukosal heling er defineret ved en endoskopisk subscore ≤ 1 (subscoren indgår i den samlede Mayo-score). Subscoren afspejler slimhindeudseendet ved en endoskopi, og scoren går fra 0-4, hvor en høj score indikerer værre sværhedsgrad af slimhindens udseende [20]. Mukosal heling er et vigtigt klinisk behandlingsmål, da det er prædiktor for behandlingseffekt og en prognostisk markør for langtidseffekt af behandlingen. Fagudvalget finder, at tidlig mukosal heling er vigtigt for patienterne.

Fagudvalget har vurderet, at en forskel på 10 procentpoint i andelen af patienter, der oplever steroidfri remission ved uge 8, er klinisk relevant.

Som fremhævet i afsnit 8 'Databehandling' er der forskellige årsager til, at fagudvalget har visse forbehold for analyserne af dette effektmål:

- Effektmålet *mukosal heling* er i GEMINI 1-studiet opgjort efter 6 uger og ikke efter 8 uger som efterspurgt i protokollen.

- I GEMINI 1-studiet er vurderingen af effektmålet foretaget lokalt, mens det i studiet af tofacitinib er foretaget centralt.

På trods af disse forskelle finder fagudvalget, at de sammenlignende analyser kan benyttes.

Tabel 13. Vurdering af klinisk merværdi: Mukosal heling, uge 8. Klinisk spørgsmål 2 (bioerfarne patienter).

	Forhåndsdefineret grundlag for vurdering		Medicinrådets vurdering (tofacitinib vs. vedolizumab)
Absolutte forskelle	10 procentpoint		46,3 procentpoint [0,6;159,4]
Relative forskelle	Stor merværdi	Nedre konf.gr. > 1,33	
	Vigtig merværdi	Nedre konf.gr. > 1,11	
	Lille merværdi	Nedre konf.gr. > 1,00	RR = 2,52 [1,02;6,23]
	Ingen merværdi	Nedre konf.gr. < 1,00	
	Negativ merværdi	Øvre konf.gr. < 1,00	
Evidensens kvalitet	Meget lav		

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

Den absolutte effektforskel på 46,3 procentpoint er større end den forhåndsdefinerede mindste klinisk relevante forskel.

Den relative effektforskel er opgjort som en relativ risiko på 2,52 for tofacitinib sammenlignet med vedolizumab. Effektestimatets nedre grænse for konfidensintervallet er større end 1,0, men ikke større end 1,11 og indikerer dermed lille merværdi.

Fagudvalget bemærker, at en større andel af de patienter, der får vedolizumab i GEMINI-studiet, opnår mukosal heling ved uge 8, sammenlignet med andelen af patienter, som opnår effektmålet i OCTAVE-studierne (se bilag 1). Der er dog samtidig stor forskel på, hvor mange patienter i placeboarmene der opnår effektmålet (20,6 % i GEMINI-studiet og 6 % i OCTAVE-studierne). Som beskrevet i afsnit 8 Databehandling, kan dette medføre, at sammenligningerne er behæftet med særlig usikkerhed. Den lave placeboeffekt i tofacitinibstudierne påvirker den indirekte sammenligning i retning af en merværdi for tofacitinib, på trods af at en mindre andel af patienterne i tofacitinibstudierne sammenlignet med GEMINI-studiet opnår mukosal heling ved uge 8.

For den samlede population af bionaive og -erfarne patienter er den absolutte forskel for sammenligningen med vedolizumab 13,2 procentpoint [-6,6;45,4] og den relative forskel er 1,32 [0,83;2,11]. Resultaterne giver dog ikke fagudvalget anledning til at ændre merværdikategorien for den bioerfarne population.

Baseret på den store forskel i placeboeffekt mellem studierne vurderer fagudvalget, at studierne ikke kan sammenlignes, hvad angår dette effektmål. Dermed har tofacitinib **ikkedokumenterbar merværdi** sammenlignet med vedolizumab vurderet på effektmålet *mukosal heling, uge 8*.

Mukosal heling, uge 52 (vigtig)

Mukosal heling er defineret ovenfor. Fagudvalget finder, at langtidseffekten af behandlingen er betydningsfuldt for patienterne.

Fagudvalget har vurderet, at en forskel på 10 procentpoint i andelen af patienter, der oplever steroidfri remission ved uge 52, er klinisk relevant.

Som fremhævet i afsnit 8 Databehandling er vurderingen af effektmålet foretaget lokalt i studiet af vedolizumab, mens det i studiet af tofacitinib er foretaget centralt. På trods af denne forskel finder fagudvalget, at de sammenlignende analyser kan benyttes.

Tabel 14. Vurdering af klinisk merværdi: Mukosal heling, uge 52. Klinisk spørgsmål 2 (bioerfarne patienter).

	Forhåndsdefineret grundlag for vurdering		Medicinrådets vurdering (tofacitinib vs. vedolizumab)
Absolutte forskelle	10 procentpoint		-23,5 procentpoint [-36,9;26,2]
Relative forskelle	Stor merværdi	Nedre konf.gr. > 1,33	
	Vigtig merværdi	Nedre konf.gr. > 1,11	
	Lille merværdi	Nedre konf.gr. > 1,00	
	Ingen merværdi	Nedre konf.gr. < 1,00	RR = 0,44 [0,12;1,63]
	Negativ merværdi	Øvre konf.gr. < 1,00	
Evidensens kvalitet	Lav		

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

Den absolutte effektforskel på -23,5 procentpoint er større end den forhåndsdefinerede mindste klinisk relevante forskel for en negativ merværdi, i vedolizumabs favør.

Den relative effektforskel er opgjort som en relativ risiko på 0,44 for tofacitinib sammenlignet med vedolizumab. Effektestimatets nedre grænse for konfidensintervallet er ikke større end 1,0 og indikerer dermed ingen merværdi.

For den samlede population af bionaive og -erfarne patienter er den absolutte forskel for sammenligningen med vedolizumab 4,5 procentpoint [-20,4;49,4], og den relative forskel er 1,09 [0,61;1,96]. Resultaterne for den samlede population peger dermed i den modsatte retning af resultaterne for de bioerfarne alene og viser ingen merværdi.

Usikkerheden i resultaterne for den bioerfarne population og resultaterne for den samlede population gør, at fagudvalget samlet vurderer, at tofacitinib har **ingen klinisk merværdi** sammenlignet med vedolizumab vurderet på effektmålet *mukosal heling, uge 52*.

Inflammatory Bowel Disease Questionnaire (IBDQ) (vigtig)

IBDQ er et velvalideret, sygdomsspecifikt livskvalitetsinstrument, der vægter symptomer og problemer, der er særlige for patienter med inflammatoriske tarmsygdomme [20,25]. Spørgeskemaet består af 32 spørgsmål fordelt på fire dimensioner: afføringssymptomer, emotionel sundhed, systemiske symptomer og social funktion. Skalaen går fra 32 til 224, hvor en højere værdi indikerer bedre livskvalitet.

Fagudvalget har vurderet, at en gennemsnitlig ændring fra baseline på 16 point eller mere er klinisk relevant.

Som fremhævet i afsnit 8 'Databehandling' er der forskellige årsager til, at fagudvalget har visse forbehold for analyserne af dette effektmål:

- Data vedr. tofacitinib er opsamlet ved uge 8 og sammenlignes med data efter ca. 1 års opfølgningstid vedr. vedolizumab.

Fagudvalget mener derfor, at resultaterne vedr. IBDQ skal tolkes meget varsomt.

Tabel 15. Vurdering af klinisk merværdi: IBDQ. Klinisk spørgsmål 2 (bioerfarne patienter).

	Forhåndsdefineret grundlag for vurdering	Medicinrådets vurdering (tofacitinib vs. vedolizumab)
Absolutte forskelle	Gennemsnitlig ændring fra baseline på 16 point eller mere	7,6 point [-10,1;25,3]
Evidensens kvalitet	Meget lav	

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

De absolutte effektforskelle på 7,6 point på IBDQ-skalaen er ikke større end den forhåndsdefinerede mindste klinisk relevante forskel. Derudover er estimatet behæftet med stor usikkerhed.

For den samlede population af bionaive og -erfarne patienter er den absolutte forskel for sammenligningen med infliximab 2,5 point [-5,2; 10,2]. Sammenlignet med vedolizumab er den absolutte forskel -1,5 point [-11,9; 9,0].

Grundet fagudvalgets forbehold for data, der er af ringe kvalitet, og at estimaterne er behæftet med stor usikkerhed, vurderer fagudvalget, at merværdien for dette effektmål er **ikkedokumenterbar.**

9.2.3 Evidensens kvalitet

Tofacitinib sammenlignet med vedolizumab

Evidensens kvalitet for klinisk spørgsmål 2 (bioerfarne patienter), hvor tofacitinib er sammenlignet med vedolizumab, er samlet set vurderet at være **meget lav**, da evidensens kvalitet for det laveste vurderede kritiske effektmål er **meget lav**.

Indledningsvist blev lægemidlernes direkte sammenligninger med placebo vurderet. Overordnet var alle studier af høj kvalitet, og der blev ikke nedgraderet for risiko for bias (se bilag 2). Der er nedgraderet for *"inconsistency"* og *"imprecision"* for flere af effektmålene.

Derudover er der for alle effektmål nedgraderet for *"indirectness"*, da alle sammenligninger mellem tofacitinib og vedolizumab er indirekte. Yderligere overvejelser vedrørende evidensens kvalitet kan ses i bilag 2.

Tofacitinib sammenlignet med infliximab

Evidensens kvalitet for klinisk spørgsmål 2 (bioerfarne patienter), hvor tofacitinib er sammenlignet med infliximab, **kan ikke vurderes**, da der ikke foreligger evidens for sammenligningen.

9.2.4 Konklusion for klinisk spørgsmål 2 (bioerfarne patienter)

Fagudvalget vurderer, at tofacitinib giver **ingen klinisk merværdi** sammenlignet med vedolizumab (meget lav evidenskvalitet) og **ikkedokumenterbar merværdi** sammenlignet med infliximab (evidensens kvalitet kan ikke vurderes) hos bioerfarne patienter med moderat til svær UC.

Den samlede kategorisering af sammenligningen af tofacitinib med vedolizumab er baseret på gennemgangen af de enkelte effektmål, som kan ses i afsnit 9.2.1, og som er opsummeret i nedenstående tabel.

Tabel 16. Samlet vurdering af klinisk merværdi. Klinisk spørgsmål 2 (bioerfarne patienter).

Effektmål	Vigtighed	Merværdi	Evidenskvalitet
Klinisk remission, uge 8	Kritisk	Ingen	Meget lav
Steroidfri remission, uge 52	Kritisk	Ingen	Meget lav
Alvorlige uønskede hændelser	Kritisk	Negativ	Meget lav
Mukosal heling, uge 8	Vigtig	Ikkedokumenterbar	Meget lav
Mukosal heling, uge 52	Vigtig	Ingen	Lav
IBDQ	Vigtig	Ikkedokumenterbar	Meget lav
Samlet		**Ingen**	**Meget lav**

Fagudvalget lægger i den samlede vurdering særligt vægt på, at der for de to kritiske effektmål, *klinisk remission uge 8* og *steroidfri remission uge 52,* ikke er vist en klinisk merværdi for tofacitinib sammenlignet med vedolizumab. Hvad angår effekt vurderes tofacitinib derfor at være sammenlignelig med vedolizumab. På baggrund af EMAs opdaterede anbefalinger vedr. brugen af tofacitinib vurderer fagudvalget, at det kritiske effektmål *alvorlige uønskede hændelser* giver negativ klinisk merværdi, grundet usikkerhed omkring bivirkningsprofilen. Da colitis ulcerosa er en kronisk sygdom, vægter fagudvalget dog effekten af tofacitinib højt for bioerfarne patienter, da det for denne patientgruppe er vigtigt, at der findes behandlingsalternativer.

Grundet de manglende data er den samlede vurdering, at der er en ikkedokumenterbar merværdi for tofacitinib sammenlignet med infliximab.

10 Fagudvalgets vurdering af samlet klinisk merværdi og samlet evidensniveau

Fagudvalget vedrørende inflammatoriske tarmsygdomme vurderer, at tofacitinib giver:

- **negativ klinisk merværdi** hos bionaive patienter med moderat til svær UC sammenlignet med infliximab og vedolizumab (meget lav evidenskvalitet)
- **ingen klinisk merværdi** hos bioerfarne patienter med moderat til svær UC sammenlignet med vedolizumab (meget lav evidenskvalitet) hos bioerfarne patienter og **ikkedokumenterbar merværdi** sammenlignet med infliximab (evidensens kvalitet kan ikke vurderes).

Fagudvalget har i vurderingen af den samlede kliniske merværdi fortrinsvist lagt vægt på de tre kritiske effektmål (*klinisk remission uge 8*, *steroidfri remission uge 52* og *alvorlige uønskede hændelser*). For klinisk spørgsmål 1, behandling af bionaive patienter, har fagudvalget særligt lagt vægt på, at det kritiske effektmål *alvorlige uønskede hændelser* har vist negativ klinisk merværdi for tofacitinib sammenlignet med infliximab og vedolizumab, grundet usikkerhed omkring bivirkningsprofilen. For klinisk spørgsmål 2, behandling af bioerfarne patienter, har fagudvalget særligt lagt vægt på, at de kritiske effektmål *klinisk remission uge 8 og steroidfri remission uge 52* har vist ingen klinisk merværdi for tofacitinib sammenlignet med vedolizumab.

11 Rådets vurdering af samlet klinisk merværdi og samlet evidensniveau

Medicinrådet finder, at tofacitinib giver:

- **negativ klinisk merværdi** hos bionaive patienter med moderat til svær aktiv colitis ulcerosa sammenlignet med infliximab og vedolizumab (meget lav evidenskvalitet)

- **ingen klinisk merværdi** sammenlignet med vedolizumab (meget lav evidenskvalitet) og **ikkedokumenterbar merværdi** sammenlignet med infliximab (evidensens kvalitet kan ikke vurderes) hos bioerfarne patienter med moderat til svær UC.

12 Relation til eksisterende behandlingsvejledning

Der foreligger en RADS-behandlingsvejledning vedrørende dyre lægemidler til behandling af kroniske inflammatoriske tarmsygdomme, inklusiv behandling af moderat til svær aktiv UC. Fagudvalget vurderer, at tofacitinib ikke bør ligestilles med de nuværende førstelinjebehandlinger (infliximab, vedolizumab og golimumab) men kan anvendes efter mindst to forskellige behandlingsprincipper har været afprøvet.

Medicinrådet har besluttet at udarbejde en fælles regional behandlingsvejledning for UC. Her vil fagudvalget revurdere tofacitinib i relation til de øvrige lægemidler med indikationen moderat til svær aktiv UC.

13 Referencer

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14 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende inflammatoriske tarmsygdomme

Forvaltningslovens § 3, stk. 2, har været anvendt i forbindelse med udpegning af medlemmer til dette fagudvalg.

Formand	**Indstillet af**
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*Har ikke deltaget i fagudvalgets arbejde vedr. denne vurdering.

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15 Versionslog

Version	Dato	Ændring
1.0	19. juni 2019	Godkendt af Medicinrådet.
1.1	1. juli 2019	Ansøger har gjort opmærksom på en skriftlig fejl, som er blevet tilrettet. Det drejede sig om ordet 'værdi' på s. 19, 26 og 27, der nu er ændret til 'merværdi'.
2.0	19. februar 2020	Medicinrådet har revurderet den kliniske merværdi af tofacitinib på baggrund af nye sikkerhedsdata og anbefalinger vedr. brug af tofacitinib offentliggjort af EMA i november 2019. Kategoriseringen af den kliniske merværdi for bionaive patienter er ændret fra ingen klinisk merværdi til negativ klinisk merværdi (afsnit 2, 9.1). Der er foretaget ændringer i teksten i afsnit 9.1.2 og 9.2.2 under effektmålet alvorlige uønskede hændelser kvalitativ gennemgang og i afsnittene 9.1.4, 9.2, 9.2.4, 10, 11 og 12.

16 Bilag 1: Resultater ved Buchers metode

Klinisk spørgsmål 1: Tofacitinib vs. infliximab (bionaive)

Effektmål	**Intervention: Tofacitinib vs. placebo**	**Komparator: Infliximab vs. placebo**	**Relativ forskel v. Buchers metode**	**Absolut forskel v. Buchers metode**
Klinisk remission, uge 8	Absolut: 23,7 % vs. 12,5 % RR = 1,85 [1,08;3,16]	Absolut: 36,4 % vs. 10,3 % RR = 3,73 [1,68;8,31]	RR = 0,50 [0,19;1,30]	-18,3 procentpoint [-29,5;10,9]
Steroidfri remission, uge 52	Absolut: 27,7 % vs. 10,9 % RR = 2,55 [1,34;4,83]	Absolut: 22,3 % vs. 6,5 % RR = 3,37 [1,66;6,86]	RR = 0,76 [0,29; 1,96]	-5,5 [-15,8; 21,5]
Alvorlige uønskede hændelser	Absolut: 5,1 % vs. 6,6 % RR = 0,77 [0,35;1,71]	Absolut: 16,1 % vs. 22,5 % RR = 0,72 [0,48;1,07]	RR = 1,07 [0,44; 2,62]	1,1 [-9,1; 26,0]
Mukosal heling, uge 8	Absolut: 38,1 % vs. 23,1 % RR = 1,64 [1,13;2,37]	Absolut: 61,2 % vs. 32,4 % RR = 1,89 [1,53;2,32]	RR = 0,87 [0,57;1,33]	-8,1 procentpoint [-26,5;20,0]
Mukosal heling, uge 52	Absolut: 40,9 % vs. 12,4 % RR = 3,31 [1,81;6,05]	Absolut: 45,9 % vs. 24,2 % RR = 1,92 [1,20;3,09]	RR = 1,72 [0,80;3,71]	33,1 procentpoint [-9,2;124,3]

Klinisk spørgsmål 1: Tofacitinib vs. vedolizumab (bionaive)

Effektmål	Intervention: Tofacitinib vs. placebo	Komparator: Vedolizumab vs. placebo	Relativ forskel v. Buchers metode	Absolut forskel v. Buchers metode
Klinisk remission, uge 8	Absolut: 23,7 % vs. 12,5 % RR = 1,85 [1,08;3,16]	Absolut: 23,1 % vs. 6,6 % RR = 3,51 [1,42;8,66]	RR = 0,53 [0,18;1,51]	-10,9 procentpoint [-18,8;11,7]
Steroidfri remission, uge 52	Absolut: 27,7 % vs. 10,9 % RR = 2,55 [1,34;4,83]	Absolut: 31,4 % vs. 13,9 % RR = 2,26 [1,16;4,43]	RR = 1,12 [0,45; 2,85]	3,9 [-17,4; 58,0]
Alvorlige uønskede hændelser	Absolut: 5,1 % vs. 6,6 % RR = 0,77 [0,35;1,71]	Absolut: 8,2 % vs. 15,9 % RR = 0,52 [0,25;1,06]	RR = 1,49 [0,51; 4,36]	4,0 [-4,0;27,6]
Mukosal heling, uge 8	Absolut: 38,1 % vs. 23,1 % RR = 1,64 [1,13;2,37]	Absolut: 49,2 % vs. 25,0 % RR = 1,97 [1,29;3,02]	RR = 0,83 [0,47;1,47]	-8,2 procentpoint [-25,9;22,9]
Mukosal heling, uge 52	Absolut: 40,9 % vs. 12,4 % RR = 3,31 [1,81;6,05]	Absolut: 59,7 % vs. 24,1 % RR = 2,39 [1,55;3,68]	RR = 1,38 [0,66;2,91]	22,9 procentpoint [-20,4;114,2]

Klinisk spørgsmål 2: Tofacitinib vs. vedolizumab (bioerfarne)

Effektmål	Intervention: Tofacitinib vs. placebo	Komparator: Vedolizumab vs. placebo	Relativ forskel v. Buchers metode	Absolut forskel v. Buchers metode
Klinisk remission, uge 8	Absolut: 12,3 % vs. 0,8 % RR = 10,25 [2,05;51,19]	Absolut: 9,8 % vs. 3,2 % RR = 3,07 [0,68;13,97]	RR = 3,34 [0,37;30,39]	22,8 procentpoint [-6,2;286,7]
Steroidfri remission, uge 52	Absolut: 27,7 % vs. 10,9 % RR = 2,55 [1,34;4,83]	Absolut: 31,4 % vs. 13,9 % RR = 2,26 [1,16;4,43]	RR = 1,12 [0,45;2,85]	3,9 procentpoint [-17,4;58,0]
Alvorlige uønskede hændelser	Absolut: 5,1 % vs. 6,6 % RR = 0,77 [0,35;1,71]	Absolut: 8,2 % vs. 15,9 % RR = 0,52 [0,25;1,06]	RR = 1,49 [0,51; 4,36]	4,0 [-4,0;27,6]
Mukosal heling, uge 8	Absolut: 23,0 % vs. 6,2 % RR = 3,72 [1,86;7,42]	Absolut: 30,5 % vs. 20,6 % RR = 1,48 [0,82;2,65]	RR = 2,52 [1,02;6,23]	46,3 procentpoint [0,6;159,4]
Mukosal heling, uge 52	Absolut: 30,1 % vs. 12,9 % RR = 2,33 [1,23;4,42]	Absolut: 41,9 % vs. 7,9 % RR = 5,30 [1,69;16,61]	RR = 0,44 [0,12;1,63]	-23,5 procentpoint [-36,9;26,2]

17 Bilag 2: GRADE-evidensprofiler

17.1 Cochrane Risk of Bias

Tofacitinib, NCT01465763 (OCTAVE Induction 1)

(Tofacitinib as Induction and Maintenance Therapy for Ulcerative Colitis, Sandbord et al., 2017)

Bias	Risk of bias	Elaboration
Selection bias		
Random sequence generation	**Unclear**	Patients were randomly assigned in a 4:1 ratio to receive induction therapy of 10 mg tofacitinib twice daily or placebo for 8 weeks. The original study protocol included also a group that received 15 mg tofacitinib twice daily, but the sponsor decided to discontinue further exploration of this dose, even though 38 patients were already randomized to this treatment. The decision was supposedly based on feedback received from regulatory authorities. The random sequence allocation is therefore judged as having a moderate risk of bias.
Allocation concealment	**Unclear**	Randomization was performed centrally with the use of a telerandomization system and was stratified in the OCTAVE Induction 1 trial according to previous treatment with TNF antagonists, glucocorticoid use at baseline, and geographic region. The details of blinding are not provided, and therefore the risk of bias is unclear.
Deviations from intended interventions	**Unclear**	The already mentioned discontinuation of one group (those randomized to 15 mg tofacitinib) poses a moderate risk of bias as it is a major deviation from the intended intervention.
Performance bias: blinding of participants and personnel. Assessment made for class of outcomes.		
Patient-reported outcomes	**Unclear**	Study claims to be double-blind, however, the details of blinding are not provided and therefore is the risk of bias impossible to judge.
Objective outcomes	**Unclear**	Ibid.
Detection bias: blinding of outcome assessment. Assessment made for class of outcomes.		

Patient-reported outcomes	**Unclear**	Study claims to be double-blind, however, the details of blinding are not provided and therefore is the risk of bias impossible to judge.
Objective outcomes	**Unclear**	Ibid.
Attrition bias: incomplete outcome data. Assessment made for class of outcomes.	**Unclear**	The patients that were randomized to treatment by 15 mg tofacitinib (i.e. those that were discontinued) were not included both in the efficacy and the safety analyses and were analyzed separately. Therefore, the risk of bias is judged as moderate.
Reporting bias: selective reporting outcome data.	**Low**	All prespecified outcomes are reported. Nothing suggests reporting bias due to selective outcome reporting, cf. clinicaltrials.gov.
Other bias	**Low**	No other concern regarding potential risk of bias.
Overall bias	**Unclear**	Overall risk of bias is in OCTAVE 1 judged as unclear. This is due to the unclear risk of bias regarding the random sequence generation, deviations from intended interventions and attrition bias, and unclear risk of bias regarding the performance bias and detection bias. The main issues were the treatment arm that was discontinued after randomization, and the unclear details of blinding.

Tofacitinib, NCT01458951 (OCTAVE Induction 2)

(Tofacitinib as Induction and Maintenance Therapy for Ulcerative Colitis, Sandbord et al., 2017)

Bias	**Risk of bias**	**Elaboration**
Selection bias		
Random sequence generation	**Unclear**	Patients were randomly assigned in a 4:1 ratio to receive induction therapy of 10 mg tofacitinib twice daily or placebo for 8 weeks. The original study protocol included also a group that received 15 mg tofacitinib twice daily, but the sponsor decided to discontinue further exploration of this dose, even though 18 patients were already randomized to this treatment. The decision was supposedly based on feedback received from regulatory authorities. The random sequence allocation is therefore judged as having a moderate risk of bias.

Allocation concealment	**Unclear**	Randomization was performed centrally with the use of a telerandomization system and was stratified in the OCTAVE Induction 2 trial according to previous treatment with TNF antagonists, glucocorticoid use at baseline, and geographic region. The details of blinding are not provided, and therefore the risk of bias is unclear.
Deviations from intended interventions	**Unclear**	The already mentioned discontinuation of one group (those randomized to 15 mg tofacitinib) poses a moderate risk of bias as it is a major deviation from the intended intervention.
Performance bias: blinding of participants and personnel. Assessment made for class of outcomes.		
Patient-reported outcomes	**Unclear**	Study claims to be double-blind, however, the details of blinding are not provided and therefore is the risk of bias impossible to judge.
Objective outcomes	**Unclear**	Ibid.
Detection bias: blinding of outcome assessment. Assessment made for class of outcomes.		
Patient-reported outcomes	**Unclear**	Study claims to be double-blind, however, the details of blinding are not provided and therefore is the risk of bias impossible to judge.
Objective outcomes	**Unclear**	Ibid.
Attrition bias: incomplete outcome data. Assessment made for class of outcomes.	**Unclear**	The patients that were randomized to treatment by 15 mg tofacitinib (i.e. those that were discontinued) were not included both in the efficacy and the safety analyses and were analyzed separately. Therefore, the risk of bias is judged as moderate.
Reporting bias: selective reporting outcome data.	**Low**	All prespecified outcomes are reported. Nothing suggests reporting bias due to selective outcome reporting, cf. clinicaltrials.gov.
Other bias	**Low**	No other concern regarding potential risk of bias.
Overall bias	**Unclear**	Overall risk of bias is in OCTAVE 2 judged as unclear. This is due to the unclear risk of bias regarding the random sequence generation, deviations from intended interventions and attrition bias, and unclear risk of bias regarding the performance bias and detection bias. The main issues were the treatment arm that was discontinued after randomization, and the unclear details of blinding.

Tofacitinib, NCT01458574 (OCTAVE Sustain)

(Tofacitinib as Induction and Maintenance Therapy for Ulcerative Colitis, Sandbord et al., 2017)

Bias	Risk of bias	Elaboration
Selection bias		
Random sequence generation	**Low**	Patients who entered the OCTAVE Sustain trial were randomly assigned again (after OCTAVE 1/2), in a 1:1:1 ratio, to receive maintenance therapy with tofacitinib at a dose of 5 mg twice daily, tofacitinib at a dose of 10 mg twice daily, or placebo for 52 weeks.
Allocation concealment	**Unclear**	Randomization was performed centrally with the use of a telerandomization system and was stratified in the OCTAVE Sustain trial according to induction-trial group assignment and remission status at maintenance-trial entry. The details of blinding are not provided, and therefore the risk of bias is unclear.
Deviations from intended interventions	**Low**	No concerns.
Performance bias: blinding of participants and personnel. Assessment made for class of outcomes.		
Patient-reported outcomes	**Unclear**	Study claims to be double-blind, however, the details of blinding are not provided and therefore is the risk of bias impossible to judge.
Objective outcomes	**Unclear**	Ibid.
Detection bias: blinding of outcome assessment. Assessment made for class of outcomes.		
Patient-reported outcomes	**Unclear**	Study claims to be double-blind, however, the details of blinding are not provided and therefore is the risk of bias impossible to judge.
Objective outcomes	**Unclear**	Ibid.

Attrition bias: incomplete outcome data. Assessment made for class of outcomes.	**Low**	The efficacy analyses were based on data from all patients who underwent randomization. The safety analyses were based on data from all patients who underwent randomization and received at least one dose of the assigned treatment. No concerns of bias.
Reporting bias: selective reporting outcome data.	**Low**	Even though the study protocol defined 26 study outcomes, all were reported and therefore nothing suggests reporting bias due to selective outcome reporting, cf. clinicaltrials.gov.
Other bias	**Low**	No other concern regarding potential risk of bias.
Overall bias	**Unclear**	Overall risk of bias is judged unclear. This is primarily due to the unclear details of the blinding, which could have caused biased concealment of allocation and subsequently performance and detection bias.

Vedolizumab, NCT00783718 (GEMINI 1)

(Vedolizumab as Induction and Maintenance Therapy for Ulcerative Colitis, Feagan et al., 2013)

Bias	**Risk of bias**	**Elaboration**
Selection bias		
Random sequence generation	**High**	For the induction therapy, the risk of bias regarding the random sequence generation is judged as high. That is due to the cohort 2 enrolling (without randomization) to open-label to receive the same active treatment as the patients in cohort 1 (which were randomized and double-blinded). For the maintenance therapy, the risk of bias is also judged as high. That is because only patients from the induction part who had a clinical response to vedolizumab at week 6 of the induction therapy, were randomly assigned in this part. Those, that did not have a response, continued receiving vedolizumab 300 mg; and those, that were receiving placebo before, continued with that.
Allocation concealment	**Unclear**	Randomization was performed centrally with the use of computer-generated randomization schedules. However, the risk of bias is judged as moderate as some of the patients were treated open-label.
Deviations from intended interventions	**High**	In 15/211 medical centers was enrollment discontinued due to various reasons, e.g. “inadequate source documentation” or “concerns about protocol compliance potentially impacting patient safety” (13 of them in India), even though at several sites was “personnel extensively retrained and demonstrated an ability to comply with all procedures”. Therefore, the risk of bias is judged as high.

Performance bias: blinding of participants and personnel. Assessment made for class of outcomes.		
Patient-reported outcomes	**Unclear**	Study claims to be double-blind, however, the details of blinding are only provided in the maintenance part, and only for a group of patients by administering them placebo every other visit to preserve blinding. Therefore, the risk of bias is impossible to judge.
Objective outcomes	**Unclear**	Ibid.
Detection bias: blinding of outcome assessment. Assessment made for class of outcomes.		
Patient-reported outcomes	**Unclear**	Study claims to be double-blind, however, the details of blinding are not provided and therefore is the risk of bias impossible to judge.
Objective outcomes	**Unclear**	Ibid.
Attrition bias: incomplete outcome data. Assessment made for class of outcomes.	**Low**	For patients who withdrew prematurely, the last observation was carried forward. Otherwise no concern.
Reporting bias: selective reporting outcome data.	**Low**	All predefined study outcomes were reported and therefore nothing suggests reporting bias due to selective outcome reporting, cf. clinicaltrials.gov.
Other bias	**Low**	No other concern regarding potential risk of bias.
Overall bias	**High**	The overall risk of bias is judged to be high. This is primarily due to non-randomized and open-label patients; and due to the discontinuation of several centers after randomization.

Infliximab, NCT00036439 (ACT 1)

(Infliximab for Induction and Maintenance Therapy for Ulcerative Colitis, Rutgeerts et al., 2005)

Bias	Risk of bias	Elaboration
Selection bias		
Random sequence generation	**Low**	Eligible patients were randomly assigned in a 1:1:1 ratio to receive intravenous infusions of infliximab at a dose of 5 mg or 10 mg / kg body weight or placebo at weeks 0, 2, and 6 and then every eight weeks through week 46. Patients were followed through week 54. The risk of bias is considered low.
Allocation concealment	**Unclear**	The study used central randomization with a dynamic treatment allocation stratified according to the investigational site and whether patients had ulcerative colitis that was refractory to corticosteroid therapy. The details of blinding are not provided, and therefore the risk of bias is unclear.
Deviations from intended interventions	**Low**	No concerns.
Performance bias: blinding of participants and personnel. Assessment made for class of outcomes.		
Patient-reported outcomes	**Unclear**	Study claims to be double-blind, however, the details of blinding are not provided and therefore is the risk of bias impossible to judge.
Objective outcomes	**Unclear**	Ibid.
Detection bias: blinding of outcome assessment. Assessment made for class of outcomes.		
Patient-reported outcomes	**Unclear**	Study claims to be double-blind, however, the details of blinding are not provided and therefore is the risk of bias impossible to judge.
Objective outcomes	**Unclear**	Ibid.

Attrition bias: incomplete outcome data. Assessment made for class of outcomes.	**Unclear**	The efficacy and safety populations consist of all 364 patients who underwent randomization, all of whom received at least one dose of study medication. However, patients who took prohibited medication because of lack of efficacy or loss of response to the study medication, who discontinued the study medication because of lack of efficacy, or who underwent a colectomy or ostomy were not considered to have had a clinical response, to be in clinical remission, or to have had mucosal healing from the time of the event onward, regardless of their Mayo score. In addition, patients with insufficient data for the assessment of a response were not considered to have had a clinical response, to be in clinical remission, or to have had mucosal healing at that visit. Moreover, according to the article, 46% of the patients discontinued the study infusions and 37% did not complete the study. Due to all these reasons, the risk of bias is judged as moderate.
Reporting bias: selective reporting outcome data.	**Low**	Nothing suggests reporting bias due to selective outcome reporting, cf. clinicaltrials.gov.
Other bias	**Low**	No other concern regarding potential risk of bias.
Overall bias	**Unclear**	Overall risk of bias is judged unclear. This is primarily due to the unclear details of the blinding, which could have caused biased concealment of allocation and subsequently performance and detection bias; and due to the unclear risk of attrition bias, caused by a proportion of patients not considered in analyses.

Infliximab, NCT00096655 (ACT 2)

(Infliximab for Induction and Maintenance Therapy for Ulcerative Colitis, Rutgeerts et al., 2005)

Bias	Risk of bias	Elaboration
Selection bias		
Random sequence generation	**Low**	Eligible patients were randomly assigned in a 1:1:1 ratio to receive intravenous infusions of infliximab at a dose of 5 mg or 10 mg / kg body weight or placebo at weeks 0, 2, and 6 and then every eight weeks through week 22. Patients were followed through week 30. The risk of bias is considered low.
Allocation concealment	**Unclear**	The study used central randomization with a dynamic treatment allocation stratified according to the investigational site and whether patients had ulcerative colitis that was refractory to corticosteroid therapy. The details of blinding are not provided, and therefore the risk of bias is unclear.
Deviations from intended interventions	**Low**	No concerns.
Performance bias: blinding of participants and personnel. Assessment made for class of outcomes.		
Patient-reported outcomes	**Unclear**	Study claims to be double-blind, however, the details of blinding are not provided and therefore is the risk of bias impossible to judge.
Objective outcomes	**Unclear**	Ibid.
Detection bias: blinding of outcome assessment. Assessment made for class of outcomes.		
Patient-reported outcomes	**Unclear**	Study claims to be double-blind, however, the details of blinding are not provided and therefore is the risk of bias impossible to judge.
Objective outcomes	**Unclear**	Ibid.
Attrition bias: incomplete outcome data. Assessment made for class of outcomes.	**Unclear**	The efficacy and safety populations consist of all 364 patients who underwent randomization, all of whom received at least one dose of study medication.

		However, patients who took prohibited medication because of lack of efficacy or loss of response to the study medication, who discontinued the study medication because of lack of efficacy, or who underwent a colectomy or ostomy were not considered to have had a clinical response, to be in clinical remission, or to have had mucosal healing from the time of the event onward, regardless of their Mayo score. In addition, patients with insufficient data for the assessment of a response were not considered to have had a clinical response, to be in clinical remission, or to have had mucosal healing at that visit. Moreover, according to the article, 29% of the patients discontinued study infusions, and 27% did not complete the study. Due to all these reasons, the risk of bias is judged as moderate.
Reporting bias: selective reporting outcome data.	**Low**	Nothing suggests reporting bias due to selective outcome reporting, cf. clinicaltrials.gov.
Other bias	**Low**	No other concern regarding potential risk of bias.
Overall bias	**Unclear**	Overall risk of bias is judged unclear. This is primarily due to the unclear details of the blinding, which could have caused biased concealment of allocation and subsequently performance and detection bias; and due to the unclear risk of attrition bias, caused by a proportion of patients not considered in analyses.

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

Klinisk spørgsmål 1 (bionaive patienter)

Tofacitinib compared to placebo for UC (bionaive)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Tofacitinib**	**placebo**	**Relative (95 % CI)**	**Absolute (95 % CI)**		
Klinisk remission, uge 8												
2	randomised trials	not serious	serious [a]	not serious	serious [b]	none	128/417 (30,7 %)	14/104 (1,5 %)	**RR 2,45** (0,93 to 6,44)	**195 more per 1.000** (from 9 fewer to 732 more)	⊕⊕◯◯ LOW	CRITICAL
Steroidfri remission, uge 52												
1	randomised trials	not serious	serious [c]	serious [d]	not serious	none	33/101 (32,7 %)	14/101 (13,9 %)	**RR 2,36** (1,35 to 4,13)	**189 more per 1.000** (from 49 more to 434 more)	⊕⊕◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Tofacitinib**	**placebo**	**Relative (95 % CI)**	**Absolute (95 % CI)**		
Alvorlige uønskede hændelser												
1	randomised trials	not serious	serious [c]	serious [d]	serious [b]	none	10/198 (5,1 %)	13/198 (6,6%)	**RR 0,77** (0,35 to 1,71)	**15 fewer per 1.000** (from 43 fewer to 47 more)	⊕◯◯◯ VERY LOW	CRITICAL
Mukosal heling, uge 8												
2	randomised trials	not serious	serious [a]	not serious	not serious	none	199/417 (47,7 %)	30/104 (28,8 %)	**RR 1,69** (1,01 to 2,80)	**199 more per 1.000** (from 3 more to 519 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Mukosal heling, uge 52												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Tofacitinib**	**placebo**	**Relative (95 % CI)**	**Absolute (95 % CI)**		
1	randomised trials	not serious	serious [c]	not serious	not serious	none	47/93 (50,5 %)	12/89 (13,5 %)	**RR 3,75** (2,13 to 6,58)	**371 more per 1.000** (from 152 more to 752 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Livskvalitet, IBDQ												
1	randomised trials	not serious	serious [c]	serious [d]	not serious	none	Absolut effektforskel (gennemsnitlig ændring fra baseline). INDUCTION 1: 19,7 (13,3-26,2) INDUCTION 2: 19,6 (12,7-26,5)				⨁⨁◯◯ LOW	IMPORTANT

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

Forklaringer

a. Heterogeniteten i metaanalysen er høj (I2 > 50 %).

b. Konfidensintervallet for den relative forskel inkluderer 1.

c. Der var kun ét studie til vurdering af dette effektmål.

d. Der er ikke publicerede data på subpopulationen af bionaive patienter. Dermed er vurderingen foretaget på baggrund af den samlede studiepopulation.

Question: Infliximab compared to placebo for UC (bionaive)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Infliximab**	**placebo**	**Relative (95 % CI)**	**Absolute (95 % CI)**		
Klinisk remission, uge 8												
2	randomised trials	not serious	serious [a]	not serious	not serious	none	88/242 (36,4 %)	25/244 (10,2 %)	**RR 3,73** (1,68 to 8,31)	**280 more per 1.000** (from 70 more to 749 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Steroidfri remission, uge 52												
2	randomised trials	not serious	not serious	serious [b]	not serious	none	29/130 (22,3 %)	9/139 (6,5 %)	**RR 3,37** (1,66 to 6,86)	**153 more per 1.000** (from 43 more to 379 more)	⨁⨁⨁◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Infliximab**	**placebo**	**Relative (95 % CI)**	**Absolute (95 % CI)**		
Alvorlige uønskede hændelser												
2	randomised trials	not serious	not serious	serious [b]	serious [c]	none	39/242 (16,1 %)	55/244 (22,5 %)	**RR 0,72** (0,48 to 1,07)	**63 fewer per 1.000** (from 117 fewer to 16 more)	⊕⊕◯◯ LOW	CRITICAL
Mukosal heling, uge 8												
2	randomised trials	not serious	not serious	not serious	not serious	none	148/242 (61,2 %)	79/244 (32,4 %)	**RR 1,89** (1,53 to 2,32)	**288 more per 1.000** (from 172 more to 427 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Mukosal heling, uge 52												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Infliximab**	**placebo**	**Relative (95 % CI)**	**Absolute (95 % CI)**		
2	randomised trials	not serious	serious [a]	serious [b]	not serious	none	111/242 (45,9 %)	59/244 (24,2 %)	**RR 1,92** (1,20 to 3,09)	**222 more per 1.000** (from 48 more to 505 more)	⨁⨁◯◯ LOW	IMPORTANT
Livskvalitet, IBDQ												
2	randomised trials	not serious	not serious	serious [b]	not serious	none	Absolut effektforskel (gennemsnitlig ændring fra baseline). 17,13 (11,06; 23,19)				⨁⨁⨁◯ MODERATE	IMPORTANT

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

Forklaringer
a. Heterogeniteten i metaanalysen er høj (I2 > 50 %).

b. ACT 1-studiet har en opfølgningstid på 54 uger, mens ACT 2-studiet har en opfølgningstid på 30 uger.

c. Konfidensintervallet for den relative forskel inkluderer 1.

Question: Vedolizumab compared to placebo for UC (bionaive)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**vedolizumab**	**placebo**	**Relative (95 % CI)**	**Absolute (95 % CI)**		
Klinisk remission, uge 8												
1	randomised trials	not serious	serious [a]	serious [b]	not serious	none	30/130 (23,1 %)	5/76 (6,6 %)	**RR 3,51** (1,42 to 8,66)	**165 more per 1.000** (from 28 more to 504 more)	⊕⊕◯◯ LOW	CRITICAL
Steroidfri remission, uge 52												
1	randomised trials	not serious	serious [a]	not serious	serious [c]	none	14/39 (35,9 %)	8/43 (18,6 %)	**RR 1,93** (0,91 to 4,10)	**173 more per 1.000** (from 17 fewer to 577 more)	⊕⊕◯◯ LOW	CRITICAL
Alvorlige uønskede hændelser												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**vedolizumab**	**placebo**	**Relative (95 % CI)**	**Absolute (95 % CI)**		
1	randomised trials	not serious	serious [a]	serious [d]	serious [c]	none	28/309 (9,1 %)	12/76 (15,8 %)	**RR 0,570** (0,310 to 1,075)	**68 fewer per 1.000** (from 109 fewer to 12 more)	⊕◯◯◯ VERY LOW	CRITICAL
Mukosal heling, uge 8												
1	randomised trials	not serious	serious [a]	serious [b]	not serious	none	64/130 (49,2 %)	19/76 (25,0 %)	**RR 1,97** (1,29 to 3,02)	**243 more per 1.000** (from 73 more to 505 more)	⊕⊕◯◯ LOW	IMPORTANT
Mukosal heling, uge 52												
1	randomised trials	not serious	serious [a]	not serious	not serious	none	43/72 (59,7 %)	19/76 (25,0 %)	**RR 2,39** (1,55 to 3,68)	**348 more per 1.000** (from 138 more to 670 more)	⊕⊕⊕◯ MODERATE	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**vedolizumab**	**placebo**	**Relative (95 % CI)**	**Absolute (95 % CI)**		
Livskvalitet, IBDQ												
1	randomised trials	not serious	serious [a]	not serious	not serious	none	Absolut effektforskel (gennemsnitlig ændring fra baseline). 25,9 (14,6-37,3).				⊕⊕⊕◯ MODERATE	IMPORTANT

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

Forklaringer
a. Der var kun ét studie til vurdering af dette effektmål.

b. GEMINI-studiet havde kun 6 ugers opfølgningstid, der var bedt om 8 ugers opfølgning.

c. Konfidensintervallet for den relative forskel inkluderer 1.

d. Populationen indeholder både bionaive og bioerfarne, samt andre doseringer end den efterspurgte.

Klinisk spørgsmål 2 (bioerfarne patienter)

Question: Tofacitinib compared to placebo for UC (bioerfarne)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Tofacitinib**	**placebo**	**Relative (95 % CI)**	**Absolute (95 % CI)**		
Klinisk remission, uge 8												
2	randomised trials	not serious	not serious	not serious	not serious	none	80/488 (16,4 %)	6/130 (4,6 %)	**RR 3,51** (1,56 to 7,86)	**116 more per 1.000** (from 26 more to 317 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Steroidfri remission, uge 52												
1	randomised trials	not serious	serious [a]	serious [b]	not serious	none	33/101 (32,7 %)	14/101 (13,9 %)	**RR 2,36** (1,35 to 4,13)	**189 more per 1.000** (from 49 more to 434 more)	⊕⊕◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Tofacitinib**	**placebo**	**Relative (95 % CI)**	**Absolute (95 % CI)**		
Alvorlige uønskede hændelser												
1	randomised trials	not serious	serious [a]	serious [b]	serious [c]	none	10/198 (5,1 %)	13/198 (6,6 %)	**RR 0,77** (0,35 to 1,71)	**15 fewer per 1.000** (from 43 fewer to 47 more)	⊕◯◯◯ VERY LOW	CRITICAL
Mukosal heling, uge 8												
2	randomised trials	not serious	not serious	not serious	not serious	none	159/488 (32,6 %)	15/130 (11,5 %)	**RR 2,78** (1,70 to 4,56)	**205 more per 1.000** (from 81 more to 411 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Mukosal heling, uge 52												
1	randomised trials	not serious	serious [a]	not serious	not serious	none	32/83 (38,6 %)	12/85 (14,1 %)	**RR 2,73** (1,51 to 4,93)	**244 more per 1.000** (from 72 more to 555 more)	⊕⊕⊕◯ MODERATE	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Tofacitinib**	**placebo**	**Relative (95 % CI)**	**Absolute (95 % CI)**		
Livskvalitet, IBDQ												
1	randomised trials	not serious	serious [a]	serious [b]	not serious	none	Absolut effektforskel (gennemsnitlig ændring fra baseline). INDUCTION 1: 19,7 (13,3-26,2) INDUCTION 2: 19,6 (12,7-26,5)				⊕⊕◯◯ LOW	IMPORTANT

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

Forklaringer
a. Der var kun ét studie til vurdering af dette effektmål.

b. Der er ikke publicerede data på subpopulationen af bionaive patienter. Dermed er vurderingen foretaget på baggrund af den samlede studiepopulation.

c. Konfidensintervallet for den relative forskel inkluderer 1.

Question: Vedolizumab compared to placebo for UC (bioerfarne)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**vedolizumab**	**placebo**	**Relative (95 % CI)**	**Absolute (95 % CI)**		
Klinisk remission, uge 8												
1	randomised trials	not serious	serious [a]	serious [b]	not serious	none	8/82 (9,8 %)	2/63 (3,2 %)	**RR 3.07** (0.68 to 13.97)	**66 more per 1.000** (from 10 fewer to 412 more)	⊕⊕◯◯ LOW	CRITICAL
Steroidfri remission, uge 52												
1	randomised trials	not serious	serious [a]	not serious	serious [c]	none	6/26 (23,1 %)	1/23 (4,3 %)	**RR 5,31** (0,69 to 40,87)	**187 more per 1.000** (from 13 fewer to 1.000 more)	⊕⊕◯◯ LOW	CRITICAL
Alvorlige uønskede hændelser												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**vedolizumab**	**placebo**	**Relative (95 % CI)**	**Absolute (95 % CI)**		
1	randomised trials	not serious	serious [a]	not serious	serious [c]	none	44/266 (16,5 %)	7/63 (11,1 %)	**RR 1,49** (0,70 to 3,15)	**54 more per 1.000** (from 33 fewer to 239 more)	⊕⊕◯◯ LOW	CRITICAL
Mukosal heling, uge 8												
1	randomised trials	not serious	serious [a]	serious [b]	serious [c]	none	25/82 (30,5 %)	13/63 (20,6 %)	**RR 1,48** (0,82 to 2,65)	**99 more per 1.000** (from 37 fewer to 340 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Mukosal heling, uge 52												
1	randomised trials	not serious	serious [a]	not serious	not serious	none	18/43 (41,9 %)	3/38 (7,9 %)	**RR 5,30** (1,69 to 16,61)	**339 more per 1.000** (from 54 more to 1.000 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Livskvalitet, IBDQ												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**vedolizumab**	**placebo**	**Relative (95 % CI)**	**Absolute (95 % CI)**		
1	randomised trials	not serious	serious [a]	not serious	serious [d]	none	Absolut effektforskel (gennemsnitlig ændring fra baseline). 14,1 (-2,5-30,7).				⨁⨁◯◯ LOW	IMPORTANT

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

Forklaringer
a. Der var kun ét studie til vurdering af dette effektmål.

b. GEMINI studiet havde kun 6 ugers opfølgningstid, der var bedt om 8 ugers opfølgning.

c. Konfidensintervallet for den relative forskel inkluderer 1.

d. Konfidensintervallet for den absolutte effektforskel inkluderer 0.

Application for the assessment of clinically added value of tofacitinib for moderate to severe Ulcerative Colitis

Contents

1 Basic information

Table 1. Contact information

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Table 2. Overview of the pharmaceutical

Proprietary name	Xeljanz
Generic name	Tofacitinib
Marketing authorization holder in Denmark	Pfizer ApS
ATC code	L04AA29 (selective) immunosuppressives
Pharmacotherapeutic group	Immunosuppressives
Active substance(s)	Tofacitinib
Pharmaceutical form(s)	Film coated tablets
Mechanism of action	Janus Kinase Inhibitor
Dosage regimen	The recommended dose is 10 mg given orally twice daily for induction for 8 weeks and 5 mg given twice daily for maintenance. For patients who do not achieve adequate therapeutic benefit by week 8, the induction dose of 10 mg twice daily can be extended for an additional 8 weeks (16 weeks total), followed by 5 mg twice daily for maintenance. Tofacitinib induction therapy should be discontinued in any patient who shows no evidence of therapeutic benefit by week 16. For some patients, such as those who have failed prior tumour necrosis factor (TNF) antagonist therapy, consideration should be given to continuation of the 10 mg twice daily dose for maintenance in order to maintain therapeutic benefit. Patients who experience a decrease in response on tofacitinib 5 mg twice daily maintenance therapy may benefit from an increase to tofacitinib 10 mg administered twice daily.

	In patients who have responded to treatment with tofacitinib, corticosteroids may be reduced and/or discontinued in accordance with standard of care.
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Tofacitinib is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent.
Other approved therapeutic indications	Tofacitinib in combination with methotrexate (MTX) is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying antirheumatic drugs. Tofacitinib can be given as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate. Tofacitinib in combination with MTX is indicated for the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy.
Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	Xeljanz is given in combination with Methotrexate (MTX) for RA and PsA
Packaging – types, sizes/number of units, and concentrations	Packages with 56 film-coated tablets, 5 mg or 10 mg
Orphan drug designation	No

2 Abbreviations

AE	Adverse event
ARR	Absolute risk reduction
BID	Bi-daily
CAI	Clinical activity index
CI	Confidence interval
CS	Corticosteroid
EPAR	European public assessment report
GI	Gastrointestinal
HRQoL	Health related quality of life
HZ	Herpes Zoster
IBDQ	Inflammatory Bowel Disease Questionnaire
IV	Intravenous
OI	Opportunistic infection
MACE	Major adverse cardiovascular event
NA	Not applicable
NMSC	Non-melanoma skin cancer
RR	Risk reduction
SAE	Serious adverse event
TNFi	Tumor necrosis factor inhibitor
UC	Ulcerative Colitis

3 Summary

Tofacitinib is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent

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

In this application, the efficacy and safety of tofacitinib 10 mg bi-daily (BID) during 8 weeks induction therapy followed by 5 mg BID maintenance therapy is compared to infliximab 5 mg/kg and to vedolizumab 300 mg given at week 0, 2 and 6 and thereafter every 8 weeks to patients with moderate to severe UC either naïve to biological therapy (bio-naïve) or have previously received biological therapy (bio-experienced). The application also includes analyses on the overall study populations. These were performed both since results with tofacitinib according to prior exposure to biological therapy are not published for some of the endpoints (i.e., "% Serious adverse events at week 8", "% Steroid-free remission week 52", "% Serious adverse events at week 8" and "IBDQ change week 52"), and also due to broad confidence intervals in the indirect analyses of the subgroups.

A systematic literature search was carried out to identify relevant studies for this comparison and a total of 9 studies were included in the final analysis:

- 9 studies to investigate tofacitinib (3 studies), infliximab (5 studies) and vedolizumab (1 study) in bio-naïve patients
- 4 studies investigating tofacitinib (3 studies) and vedolizumab (1 study) in the bio-experienced population
- 6 studies to investigate tofacitinib (3 studies), infliximab (2 studies) and vedolizumab (1 study) in the overall study populations

In ***bio-naïve patients***, tofacitinib compared to infliximab showed an absolute difference in the rate of mucosal healing at week 8 within the interval proposed to constitute a comparable efficacy. For clinical remission at week 8, the estimated absolute difference was above 10% in favor of infliximab. However, the difference was not statistically significant and with broad CIs (the lower CI was continuously well below 10% and in favor of tofacitinib) the current data do not support a difference above 10%. Conversely, at week 52, mucosal healing is significantly improved in the tofacitinib group compared to the infliximab group, but as for infliximab at week 8, the CI is broad and within the relevant difference of 10%. The differences in remission and mucosal healing between vedolizumab and tofacitinib were all non-significant and, with inclusion of CIs, within the specified clinically relevant margin suggesting comparable efficacy. The estimated absolute difference for remission at week 8 was slightly above the margin of 10% in favor of vedolizumab when comparing central with local reading and the difference in steroid free remission at week 52 was above the estimated clinically relevant difference of 10% in favor of tofacitinib. However, as the estimates were uncertain with wide CIs, the current data cannot determine a clinically relevant difference.

For ***bio-experienced patients*** the indirect comparison between tofacitinib and vedolizumab resulted in estimates of absolute differences with high uncertainty as indicated by broad CIs and accordingly no clinically relevant differences were determined.

For early outcomes of clinical remission and mucosal healing at week 8, the absolute difference was in favor of tofacitinib and beyond the clinically relevant margin of 10%. However, with broad CIs no conclusion can be made regarding potential differences. Likewise, for mucosal healing at week 52, the estimated absolute difference was in favor of vedolizumab, but as for the early outcomes, the estimates where uncertain as indicated by broad CIs and conclusions regarding potential differences with the current data are not possible.

In the ***overall study populations***, comparing tofacitinib and vedolizumab, differences in efficacy were within the limits considered to be clinically relevant and statistically non-significant for clinical remission week 8, steroid free remission week 52, mucosal healing week 8 and IBDQ change. The same was found when comparing infliximab and tofacitinib, apart from a statistically non-significant difference in clinical remission week 8 (10.2%). As for mucosal healing week 52, there was a potential clinically relevant difference in favor of tofacitinib compared to both vedolizumab (12.9%) and infliximab (31.9%), but neither of these was statistically significant.

Safety as measured by SAEs for tofacitinib, vedolizumab and infliximab treated patients in the individual studies were all comparable to the placebo arms during induction and maintenance treatment up to 52 weeks. There were no significant differences between tofacitinib versus infliximab and tofacitinib versus vedolizumab with the estimates, however, being uncertain as reflected by wide CIs.

Of note, there are some significant differences between the studies which could potentially have an impact on the comparability of the outcomes. Most importantly, patients in the infliximab studies were all bio-naïve. Moreover, the difference in allowed background medication (immunosuppressants allowed in most infliximab studies, but not in tofacitinib studies), time point of measurements and design of the studies (e.g. responder selection versus non-responder selection for maintenance therapy) could also have an impact.

When comparing the clinical value of tofacitinib in moderate to severe UC for (i) bio-naïve, (ii) bio-experienced patients and (iii) without taking into account prior exposure to biological therapy, the current data suggest that tofacitinib is comparable to infliximab and vedolizumab.

A narrative description of the safety profile based on the EPAR/summary of product characteristics likewise shows comparable safety profile with a few exceptions. For tofacitinib, herpes zoster and lipid changes are reported as adverse events of special interest, whereas infusion related reactions for vedolizumab and infliximab are reported as adverse events of special interest.

4 Literature search

Databases and search strategy

A combined search for relevant literature for clinical question 1 (bio-naïve patients) and 2 (bio-experienced patients) was carried out in MEDLINE (via PubMed) and CENTRAL (via Cochrane library) according to the terms indicated in the protocol and as described in Appendix 9.1. A total of 329 publications were identified in MEDLINE and 540 in CENTRAL. After removal of duplicates a total of 761 were reviewed at abstract level leading to exclusion of 749 publications (see PRISMA, Appendix 9.1). The remaining 12 publications were reviewed in full where after additionally 3 were excluded (see Appendix 9.1. for list of papers) leaving a total of 9 publications addressing the clinical questions for patients with moderate to severe UC that are either bio-naïve (question 1) or bio-experienced (question 2) and treated with tofacitinib, infliximab or vedolizumab at the relevant doses.

A second review of the extracted literature and cross-referencing with 4 recently published network meta-analyses as well as the most recent treatment guideline for UC from "Rådet for anvendelse af dyr sygehusmedicin" (1-5), resulted in the identification of 1 additional study to be included in the analysis.

Following submission of the application (30 January 2019), the Medicines Council asked for an updated literature search (using same search string) including possible publications from time of original search (02 November 2018 to 30 January 2019. These searches did not reveal additionally relevant publications (see Appendix 9.1).

This revised application also includes analyses of efficacy and safety regardless of patients' prior exposure to biological therapy (question 3). These analyses are based on the same publications identified to address clinical questions 1 and 2.

4.1 Relevant studies

A total of 10 publications covering 9 relevant studies were identified in the literature search: OCTAVE induction 1 &2 and OCTAVE Sustain investigating tofacitinib, GEMINI 1 investigating vedolizumab and ACT 1, ACT 2, UC-SUCCESS, Jiang-study (Jiang) and Kobayashi-study (Kobayashi), studying infliximab for the treatment of moderate to severe UC (see Table 3). All studies are completed phase 3 studies.

In addition to the publications, the European public assessment report (EPAR) for each of the therapies has been consulted throughout the report.

Table 3. Relevant studies included in the assessment

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question <x>*
Tofacitinib as Induction and Maintenance Therapy for Ulcerative Colitis. Sandborn WJ et al, NEJM, 2017(6)	OCTAVE	NCT01465763 NCT01458951 NCT01458574	April 2012- May 2015 June 2012- June 2015 July 2012- May 2016	1+2+3
Tofacitinib in Patients with Ulcerative Colitis: Health-Related Quality of Life in Phase 3 Randomised Controlled Induction and	OCTAVE	NCT01465763 NCT01458951 NCT01458574	April 2012- May 2015 June 2012- June 2015 July 2012- May 2016	1+2+3

Maintenance Studies, Panes et al., JCC, 2018(7)				
Vedolizumab as induction and maintenance therapy for ulcerative colitis. Feagan BG et al., NEJM.(8)	GEMINI 1	NCT00783718	Jan 2009- May 2012	1+2+3
Efficacy of Vedolizumab Induction and Maintenance Therapy in Patients With Ulcerative Colitis, Regardless of Prior Exposure to Tumor Necrosis Factor Antagonists. Feagan BG et al, Clin Gastroenterol Hepatol. 2017(9)	GEMINI 1	NCT00783718	Jan 2009- May 2012	1+2+3
Effects of vedolizumab on health-related quality of life in patients with ulcerative colitis: results from the randomised GEMINI 1 trial. Feagan BG et al., Aliment Pharmacol Ther. 2017 (10)	GEMINI 1	NCT00783718	Jan 2009- May 2012	1+2+3
Infliximab for induction and maintenance therapy for ulcerative colitis. Rutgeerts P et al., NEJM. 2005 Erratum in: NEJM. 2006 May 18;354(20):2200.(11)	ACT 1 and ACT 2	NCT00036439 NCT00096655	Feb 2002- jan 2007 May 2002- Aug 2007	1+3
The effects of infliximab therapy on health-related quality of life in ulcerative colitis patients. Feagan BG et al., Am J Gastroenterol. 2007 Erratum in: Am J Gastroenterol. 2007 Jun;102(6):1338.(12)	ACT 1 and ACT 2	NCT00036439 NCT00096655	Feb 2002- jan 2007 May 2002- Aug 2007	1+3
Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis. Panaccione R et al., Gastroenterology. 2014 (13)	UC-SUCCESS	NCT00537316	July 2007-feb 2010	1
First trough level of infliximab at week 2 predicts future outcomes of induction therapy in ulcerative colitis-results from a multicenter prospective randomized controlled trial and its post hoc analysis. Kobayashi T et al., J. Gastroenterol. 2016(14)	Kobayashi et al	Japic CTI-060298	July 2006 –dec 2008	1

Low-dose Infliximab for Induction and Maintenance Treatment in Chinese Patients With Moderate to Severe Active Ulcerative Colitis. Jian et al., J Clin(15) Gastroenterol, 2015	Jiang et al	NA	Dec 2008-dec 2013	1

4.2 Main characteristics of included studies

The main characteristics of the included studies are described in Appendix 9.2, Table A2.

Selected baseline characteristic for the individual studies are listed in Table 4.

Overall, gender, age, disease extent and severity are comparable between the studies despite the time span between enrollment in the first and last study (2002-2012). Mean disease duration range from 4.3 years in Jiang to 8.6 years in OCTAVE Sustain. Approximately half of the patients were on background glucocorticoid treatment with the lowest percentage reported in the UC-SUCCESS trial (34.2-47.5%) and highest in Kobayashi (65.5-66.3%) (see Table 4).

One major difference between the studies, however, is the inclusion of bio-experienced patients as well as the allowed background medication during the trials. Accordingly, the tofacitinib and vedolizumab trials included bio-experienced patients- 45.5%-58% and 48%, respectively- whereas the Infliximab trials included only bio-naïve patients. In addition, the tofacitinib trials did not allow immunosuppressant drugs (azathioprine or mercaptopurine) as background medication during the trials, which is in contrast to both the vedolizumab and infliximab trials where 34.4%-54.5% of patients are reported to use immunosuppressants. In UC-SUCCESS all patients in the comparator group received azathioprine.

Table 4. Baseline characteristics

	OCTAVE 1	OCTAVE 2	OCTAVE Sustain	GEMINI 1	ACT 1	ACT 2	UC-SUCCESS	Kobayas-hi et al	Jiang et al
Male (%)	*-58.2-63.1*	*49.1-60.4*	*-52.0-58.6*	*58.7*	*59.0-64.5*	*56.7-62.8*	*42-60*	*63.5-64.4*	*58.5-63.4*
Age (years; (mean ±SD)	*41.3(14.1) - 41.8(15.3)*	*40.4(13.2) - 41.1(13.5)*	*41.9(13.7) - 43.4(14.0)*	*40.3(13.1)*	*41.4(13.7) - 42.4(14.3)*	*39.3(13.5) - 40.5(13.1)*	*38.0(12.2) - 40.7(13.2)*	*37.8(12.9) - 40.0 (12.7)*	*34.1(13.8) -34.5 (14.9)*
Disease duration (years; mean ±SD)	*8.3 (7.2)*	*7.9 (6.8)*	*8.6 (7.2)*	*6.9 (6.4)*	*5.9(5.4)- 8.4 (8.1)*	*6.5(6.7)- 6.7 (5.3)*	*5.2(5.1)- 6.6 (7.8)*	*7.1(6.6)- 8.1 (7.2)*	*4.3(2.5)- 4.4(2.8)*
Disease extent	*13.7-15.6% proctosig moiditis* *30.3-33.3% left sided colitis* *53.1-54.1% extensive/ pancolitis*	*14.4-15.7% proctosig moiditis* *34.8-35.1% left sided colitis* *49.3-50.5% extensive/ pancolitis*	*10.6-16.8% proctosig moiditis* *30.6-34.3% left sided colitis* *52.0-54.5% extensive/ pancolitis*	*13.0% proctosig moiditis;* *37.9% left sided colitis,* *12.2% proximal to the splenic flexure, 37% all colon*	*52.9-55.4% left sided colitis,* *44.6-47.1% extensive*	*58.3-62.5% left sided colitis,* *37.5-41.7% extensive*	NA	*19.2-20.2% left sided colitis,* *79.8-80.8% extensive*	*36.6-41.5% left sided colitis* *58.5-63.4% pancolitis*
Disease severity (total Mayo score ±SD)*	*9.0 (1.4) - 9.1 (1.4)*	*8.9 (1.5) - 9.0 (1.5)*	*3.3 (1.8) – 3.4 (1.8)*	*8.6 (1.8)*	*8.4 (1.4)- 8.5 (1.7)*	*8.3 (1.5)- 8.5 (1.5)*	*8.31 (1.4)- 8.6 (1.3)*	*8.5(1.4) - 8.6(1.4)*	*NA*
Previous treated with TNFi (%)	*53.3-53.4%*	*54.5-58.0%*	*45.5-51.3%*	*48.2%*	*0%*	*0%*	*0%*	*0%*	*0%*
Treated with glucocorticoids at study entry (%)	*45-47.5%*	*46.2-49.1%*	*44.2-51.0%*	*53.7%*	*57.9 – 65.3%*	*48.8 – 55.0%*	*34.2 – 47.5%*	*65.4 – 66.3%*	*51.2-53.7%*
Using immuno suppressants (%)	*0*	*0*	*0*	*34.4%:*	*43.8-54.5%:*	*41.7-43.9%:*	NA	*47.1-48.1%:*	*29.3-31.7%*

*determined based on centrally read endoscopy for tofacitinib and locally read endoscopy for Vedolizumab and Infliximab

5 Clinical questions

5.1 Clinical question 1: What is the added clinical value of tofacitinib for bio-naïve patients with moderate to severe UC compared to infliximab and vedolizumab respectively?

5.1.1 Presentation of relevant studies

8 studies were identified that include investigations of tofacitinib, vedolizumab or infliximab at the relevant dosing regimens in bio-naïve moderate to severe UC patients.

Tofacitinib

The study program for tofacitinib included two separate phase 3 randomized, controlled, double-blinded, 8 week induction studies, OCTAVE 1 and 2, and a randomized, controlled double-blinded maintenance study, OCTAVE Sustain. OCTAVE 1 and 2 had similar trial design and included 598 and 541 patients respectively, that were randomized 4:1 to tofacitinib 10 mg bi-daily (BID) or placebo. Primary endpoint was remission at week 8, defined as a total Mayo score of ≤2, no subscore >1 and a rectal bleeding subscore of 0. OCTAVE Sustain investigated the maintenance treatment in patients who had a clinical response to induction treatment in either OCTAVE 1 or 2 with a follow-up time to week 52. Clinical response was defined as a decrease from induction-trial baseline in the total Mayo score of at least 3 points and at least 30%, with an accompanying decrease in the rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 0 or 1. At entry into the maintenance trial all patients (n = 593) were re-randomized to placebo (n = 198), 5 mg BID tofacitinib (n = 198) or 10 mg BID tofacitinib (n =197). Primary endpoint in OCTAVE Sustain was remission (as described for week 8) at week 52.

Of note, in addition to investigator (local) assessment, for all endoscopy evaluations in the OCTAVE studies– including those to assess endoscopic remission, clinical remission and steroid-free remission- a central reading procedure was employed. This is an off-study site assessment where blinded assessors evaluated and rated the endoscopy videos. This is in contrast to earlier practice -including those for the comparator trials which were carried out earlier than the tofacitinib trials- where local assessment by the investigator was employed as the only assessment. This difference in endoscopy assessment procedure may have an impact on the outcomes above (see also (16)). In general, the local endoscopic readings are numerically greater than efficacy assessed by central readings for tofacitinib which suggest that comparison between central read and local read endoscopy efficacy assessments in different studies may pose some challenges (Table 5 and 6 and (17)).

Accordingly, as local read endoscopy was also recorded in the OCTAVE program, both centrally read results and locally read results are provided for tofacitinib to improve comparison to the comparators. Data for tofacitinib central reading is provided in peer-reviewed publications for bio-naïve and bio-experienced patients and local readings are provided for the overall population in the tofacitinib EPAR. Locally read endoscopy data for the tofacitinib subgroups of bio-naïve and bio-experienced patients is data on file.

Steroid free clinical remission at week 52 in patients receiving steroids at baseline was a secondary endpoint in the tofacitinib trials and has only been reported in peer-review for the pooled population and is therefore only included in the analyses of the overall population (section 5.3).

Vedolizumab

The Vedolizumab study program includes one phase 3, 52 week study, GEMINI 1, investigating both induction and maintenance therapy. The induction trial consisted of two cohorts: one randomized controlled, double blinded cohort (cohort 1) including 374 patients and one open label cohort (cohort 2), including 521 patients. Cohort 2 was included to ensure adequate sample size in the maintenance trial. Primary endpoint for the induction period was clinical response (defined as above for clinical response in OCTAVE) at week 6. Similar to the OCTAVE studies, only vedolizumab patients obtaining a clinical response in the induction phase continued in the randomized, double blinded and controlled maintenance phase. However, placebo patients continued with placebo treatment during the maintenance phase which is in contrast to the OCTAVE program where all induction responding patients were re-randomized at entry into the maintenance trial. Thus the double-blinded, randomized maintenance trial for vedolizumab includes only patients who have responded to vedolizumab during induction whereas the maintenance trial for tofacitinib includes also patients treated with placebo during induction.

A total of 373 vedolizumab responding patients were eligible for the GEMINI 1 maintenance trial and were randomized 1:1:1 to treatment with vedolizumab every 4 weeks, every 8 weeks or placebo. The primary endpoint was clinical remission at week 52 defined as a total Mayo score of ≤2, no subscore >1 and a rectal bleeding subscore of ≤1, which is slightly different from the OCTAVE trial definition where the rectal bleeding subscore is defined as 0. In addition, as noted above, endoscopy was carried out by local reading.

Infliximab

The pivotal study program for infliximab consisted of two phase 3, randomized, controlled and double-blinded trials, ACT 1 and ACT 2, each investigating both induction and maintenance therapy but with different follow-up time (54 weeks and 30 weeks, respectively). Both ACT 1 and ACT 2 included 364 patients randomized 1:1:1 to receive i.v. dose of infliximab of 0 mg/kg, 5 mg/kg or 10 mg/kg. In contrast to the OCTAVE and GEMINI 1 studies, all patients continued through to the maintenance period regardless of response in the induction phase. Thus, there was no selection of responding patients.

Primary endpoint in both ACT 1 and ACT 2 was clinical response (similar definition to clinical response defined in the OCTAVE studies) at week 8. Secondary endpoints were clinical response and clinical remission with discontinuation of steroids at week 30 for both studies and week 54 for ACT 1, with remission defined as for the GEMINI 1 trial.

Besides ACT 1 and ACT 2, Infliximab has also been investigated in the Asian population in a phase 3, randomized, controlled, double-blinded study (Kobayashi et al) including 208 Japanese patients and the single-center, double blinded, randomized, controlled Jiang study including 123 Chinese patients and 2 infliximab doses (3.5 mg/kg and 5 mg(kg). An additional randomized, double-blinded infliximab study included 231 patients and investigated infliximab as monotherapy compared to combination therapy with azathioprine. The latter study, UC-SUCCESS, was terminated early and only week 16 data have been published. In addition, UC-SUCCESS did not include a placebo group. Accordingly, comparisons were made between infliximab and the azathioprine group. Primary endpoint for the Kobayashi and Jiang studies were clinical response at week 8 and secondary endpoints included clinical remission at week 30, defined as for the GEMINI 1 trial. Of note, the two studies included only Asian (Japanese and Chinese) patients and the author propose that there may be some differences in their population compared to other populations, such as a different gender ratio or increased sensitivity (14, 15). Additionally, the Kobayashi study also reports on inclusion of 18 patients with acute severe UC, which could potentially impact the results. Primary endpoint for UC-SUCCESS was corticosteroid free remission at week 16. Thus, besides a

comparator group that could potentially have an impact on the results, the time point for this trial varies considerably from the time point selected for all the other trials addressing steroid free remission at week 30-54, which could have additional impact on this outcome.

In addition to the differences in endoscopic reading (central and local), primary endpoint at induction (remission or response), definition of remission (rectal bleeding subscore of 0 or ≤1), patient inclusion in maintenance studies (e.g. responders or all) and time point for primary endpoints (week 6, 8, 16, 30, 52 and 54) the trials also differed in the inclusion of bio-experienced patients as well as in the allowed background medications as mentioned in section 4.2. Accordingly in the OCTAVE and GEMINI studies both bio-naïve and bio-experienced were included.

A total of 279 bio-naïve patients were included in OCTAVE 1, 243 bio-naïve patients in OCTAVE 2 and 310 in the OCTAVE Sustain maintenance trial. In Gemini 1, 206 bio-naïve patients were included in the randomized, controlled and double blinded induction cohort 1, 258 bio-naïve patients in the open label induction cohort 2 and 224 bio-naïve patients in the maintenance phase of GEMINI 1. In the infliximab trials, all patients are bio-naïve. In regards to background medication, the OCTAVE program did not allow immunosuppressants (azathioprine and mercaptopurine), which are in contrast to the comparator trials where background immunosuppressant treatment is reported in approximately 34-55% of patients (Table 4).

5.1.2 Results per study

Details of the individual study statistical procedures can be found in Appendix 9.2, Table A2

Tofacitinib: OCTAVE study program

The efficacy analyses were based on data from all patients who underwent randomization. The safety analyses were based on data from all patients who underwent randomization and received at least one dose of the assigned treatment.

The primary efficacy end point for OCTAVE induction 1 and 2 was remission (a total Mayo score of ≤2, with no subscore >1 and a rectal bleeding subscore of 0) at 8 weeks. For OCTAVE Sustain the primary endpoint was remission at week 52.

The key secondary end point was mucosal healing (a Mayo endoscopic subscore of ≤1) at 8 (OCTAVE 1 and 2) and 52 weeks (OCTAVE Sustain) as well as sustained (both week 24 and 52) glucocorticoid free remission among patients in remission at entry in OCTAVE Sustain. Additional secondary endpoints included clinical response, endoscopic remission as well as symptomatic remission and deep remission at week 8, 24 and 52. HRQoL outcomes included IBDQ change and IBDQ remission at week 8 and 52.

The family-wise type 1 error rate was controlled at 0.05 for the primary and key secondary end points with the use of a fixed-sequence testing

Infliximab: ACT 1 and ACT 2, UC-SUCCESS and Kobayashi

ACT 1 and ACT 2: All efficacy analyses were performed on the intention-to-treat population

The primary end point was a clinical response at week 8.

Secondary endpoints included a clinical response or clinical remission (defined as a Mayo score of = 2 points, with no individual subscore > 1) with discontinuation of corticosteroids at week 30 (ACT 1 and ACT

2) and at week 54 (ACT 1), clinical remission and mucosal healing at weeks 8 ,30 and at week 54 (ACT 1 only), and a clinical response at week 8 in patients with a history of disease refractory to corticosteroids.

For the UC-SUCCESS trial the full analysis set was used for analysis of efficacy. The full analysis set consisted of all patients who were randomized, received at least 1 dose of study treatment, and had data available at baseline and at least 1 post baseline evaluation.

The primary end point was the proportion of patients in corticosteroid (CS)-free remission, defined as a total Mayo score of 2 points or less, with no individual subscore exceeding 1 point, without the use of CSs at week 16. Secondary end points included the percentage of patients with partial Mayo response at week 8, the percentage of patients with Mayo response at week 16, the percentage of patients with mucosal healing at week 16 and changes in Mayo, IBDQ, and SF-36 scores from baseline to weeks 8 and 16.

Hochberg's step-down approach was used to control type 1 error during treatment group comparisons for the primary end point and secondary end point comparisons.

As noted above, UC-SUCCESS did not include a placebo group but rather comparisons were made between the azathioprine group and the infliximab group. As described, several of the other studies allowed use of immunosuppressants in both the placebo and active arms and approximately half of patient were reported to use immunosupressants in the studies. However, in GEMINI 1 for example, patients are included if they have moderate to active disease despite being on a stable dose of azathioprine whereas in UC-SUCCESS patients are included if they have moderate to severe disease without concomitant treatment with azathioprine. Thus the included patient populations may differ in their response to azathioprine which can potentially impact on the outcomes - in particularly for the later outcomes in UC-SUCCESS where azathioprine has had time to fully impact on the disease (18).

In the Kobayashi study, efficacy was assessed in the full analysis set.

The primary end point was a clinical response at week 8. Secondary endpoints included clinical remission or mucosal healing, response at week 8 as well as clinical response or clinical remission at week 30. The Mayo score was determined at weeks 0, 8, and 30. The clinical activity index was determined at all visits.

The Jiang study investigated the efficacy of infliximab in Chinese patients in the full analysis set.

The primary endpoint was a clinical response at week 8. Secondary end points were clinical response or clinical remission with discontinuation of corticosteroids at week 30, clinical remission and mucosal healing at weeks 8 and 30, and clinical response at week 8 in patients with a medical history of disease refractory to corticosteroids.

<u>Vedolizumab: GEMINI 1</u>

All analyses were performed according to an intention-to-treat principle.

The primary endpoint was a clinical response at week 6 (induction period) and remission at week 52.

Secondary endpoints included clinical remission week 6 and durable clinical response (response at both weeks 6 and 52), durable clinical remission (remission at both weeks 6 and 52), mucosal healing at week 52, and glucocorticoid-free remission at week 52 in patients receiving glucocorticoids at baseline. Health-related quality of life was evaluated with the use of the IBDQ.

To control for multiple comparisons, a closed sequential procedure was used for primary and secondary outcomes, and a P value of 0.05 or lower was required to proceed to the analysis of each subsequent outcome.

RESULTS

An overview of the absolute risk reduction (ARR) from placebo for the selected outcomes for the individual studies can be seen in Table 5 for induction therapy and Table 6 for maintenance therapy. Risk reductions (RR) can be found in Appendix 9.3, Table A3. Forest plots for tofacitinib and infliximab can be found in Appendix 9.5.

Absolute risk reduction (ARR) values for the individual study results were calculated based on the estimated RR and the event rate in the comparator (placebo) arm according to the following equation: (RR-1)*event rate placebo. Accordingly, for all positive outcomes (remission, mucosal healing) an RR>1 is in favor of tofacitinib whereas for negative outcomes (serious adverse events) and RR>1 is in favor of comparators.

Table 5. Induction therapy: Absolute difference from control for tofacitinib, vedolizumab and infliximab for selected outcomes in patients with moderate to severe UC and naïve to biological therapy

Outcome		Tofacitinib 10 mg BID		Vedolizumab iv 300mg week 0, 2 and 6	Infliximab 5 mg/kg Week 0, 2, 6				
		OCTAVE 1	OCTAVE 2	GEMINI 1	ACT 1	ACT 2	UC SUCCESS	Kobayashi	Jiang
% Clinical remission week 6/8 (95%CI)	Central endoscopy	9.4 (-2.5; 32.1)	13.5 (-0.2-49.8)	NA	NA	NA	NA	NA	NA
	Local endoscopy	12.7 (-1.1; 36.9)	22.8 (3.2-82.9)	16.5 (2.8;50.4)	24.0 (9.1;48.0)	28.2 (10.1;66.9)	NA	9.6 (-0.3; 29.2)	31.7 (6.2;80.2)
% Mucosal healing week 6/8/16 (95% CI)	Central endoscopy	13.3 (-1.4; 36.7)	17.3 (0.5-48.3)	NA	NA	NA	NA	NA	NA
	Local endoscopy	13.6 (-1.8-35.8)	25.5 (5.1-62.8)	24.2 (7.1;50.4)	28.1 (12.7;48.6)	29.4 (13.7;50.6)	17.7 (1.3; 41.2)	18.3 (3.9; 39.1)	34.1 (7.8;82.0)
% Serious adverse events week 6/8/14 (95% CI)		NA*	NA*	-7.7 (-9.3-; -3.7)	NA	NA	NA		-3.8 (-8.6;6.9)

NA, not available. *Data for subgroup bio-naïve patients not published. See Section 5.3, Table 9 for data on the overall population.

Table 6. Maintenance therapy: Absolute difference from placebo for tofacitinib, vedolizumab and infliximab for selected outcomes in patients with moderate to severe UC and naïve to TNFi therapy

Outcome		Tofacitinib 5 mg BID	Vedolizumab 300 mg every 8 weeks	Infliximab 5mg/kg every 8 weeks				
		OCTAVE SUSTAIN	GEMINI 1	ACT 1	ACT 2	UC SUCCESS	Kobaya-shi	Jiang
% Steroid free remission week 52 (Range 16-54) (95% CI)	Central endoscopy	NA*	NA	NA	NA	NA	NA	NA
	Local endoscopy	NA*	17.3 (-1.7;57.6)	16.9 (2.6;49.0)	15 (0.9;75.9)	-1.6 (-11.4;15.8)	NA	36.1 (0.9;290.8)
% Mucosal healing week 52 (range 30-54) (95% CI)	Central endoscopy	28.5 (10.0;62.5)	NA	NA	NA	NA	NA	NA
	Local endoscopy	37.1 (15.3;75.3)	34.7 (13.7;67.1)	27.3 (11.5;51.4)	16.2 (3.2;34.3)	NA	12.5 (-0.5;31.5)	31.7 (6.2;80.2)
% Serious Adverse Events week 52 (range 16-54) (95% CI)		NA*	-6.7 (-11;1.2)	-4.1 (-12;8.3)	-8.8 -13.8;0.6)	-7.7 (-7.6;2.7)	-1.0 (-8.6;12.8)	-2.4 (-8.0;20.9)
% IBDQ remission week 52		NA*	NA	NA	NA	NA	NA	NA
IBDQ change week 52 (mean, 95% CI)		NA*	25.9 (14.6; 37.3)	20 (11.56; 28.44)	14 (5.20; 22.80)	NA	NA	NA

NA, not available. *Data for subgroup bio-naïve patients not published. See Section 5.3, Table 9 for data on the overall population.

5.1.3 Comparative analyses

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

Indirect comparison was performed using Bucher method with input from above meta-analysis. As for the individual studies, ARR was calculated from the RR according to the following equation: ARR= (RR-1)*comparator event rate. Comparator event rate was calculated from the selected comparator studies. P-values are calculated using Chi-Square.

All the patients included in the infliximab studies are bio-naïve. In contrast approximately half of the patients included in tofacitinib and vedolizumab trials are bio-naïve and the other half is bio-experienced. Accordingly, the following analyses are performed on the subgroup of bio-naïve patients in these studies. Unfortunately, the effect of tofacitinib on "% Steroid free remission week 52", "% Serious adverse events week 8", "% Serious adverse events week 52" and "IBDQ Change week 52" have not been published for the subgroup of bio-naïve patients. Please refer to Section 5.3 for analyses on these endpoints in the overall tofacitinib treated population.

For infliximab the pivotal phase 3 trials were ACT 1 and ACT 2. Since then, the UC-SUCCESS and the studies in the Asian population: Jiang and Kobayashi have been published. However due to differences in the study

designs (for example study population and follow-up time), the primary indirect comparisons were produced with inclusion of only ACT 1 and 2. Sensitivity analyses including UC-SUCCESS, Jiang and Kobayashi were additionally performed to describe potential impact of these studies on the outcomes.

A detailed description of the outcomes can be found in Appendix 9.4, Table A4a.

Clinical remission week 8 (critical)

Two analyses are presented to evaluate clinical remission at week 8. Data for tofacitinib has been published in peer-review on clinical remission using centrally read endoscopy data. In the first analysis, tofacitinib clinical remission data, based on central read endoscopy, is compared to vedolizumab and infliximab induced clinical remission during induction based on local read endoscopy. However, as evidence suggest that centrally read data differ from locally read (see also tofacitinib EPAR), a second analysis comparing remission data based on local read endoscopy for tofacitinib with remission data based on local read endoscopy for vedolizumab and infliximab is also presented.

The absolute difference in effect between tofacitinib 10 mg BID and vedolizumab 300 mg in clinical remission following induction therapy is -10.9% (95% CI: -18.8-11.7) in favor of vedolizumab when central reading (tofacitinib) is compared to local reading (vedolizumab). The RR is 0.527. When more appropriate local-to-local reading is compared, the difference in effect is -7.0% (95% CI: -18.8-37.5) and the RR is 0.698 in favor of vedolizumab. For tofacitinib 10 mg BID compared to infliximab 5 mg/kg, the difference is -18.3% (95% CI: -29.5-10.9, p =0.152) for central read compared to local read. When a more appropriate comparison between “local read” and “local read” data is applied, the difference is -12.5% (95% CI -29.6-47.4, p= 0.512). The RR of 0.496 and 0.657 is in favor of infliximab, but the estimate is highly uncertain, with wide confidence intervals and difference that is statistically non-significant. The clinical meaningful difference for remission is indicated to be 10%. Although the estimated absolute difference between tofacitinib and infliximab is above this, the lower limit of the CIs (-29.5% and -29.6%) is well below the 10%. Accordingly the current evidence suggests that there is no difference in clinical remission at week 8 between tofacitinib, vedolizumab and infliximab.

The Kobayashi and Jiang studies also measured clinical remission for induction, but in trials that included a somewhat different patient population. To investigate if these studies would change the results of the indirect comparison between tofacitinib and infliximab we performed a sensitivity analysis. Including the Kobayashi study in the indirect comparison resulted in absolute differences between tofacitinib 10 mg BID and infliximab 5 mg/kg of -12.0% (95% CI: -22.7-11.5) and -5.7% (-23.2-48.3) for central versus local comparison and local versus local comparison respectively. Thus this study decreased the overall difference but did not significantly change the conclusion from the primary analysis. Inclusion of the Jiang study resulted in absolute differences of -16.8% (95% CI: -27.9-8.1, p =0.148) for central versus local comparison and -8.8% (95% CI: -28.7-50.1, p = 0.642) for local versus local comparison. Thus inclusion of this study increased the overall difference but did not change the conclusion from the primary analysis.

Steroid free remission week 52 (critical)

Unfortunately, the effect of tofacitinib on “% Steroid free remission week 52” has not been published for the subgroup of bio-naïve patients. Please refer to Section 5.3 for analyses on these endpoints in the overall tofacitinib treated population.

Serious adverse events (critical)

Unfortunately, the effect of tofacitinib on "% Serious adverse events week 8" and "% Serious adverse events week 52" have not been published for the subgroup of bio-naïve patients. Please refer to Section 5.3 for analyses on these endpoints in the overall tofacitinib treated population.

Mucosal healing week 8 (important)

As for remission data, two comparisons are presented for mucosal healing at week 8: Central read data for tofacitinib 10 mg BID compared to local read data for vedolizumab 300 mg and infliximab 5 mg/kg and local read data for tofacitinib 10 mg BID compared to local read data for vedolizumab 300 mg and infliximab 5 mg/kg.

The absolute difference in mucosal healing between tofacitinib and vedolizumab is non-significant at -8.2% (95% CI: -25.9;22.9) (central versus local) or -7.0% (95% CI: -27.5;32.9) (local versus local) in favor of vedolizumab (RR: 0.833 and 0.858). The absolute difference between tofacitinib and infliximab is in favor of infliximab at -8.1% (95% CI: -26.5;20.0) when comparing central to local data. When comparing local to local data the absolute difference is smaller at -6.5% (95% CI: -29.6; 33.7). Both differences are statistically non-significant. The RR is 0.868 and 0.894 respectively. The suggested clinical relevant difference is 10 % according to the protocol and the absolute difference is below this margin in both comparisons. Thus current data suggest that tofacitinib is comparable to infliximab and vedolizumab in inducing mucosal healing at week 8.

The Kobayashi study, the Jiang study and the UC-SUCCESS study also included mucosal healing data at week 8. Including the UC-SUCCESS study in the indirect comparison decreased the absolute value slightly but did not significantly change the outcome (central versus local read: ARR -4.7% (95% CI -23.2; 23.3) and local versus local read: ARR -3.0% (95% CI -26.6;37.5). Similarly, inclusion of the Kobayashi and the Jiang study also did not change the outcome significantly: ARR -6.4% (95% CI -25.0; 21.6) and -9.4 (95% CI: -27; 17.3) respectively for central versus local reading and ARR -4.7% (95% CI -28.4; 36.0) and -7.8 (95% CI: -30.1;30.6) respectively for local versus local read.

Mucosal healing week 52 (important)

The absolute difference between tofacitinib and vedolizumab for mucosal healing at week 52 is estimated to be 22.9% (95% CI: -20.4; 114.2) (central versus local) and 34.0% (95% CI: -13.7; 131) (local versus local reading) (RR of 1.384 and 1.569 respectively) in favor of tofacitinib. The clinical relevant difference is estimated to be 10% and the estimate for both central-local and local-local comparison is well above this limit in favor of tofacitinib. However, the CIs again are wide and the difference statistically non-significant and accordingly it cannot be determined if there is a clinical relevant difference with the current data. In comparison to infliximab, the absolute difference between tofacitinib and infliximab is 33.1% (95% CI: -9.2; 124.3) (central versus local) and 43.7% (95% CI: -3.0; 141) (local versus local) in favor of tofacitinib (RR: 1.722 and 1.952, p =0.075). This is in contrast to mucosal healing at week 8 which was in favor of infliximab. However, although bordering statistical significance (p= 0.075) and the estimate being well above the 10% relevant difference the CI are again broad and the difference between tofacitinib and infliximab could potentially be less than the specified clinical relevant difference of 10%.

Kobayashi and Jiang also included mucosal healing in the maintenance phase. Inclusion of these results in the indirect comparison between tofacitinib and infliximab resulted in absolute differences of 40.5% (95% CI: -1.6;123.9, p= 0.063) and 51.9% (95% CI 6.0;139.6, p =0.019) for central versus local read comparison and local versus local comparison respectively. Thus inclusion of Kobayashi increases the absolute

difference estimate in favor of tofacitinib. In particular for local to local comparison where the difference becomes statistically significant (p =0.019) and is well beyond (51%) the suggested 10% relevant clinical difference. However, with broad CI (lower CI of 6%) the estimate is uncertain and it is not possible to draw conclusion regarding whether there is a clinical relevant difference of 10%. Inclusion of the Jiang study resulted in estimated absolute differences of 30.3% (95% CI: -8.6; 108.7, p =0.164) for central versus local comparison and 40.6% (95% CI: -1.9; 40.6, p = 0.066) for local versus local read comparison. Thus inclusion of this study only marginally changes the outcome of the primary analysis and do not change the overall conclusion.

IBDQ remission and change (important)

IBDQ remission data in bio-naïve patients could not be identified for any of the studies and accordingly no comparison could be performed.

The effect of tofacitinib on "IBDQ change" has been published for the subgroup of bio-naïve patients. However, the reported values are not correct and the corrected data are not yet published. Please refer to section 5.3 for analyses on these endpoints in the overall tofacitinib treated population.

Summary

Tofacitinib (pooled data) for the treatment of moderate to severe UC in bio-naïve patients has shown improvements compared to placebo in clinical remission and mucosal healing at week 8 and 52.

Compared to infliximab, tofacitinib has shown efficacy results for mucosal healing at week 8 within the margins that are specified to be clinically relevant differences suggesting comparability between tofacitinib and infliximab for this outcome. For clinical remission at week 8, the estimated absolute difference was above 10% in favor of infliximab. However, the difference was not statistically significant and with broad CIs, the lower CI was continuously well below 10% and in favor of tofacitinib. Thus current data are not able to estimate if there is a difference beyond 10% between tofacitinib and infliximab in induction of clinical remission at week 8. The difference in mucosal healing at week 52 (span 30-54) was numerically greater (30.3-51.9%), and above the clinically relevant difference of 10% in patients treated with tofacitinib compared to infliximab. This difference became statistically significant when sensitivity analysis was performed including the Japanese Kobayashi study and borderline significant (p =0.066) when including the Jiang study. However, the broad CIs indicated uncertainty in the estimate and the lower CI was continuously lower than the 10% clinical relevant margin.

The differences in efficacy outcomes (remission and mucosal healing) between vedolizumab and tofacitinib were both non-significant and, with inclusion of CIs, within the specified clinically relevant margin suggesting comparable efficacy. The estimated absolute difference for remission at week 8 was slightly above the margin of 10% in favor of vedolizumab when comparing central with local reading. However, as the estimates were uncertain with wide CIs, the current data cannot determine a clinically relevant difference.

Of note, there are some differences between the studies which could potentially have an impact on the comparability of the outcomes. This includes the difference in allowed background medication (immunosuppressants allowed in most infliximab studies, but not in tofacitinib studies), time point of measurements and design of the studies (e.g. responder selection versus non-responder selection for maintenance therapy).

5.2 Clinical question 2: What is the added clinical value of tofacitinib for bio-experienced patients with moderate to severe UC compared to infliximab and vedolizumab respectively?

5.2.1 Presentation of relevant studies

A total of four studies were identified that include bio-experienced moderate to severe UC patients: Three for tofacitinib (OCTAVE 1 +2 and OCTAVE Sustain) and one for vedolizumab (GEMINI 1). No randomized, controlled trials at the relevant dosing and population were identified for infliximab.

All four studies have been described in Section 5.1 and Appendix, Table A2. In brief, OCTAVE induction 1 and 2 and OCTAVE Sustain are randomized controlled double-blinded, phase 3 trials investigating tofacitinib efficacy and safety as induction and maintenance therapy in moderate to severe UC patients respectively. A total of 316 bio- experienced patients were included in OCTAVE 1, 299 bio-experienced patients in OCTAVE 2 and 283 bio- experienced patients in OCTAVE Sustain. The majority of patients were TNFi experienced, but a subset of 2.4 -2.8% of the included patients had previous treatment with a biologic other than a TNFi (19).

GEMINI 1 covers one induction trial with 2 cohorts (one randomized, controlled double-blind and one open label) and one randomized, controlled, double-blinded maintenance trial investigating vedolizumab efficacy and safety in moderate to severe UC. Both OCTAVE Sustain and GEMINI 1 have 52 weeks follow-up and for both maintenance trials only patients responding to induction treatment, as measured by a clinical response, were included. However, in contrast to the tofacitinib trial, where all patients with a response was re-randomised at week 8, placebo patients in GEMINI 1 induction were not re-randomised at entry into the maintenance phase but continued on placebo treatment. Accordingly only patients with a response to vedolizumab were re-randomized at entry into the maintenance phase. A total of 168 TNFi experienced patients were included in cohort 1, 263 TNFi experienced patients in cohort 2 and 121 TNFi experienced patients in the maintenance trial. The eligibility criteria for entering GEMINI 1 was inadequate response, loss of response or intolerance to infliximab as this was the only available TNFi at the time of the study initiation and, unlike the OCTAVE program where a small subset of patients had been treated with other biologics, all patients are reported to be TNFi experienced (9).

An additional difference between the two studies is the permitted background medication. In the tofacitinib trials, immunosuppressants (azathioprine or mercaptopurine) were not allowed whereas 22-32% of the TNFi experienced population in the GEMINI 1 trial took background immunosuppressant medicine at baseline. Finally, as for the bio-naïve population, endoscopic procedure (central and local read), definition of remission (rectal subscore of 0 or ≤1), time point for measurement of the induction primary endpoint (6 weeks and 8 weeks) as well as primary endpoint for induction (remission or response) were some of the additional parameters differing between the OCTAVE study design and the GEMINI 1 design which could potentially have an impact on the outcomes of interest.

5.2.2 Results per study

The outcome analyses for the OCTAVE program and GEMINI 1 are described above (see section 5.1.1.)

An overview of the outcomes for bio-experienced patients for the individual studies can be seen in Table 7 for induction and Table 8 for maintenance therapy. RR and ARR have been calculated similarly to the calculations for the bio-naïve population. Detailed information of outcomes can be found in Appendix 9.3, Table A3.

Table 7: Induction therapy: Outcomes for moderate to severe UC patients with previous bio-experience. Absolute differences from placebo

Outcome		Tofacitinib 10 mg BID		Vedolizumab iv 300mg week 0, 2 and 6
		OCTAVE 1	OCTAVE 2	GEMINI 1
% Clinical remission week 6/8 (95% CI)	Central endoscopy	11.1 (0.2;89)	12.0 (7.8;16.1)[#]	NA
	Local endoscopy	13.9 (1.3;52.9)	9.5 (-0.1;39.9)	6.6 (-1.0;41.2)
% Mucosal healing week 6/8 (95% CI)	Central endoscopy	17.9 (2.9;57.5)	15.6 (2.0;51.9)	NA
	Local endoscopy	24.7 (6.5;62.0)	17.2 (2.7;45.8)	9.9 (-3.6;34)
% Serious adverse events week 6/8 (95% CI)		NA*	NA*	-0.8 (-3.6; 8,8)

NA, not available. *Data for subgroup bio-experienced patients not published. See section 5.3, Table 9 for data on the overall population. [#]See table A3d.

Table 8: Maintenance therapy: Absolute difference from placebo for tofacitinib and vedolizumab for selected outcomes in patients with moderate to severe UC with prior bio-experience

Outcome		Tofacitinib 5 mg BID	Vedolizumab 300 mg every 8 weeks
		OCTAVE SUSTAIN	GEMINI 1
% Steroid free remission week 52 (95% CI)	Central endoscopy	NA*	NA
	Local endoscopy	NA*	18.7 (-1.4; 173.4)
% Mucosal healing week 52 (95% CI)	Central endoscopy	17.2 (2.9; 44.3)	NA
	Local endoscopy	24.4 (7.2; 55.5)	34.0 (5.5; 123.2)
% Serious Adverse Events week 52 (95% CI)		NA*	5.4 (-3.3-23.9)
% IBDQ remission week 52 (95% CI)		NA*	NA
IBDQ change from baseline week 52		NA*	14.1 (-2.5, 30.7)

NA, not available. *Data for subgroup bio-experienced patients not published. See Section 5.3, Table 10 for data on the overall population.

5.2.3 Comparative analyses

We were not able to identify data investigating infliximab in bio-experienced patients. Approximately half of the patients included in the OCTAVE program (tofacitinib) and in GEMINI 1 (vedolizumab) are bio-experienced and the following analyses are performed on the subgroup of bio-experienced patients in these studies.

As for clinical question 1, Inverse variance method was used to combine results from 2 or more studies in the meta-analysis. Review Manager v5.3 was used for the calculation. 95% Confidence intervals were calculated in SAS or Review Manager v5.3.

Indirect comparison was performed using Bucher method with input from above meta-analysis. As for the individual studies, ARR was calculated from the RR according to the following equation: ARR= (RR-1)*comparator event rate. Comparator event rate was calculated from the included comparator studies. P-values are calculated using Chi-Square.

A detailed description of the outcomes can be found in Appendix 9.4, Table A4b.

As for the bio-naïve patient population, data presented in the publication for tofacitinib is based on central read endoscopy data. Conversely, data presented in publications for vedolizumab is based on local read endoscopy data. In order to compare the two therapies in the best possible way, two comparisons are therefore presented for clinical remission at week 8, steroid free remission week 52 and mucosal healing week 8 and 52: Central read endoscopy data for tofacitinib 10 mg BID compared to local read endoscopy data for vedolizumab 300 mg and local read data for tofacitinib (data on file) compared to local read data for vedolizumab.

Unfortunately, the effect of tofacitinib on "% Steroid free remission week 52", "% Serious adverse events week 8", "% Serious adverse events week 52" and "IBDQ Change week 52" have not been published for the subgroup of bio-experienced patients. Please refer to Section 5.3 for analyses on these endpoints in the overall tofacitinib treated population.

Clinical remission week 8 (critical)

The absolute difference between tofacitinib 10 mg BID and vedolizumab 300 mg is in favor of tofacitinib with a 22.8% (95% CI: -6.2;286.7) difference for the central read data compared to the local read vedolizumab data and 1.4% (95% CI: -7.8; 52.3) difference for local versus local comparison. The difference is beyond the clinical relevant difference in favor of tofacitinib when comparing central versus local data but with wide CIs and when comparing local to local data the difference is within the border of 10% specified to be a clinical relevant difference. The RR is 3.336 and 1.142 respectively.

Steroid free remission week 52 (critical)

Unfortunately, the effect of tofacitinib on "% Steroid free remission week 52" has not been published for the subgroup of bio-experienced patients. Please refer to section 5.3 for analyses on these endpoints in the overall tofacitinib treated population.

Serious adverse events (critical)

Unfortunately, the effect of tofacitinib on "% Serious adverse events week 8" and "% Serious adverse events week 52" have not been published for the subgroup of bio-experienced patients. Please refer to section 5.3 for analyses on these endpoints in the overall tofacitinib treated population.

Mucosal healing week 8 (important)

The absolute difference between tofacitinib 10 mg BID and vedolizumab 300 mg every 8 weeks for mucosal healing following induction therapy is in favor of tofacitinib and statistically significant at 46.3% (95% CI: 0.6; 159.4, p =0.046) for central read compared to local read endoscopy data. For local read compared to local read endoscopy data, the difference is no longer statistically significant at 26.9% (95% CI: -3.8; 92.8, p

= 0.105). The RR is 2.519 and 1.882 respectively. Thus for both central-local and local-local comparison the estimated absolute difference is in favor of tofacitinib beyond the 10% margin. However only for central versus local comparison is this difference statistically significant and for both comparisons the lower CIs are well below the 10%, suggesting that the current data cannot determine a clinical relevant difference.

Mucosal healing week 52 (important)

The absolute difference between 5 mg BID tofacitinib and vedolizumab 300 mg every 8 weeks is -23.5% (95% CI: -36.9; 26.2, p =0.218) when central read data are compared to local read endoscopy data. When comparing local read endoscopy data for tofacitinib to local read endoscopy data for vedolizumab the difference is -20.3% (95% CI: -35.9; 36.1, p = 0.313). The RR is 0.439 and 0.515 respectively in favor of vedolizumab and the ARR is beyond the clinical relevant margin. However, with the broad CIs and p-values, the current data cannot determine if there is a clinically relevant difference.

IBDQ remission and change (important)

Data for IBDQ remission in bio-experienced patients at week 52 was not available for tofacitinib and vedolizumab, hence a comparison could not be performed.

The effect of tofacitinib on "IBDQ change" has been published for the subgroup of bio-experienced patients. However, the reported values are not correct and there corrected data are yet not published. Please refer to section 5.3 for analyses on these endpoints in the overall tofacitinib treated population.

Summary

In summary, tofacitinib induction (10 mg BID) and maintenance (5 mg BID) therapy has shown statistically significant improvements compared to control in bio-experienced patients for clinical remission and mucosal healing week 8 and week 52.

In general, the indirect comparison between tofacitinib and vedolizumab resulted in estimates of absolute differences with high uncertainty as indicated by broad CIs and accordingly no clinical relevant differences could be determined. For the early outcomes of clinical remission and mucosal healing at week 8, the absolute difference was in favor of tofacitinib and beyond the clinically relevant margin of 10%. However, with broad CIs no conclusion can be made regarding potential differences. Likewise for mucosal healing at week 52, the estimated absolute difference was in favor of vedolizumab, but as for the early outcomes, the estimates where uncertain as indicated by broad CIs and accordingly it is not possible to draw conclusions regarding potential differences with the current data.

5.3 Clinical question 3: What is the added clinical value of tofacitinib for patients with moderate to severe UC (bio-naïve and bio-experienced) compared to infliximab and vedolizumab respectively?

5.3.1 Presentation of relevant studies

6 studies were identified that include investigations of tofacitinib (OCTAVE 1, OCTAVE 2, and OCTAVE Sustain), vedolizumab (GEMINI 1) and infliximab (ACT 1 and ACT 2) at the relevant dosing regimens in moderate to severe UC patients. To address clinical question 1 (Section 5.1), sensitivity analyses were performed including three additional studies with infliximab in bio-naïve patients (UC-SUCCESS, Jiang, and Kobayashi). This was not deemed necessary to address clinical question 3.

All six studies, including differences in design and permitted background medication, have been described in Section 5.1, in Section 5.2 and Appendix, Table A2. In brief, OCTAVE induction 1 and 2 and OCTAVE Sustain are randomized controlled double-blinded, phase 3 trials investigating tofacitinib efficacy and safety as induction and maintenance therapy in moderate to severe UC patients, respectively. A total of 598 patients were included in OCTAVE 1, 541 patients in OCTAVE 2 and 593 patients in OCTAVE Sustain. In OCTAVE 1 and 2 combined and OCTAVE Sustain, 53% and 48% of the patients were bio-experienced (19).

GEMINI 1 covers one induction trial with 2 cohorts (one randomized, controlled double-blind and one open label) and one randomized, controlled, double-blinded maintenance trial investigating vedolizumab efficacy and safety in moderate to severe UC. A total of 374 patients were included in cohort 1, 521 patients in cohort 2 and 373 patients in the maintenance trial. In GEMINI 1 Induction and maintenance, 48% and 35% of the patients were bio-experienced, respectively (8).

The pivotal study program for infliximab consisted of two phase 3, randomized, controlled and double-blinded trials, ACT 1 and ACT 2, each investigating both induction and maintenance therapy. Both ACT 1 and ACT 2 included 364 patients. In ACT 1 and ACT 2, all patients were bio-naïve (11).

5.3.2 Results per study

The outcome analyses for the OCTAVE program, GEMINI 1 and ACT 1 and 2 are described above (see section 5.1.1.)

An overview of the outcomes for UC patients in the individual studies can be seen in Table 9 for induction and Table 10 for maintenance therapy. RR and ARR have been calculated similarly to the calculations for the bio-naïve and bio-experienced populations. Detailed information of outcomes can be found in Appendix 9.3, Table A3.

Table 9. Induction therapy: Absolute difference from control for tofacitinib, vedolizumab and infliximab for selected outcomes in patients with moderate to severe UC.

Outcome		Tofacitinib 10 mg BID		Vedolizumab iv 300mg week 0, 2 and 6	Infliximab 5 mg/kg Week 0, 2, 6	
		OCTAVE 1	OCTAVE 2	GEMINI 1	ACT 1	ACT 2
% Clinical remission week 6/8 (95%CI)	Central endoscopy	10.3 (1.7-26.3)	13.0 (2.6-40.8)	NA	NA	NA
	Local endoscopy	13.3 (3.3-30.1)	15.6 (4.1-41.3)	11.5 (2.7-29.8)	24.0 (9.1;48.0)	28.2 (10.1;66.9)
% Mucosal healing week 6/8/16 (95% CI)	Central endoscopy	15.7 (4.7-32.7)	16.8 (5.1-36.8)	NA	NA	NA
	Local endoscopy	19.5 (7.2-36.8)	21.2 (7.9-42.2)	16.1 (4.8-31.5)	28.1 (12.7;48.6)	29.4 (13.7;50.6)
% Serious adverse events week 6/8/14 (95% CI)		-0.7 (-2.8-4.9)	-3.8 (-6.1-1.1)	-4.5 (-5.9 - -0.3)	NA	NA

NA, not available.

Table 10: Maintenance therapy: Absolute difference from placebo for tofacitinib, vedolizumab and infliximab for selected outcomes in patients with moderate to severe UC.

Outcome		Tofacitinib 5 mg BID	Vedolizumab 300 mg every 8 weeks	Infliximab 5mg/kg every 8 weeks	
		OCTAVE SUSTAIN	GEMINI 1	ACT 1	ACT 2
% Steroid free remission week 52 (Range 16-54) (95% CI)	Central endoscopy	16.8 (3.7-41.7)	NA	NA	NA
	Local endoscopy	18.8 (4.8-43.4)	17.5 (2.2-47.6)	16.9 (2.6-49.0)	15 (0.9-75.9)
% Mucosal healing week 52 (range 30-54) (95% CI)	Central endoscopy	23.2 (10.5-42.8)	NA	NA	NA
	Local endoscopy	31.1 (16.1-53.6)	31.8 (15.1-56.5)	27.3 (11.5-51.4)	16.2 (3.2-34.3)
% Serious Adverse Events week 52 (range 30-54) (95% CI)		-1.5 (-4.3- 4.7)	-7.7 (-11.9- 0.9)	-4.1 (-12-8.3)	-8.8 (-13.8-0.6)
% IBDQ remission week 52		27.8 (18.9-36.7)	NA	NA	NA
IBDQ change week 8* (mean, 95% CI)		19.7 (13.3-26.2) 19.6 (12.7-26.5)	21.1 (11.8-30.4)	20 (11.6-28.4)	14 (5.2-22.8)

NA, not available. *Results are from OCTAVE Induction 1 and 2 (baseline to week 8). For details, see chapter 5.1.3 (IBDQ Remission and change).

5.3.3 Comparative analyses

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

Indirect comparison was performed using Bucher method with input from above meta-analysis. As for the individual studies, ARR was calculated from the RR according to the following equation: ARR= (RR-1)*comparator event rate. Comparator event rate was calculated from the selected comparator studies. P-values are calculated using Chi-Square.

All patients included in the infliximab studies are bio-naïve. Importantly, approximately half of the patients included in tofacitinib and vedolizumab trials are bio-naïve and the other half is bio-experienced.

A detailed description of the outcomes can be found in Appendix 9.4, Table A4c.

As for the bio-naïve and bio-experienced patient populations, data presented in the publication for tofacitinib is based on central read endoscopy data. Conversely, data presented in publications for vedolizumab and infliximab is based on local read endoscopy data. In order to compare the therapies in the best possible way, two comparisons are therefore presented for clinical remission at week 8, steroid free remission week 52 and mucosal healing week 8 and 52: Central read endoscopy data for tofacitinib 10 mg BID compared to local read endoscopy data for vedolizumab and infliximab and local read data for tofacitinib (data on file) compared to local read data for vedolizumab and infliximab.

Clinical remission week 8 (critical)

The absolute difference in effect between tofacitinib 10 mg BID and vedolizumab 300 mg in clinical remission following induction therapy is -1.3% (95% CI: -11.1-25.5) in favor of vedolizumab when central reading (tofacitinib) is compared to local reading (vedolizumab). The RR is 0.925. When more appropriate local-to-local reading is compared, the difference in effect is -2.5% (95% CI: -11.2-19.4) and the RR is 0.852 in favor of vedolizumab.
For tofacitinib 10 mg BID compared to infliximab 5 mg/kg, the difference is -8.0% (95% CI: -26.4-44.4) for central read compared to local read. When a more appropriate comparison between “local read” and “local read” data is applied, the difference is -10.2% (95% CI -26.5-33.0). The RR of 0.780 and 0.718 is in favor of infliximab, but the difference is not statistically significant (p=0.642 and p=0.507, respectively).

The clinically meaningful difference for remission is indicated to be 10%. The estimated absolute difference between tofacitinib and infliximab is just above this (-10.2%) in favour of infliximab, but with a wide confidence interval. Tofacitinib 10 mg and vedolizumab appeared to have the same efficacy (-2.5%). Accordingly the current evidence suggests that there is no difference in clinical remission at week 8 between tofacitinib, vedolizumab and infliximab.

Steroid free remission week 52 (critical)

The absolute difference for steroid free remission at week 52 between tofacitinib 5 mg BID and vedolizumab 300 mg every 8 weeks was 3.9% (95% CI: -17.4 – 58.0; central versus local) and 1.3% (95%CI: -17.8-47.1; local versus local) in favor of tofacitinib. The estimate is below the 10% margin indicated to be clinically relevant and the RR (1.042, p=0.927) underscores that there do not seem to be a difference in efficacy comparing tofacitinib and vedolizumab.

In comparison to infliximab, the difference is -5.5% (95% CI: -15.8- 21.5) (central versus local reading) and -6.7% (95% CI: -16 - 16.2) (local versus local reading) in favor of infliximab (RR: 0.755 and 0.699). The difference between tofacitinib and infliximab is within the specified margin of 10% and not statistically significant.

The clinically meaningful difference for steroid-free remission week 52 is indicated to be 10%. The estimated absolute difference comparing tofacitinib with vedolizumab and infliximab is below this margin. Accordingly the current evidence suggests that there is no difference in steroid-free remission at week 52 between tofacitinib, vedolizumab and infliximab.

Serious adverse events (critical)

SAEs were reported infrequently in all studies. All therapies showed (non-significant) reduced occurrences of SAEs compared to the placebo treated groups in the individual studies (see Tables 9 and 10). Likewise there were no statistical differences between tofacitinib, vedolizumab and infliximab.

At week 52 (range 30-54) the absolute difference in SAE between tofacitinib and vedolizumab was 4% (95% CI: -4.0-27.6) in favor of vedolizumab. Between tofacitinib and infliximab, the absolute difference in SAE was 1.1% (95% CI: -9.1-26.0) in favor of infliximab. Thus, the estimated absolute difference between tofacitinib and vedolizumab/infliximab is below the 5% specified in the protocol to be clinically relevant and the RRs were not statistically significant different.

The absolute difference in SAE for tofacitinib 10 mg BID induction therapy at 8 weeks compared to vedolizumab 300 mg at week 6 was 1.9% (95% CI: -1.0-11.8) in favor of vedolizumab, with RR 1.872 (p=0.311). SAE events were not reported specifically for the induction period for infliximab in ACT 1 and 2.

The clinically meaningful difference for serious adverse events was 5%. The current evidence does not suggest that there is any difference in frequency of serious adverse event between tofacitinib, vedolizumab and infliximab.

Mucosal healing week 8 (important)

The absolute difference in mucosal healing between tofacitinib and vedolizumab was 13.2% (95% CI: -6.9-45.4) (central versus local) or 9.5% (95% CI: -7.8-36.0) (local versus local) in favor of tofacitinib (RR: 1.323, p=0.238 and 1.233, p=0.331). The absolute difference between tofacitinib and infliximab is also in favor of tofacitinib at 9.4% (95% CI: -13.7-43.8; central to local) and 4.5% (95% CI: -14.6- 31.6). The RR is 1.153 and 1.074, respectively (both differences are statistically non-significant).

The suggested clinically relevant difference is 10 % according to the protocol and the absolute difference is below this margin in both comparisons. Thus, current data suggest that tofacitinib is comparable to infliximab and vedolizumab in inducing mucosal healing at week 8.

Mucosal healing week 52 (important)

The absolute difference between tofacitinib and vedolizumab for mucosal healing at week 52 is estimated to be 4.5% (95% CI: -20.4-49.4; central versus local) and 12.9% (95% CI: -14.9-61.8; local versus local

reading) (RR of 1.088, p=0.779 and 1.250, p=0.437, respectively) in favor of tofacitinib. In comparison to infliximab, the absolute difference between tofacitinib and infliximab is 21.8% (95% CI: -10.4-83.0; central versus local) and 31.9% (95% CI: -4.2-99.1; local versus local) in favor of tofacitinib (RR: 1.474, p=0.237 and 1.694, p =0.097). However, although bordering statistical significance (p= 0.097) and the estimate being well above the 10% relevant difference, the CI are again broad and the difference between tofacitinib and infliximab could potentially be less than the specified clinical relevant difference of 10%.

The clinically relevant difference was estimated to be 10%. In comparison to both vedolizumab and infliximab, the difference was above this limit and in favor of tofacitinib. However, the differences were not statistically significant and accordingly, the current data suggest that tofacitinib is comparable to infliximab and vedolizumab in inducing mucosal healing at week 52.

IBDQ remission and change (important)

IBDQ remission data with confidence intervals could only be identified for tofacitinib and accordingly a proper comparison could not be performed. In OCTAVE Sustain, significantly and clinically relevant more patients achieved IBDQ remission compared to the control arm with an absolute difference between tofacitinib and placebo of 27.8% (95% CI: 18.9-36.7). IBDQ data from GEMINI 1 is published, but IBDQ Remission at week 52 is only presented as a figure without indication of variation (10). This figure indicates an absolute difference of approximately 21% with vedolizumab versus placebo. *The difference between tofacitinib and vedolizumab in rate of IBDQ Remission appears to be below the 10% indicated and therefore to be clinically not relevant (but without a proper statistical analysis of the difference).*

Data for IBDQ change from baseline in OCTAVE Induction to week 52 of OCTAVE Sustain have not been published and is not available. The absolute difference in IBDQ change between tofacitinib and placebo was 19.7% and 19.6% in OCTAVE Induction 1 and 2, respectively. All patients included in OCTAVE Sustain were responders to induction treatment, and the change in IBDQ during OCTAVE Sustain does therefore not properly reflect the response to tofacitinib. Panés *et al.* (7) showed that patients treated with tofacitinib 5 mg only have a minor further improvement in IBDQ during OCTAVE Sustain (mean change +3.7 vs -27.5 with placebo). Therefore, the data on IBDQ change included in this analysis is from OCTAVE Induction 1 and 2 (change from baseline to 8 weeks) (Table A3i).

Meta-analysis showed that all therapies increased IBDQ score above 16 points (indicated to be a clinically relevant score) when compared to placebo treatment. Tofacitinib increased IBDQ score by a mean of 19.7 (95% CI: 15.0-24.4), infliximab by a mean of 17.1 (95% CI: 11.1, 23.2) and vedolizumab by 21.1 (95% CI: 11.8-30.4). The difference between tofacitinib and infliximab was 2.5 (95% CI: -5.2-10.2, p = 0.52) and -1.5 (95% CI: -11.9-9.0, p=0.79) between tofacitinib and vedolizumab suggesting comparable impact on IBDQ change.

Comparison between studies did not show differences above 16 point in IBDQ Change. Accordingly, the current data suggest that tofacitinib is comparable to infliximab and vedolizumab in inducing change in IBDQ.

Summary

Tofacitinib for the treatment of moderate to severe UC has shown improvements compared to placebo in efficacy outcomes that include clinical remission, steroid free remission, mucosal healing, IBDQ remission and IBDQ change from baseline without increasing the risk of SAEs.

Comparing tofacitinib and vedolizumab, differences in efficacy were within the limits considered to be clinically relevant and statistically non-significant for clinical remission week 8, steroid free remission week 52, mucosal healing week 8 and IBDQ change. The same was found when comparing infliximab and tofacitinib, apart from a statistically non-significant difference in clinical remission week 8 (10.2%). As for mucosal healing week 52, there was a potential clinically relevant difference in favor of tofacitinib compared to both vedolizumab (12.9%) and infliximab (31.9%), but neither of these differences was statistically significant.

Safety as measured by SAEs for tofacitinib, vedolizumab and infliximab treated patients in the individual studies were all comparable to the placebo arms during induction and maintenance treatment up to 52 weeks. Between the therapies there were no significant differences between tofacitinib versus infliximab and tofacitinib versus vedolizumab with the estimates, however, being uncertain as reflected by wide CIs.

Of note, there are some significant differences between the studies which could potentially have an impact on the comparability of the outcomes. Most importantly, patients in the infliximab studies were all bio-naïve. Moreover, there was also a difference in fraction of bio-experienced patients in the maintenance studies of tofacitinib (48%) versus vedolizumab (35%). Moreover, the difference in allowed background medication (immunosuppressants allowed in most infliximab studies, but not in tofacitinib studies), time point of measurements and design of the studies (e.g. responder selection versus non-responder selection for maintenance therapy) could also have an impact.

When comparing the clinical value of tofacitinib for patients with moderate to severe UC without taking into account prior exposure to biological therapy, the current data suggest that tofacitinib is comparable to infliximab and vedolizumab.

6 Narrative description of the safety profile based on EPARs

In general the adverse event (AE) profile of tofacitinib in moderate to severe UC is comparable to that reported for tofacitinib in rheumatoid arthritis (RA), where tofacitinib has been investigated in one of the largest clinical trial programs for RA with a reported safety follow-up up to 9 years (19-21). Additionally, the safety profile for tofacitinib was consistent with that of other biologic agents approved for treatment of UC with the exception of Herpes Zoster (HZ) and infusion reactions (19, 22, 23).

A total of 1240 subjects with moderate-to-severe UC received at least 1 dose of placebo, tofacitinib 5 mg BID or tofacitinib 10 mg BID. Among these subjects, 1157 subjects received at least 1 dose of tofacitinib 5 mg BID or 10 mg BID, with 762 subjects exposed to tofacitinib for at least 6 months, and 653 subjects exposed for at least 12 months. In total, the UC program encompasses 1613 patient-years (PY) of exposure to tofacitinib, with up to 4.4 years of tofacitinib treatment.

The tofacitinib safety profile has been described in 3 cohorts: the first cohort include data from inductions studies (Phase 2 and Octave Induction 1+2 studies), the second cohort describes the maintenance safety profile in the OCTAVE Sustain study and the third cohort describes the safety profile in the entire study program including the phase 2, phase 3 and long term, open label follow-up studies. The latter includes both patients receiving 5 mg BID and 10 mg BID at any time during the induction, maintenance or open label period.

In both the induction and maintenance studies, the proportions of subjects with AEs, SAEs, and severe AEs were similar between the placebo group and the tofacitinib groups.

6.1 Common AEs

The most common reported adverse events for tofacitinib during induction were headache (7.8%) and nasopharyngitis (6.0%) compared to 6.7% and 5.0%, respectively, in placebo. In the maintenance period the most frequently reported AEs among tofacitinib-treated subjects were colitis ulcerative, nasopharyngitis and arthralgia (see Table 9). In comparison the most commonly reported AEs for vedolizumab in GEMINI 1 (induction and maintenance) were similarly colitis ulcerative, headache, nasopharyngitis and arthralgia (see Table 9). For infliximab the most common adverse events reported in ACT 1 and ACT 2 were headache; upper respiratory infection (16.5% and 13.2 versus 23.1% and 13.3), colitis ulcerative, arthralgia and abdominal pain (Table 9) (11, 19, 22, 23).

Table 9. Common adverse events for tofacitinib, vedolizumab and infliximab as described in the EPAR

	OCTAVE maintenance (52 weeks)		GEMINI 1 (52 weeks)		ACT 1/ACT 2 (54 weeks/30 weeks)	
Preferred term	Tofacitinib 5 mg BID	placebo	Vedolizumab Every 8 weeks	placebo	Infliximab 5 mg/kg	placebo
Colitis Ulcerative (%)	18.8	35.86	12	23	19/9.1	33.1/16.3
Headache (%)	8.59	6.06	13	12	18.2/15.7	22.3/14.6
Nasopharyngitis (%)	9.6	5.56	16	12	9.9/5.8	8.3/2.4
Arthralgia (%)	8.59	9.6	9	12	17.4/13.2	14.9/4.9

SAEs have been described elsewhere in this report. Briefly, in the placebo-controlled studies of tofacitinib (Cohort 1 and Cohort 2), the proportion of subject with SAEs were similar among the placebo and the tofacitinib groups. The most frequently reported SAE (preferred term) for tofacitinib was colitis ulcerative which was reported for 1.8% of patients receiving 5 mg BID tofacitinib maintenance treatment and for 4.7% in the overall tofacitinib cohort 3 (all doses). There was no clustering into other preferred terms for serious adverse events (19). Similarly to tofacitinib, the most frequently reported SAE for infliximab was colitis ulcerative and gastrointestinal disorders for vedolizumab (22, 23).

6.2 AEs of special interest

In addition to the overall tofacitinib safety profile, AEs of special interest included: Infections (serious infections, opportunistic infections (OIs), herpes zoster and tuberculosis), malignancies (excluding NMSC), non-melanoma skin cancer (NMSC), major adverse cardiovascular event (MACE), Hepatic injury cases, gastrointestinal perforation, Interstitial lung disease, selected hematologic events (anaemia, neutropenia, lymphopenia), AEs of renal impairment and AEs of CK elevation and rhabdomyolysis.

Serious infections

The rate of serious infections in cohort 1 (induction) was not significantly different from placebo with 0.9% in tofacitinib treated patients compared to 0% in placebo treated patients. For the 52 weeks follow up in maintenance, the rate was 1% in both placebo and tofacitinib 5 mg BID treated patients with a calculated IR of 1.35 for tofacitinib and 1.94 for placebo and comparable rates were also observed in cohort 3 suggesting that the risk of serious infection does not increase with longer exposure. Serious infections for infliximab is reported in similar ranges (1% for both placebo and infliximab 5 mg/kg) and for vedolizumab serious infections is reported for 2% in vedolizumab and 3% in placebo treated patients in the 52 weeks follow-up (8, 23).

TB was reported infrequently in the study programs with one suspected but not confirmed report of TB for a tofacitinib 10 mg BID treated patient, 1 confirmed TB for infliximab but at the high dose (10 mg/kg) and one confirmed TB for vedolizumab in long term (36 months) follow-up.

Opportunistic infections (OI)

3 (0.3%) tofacitinib patients in the induction phase experienced an OI compared to none in the placebo group. In the maintenance phase 2 patients in the tofacitinib 5 mg BID experienced an OI compared to 1 patient in the placebo arm (21). The IR was 1.36/100 patient year (PY) for tofacitinib 5 mg BID and 0.97/100 PY for placebo treated patients. All but one event was HZ. As for serious infections, the IR for OIs is comparable in cohort 3 suggesting that the risk does not increase with longer exposure time. The rate of OIs are not provided for vedolizumab but it is reported that the majority of Clostridium difficile, candida, and herpes infections, although not severe in intensity, are seen in vedolizumab treated groups with similar frequency in every 8 week and every 4 week treatment dose regimens (22). For Infliximab, 5 cases of herpes zoster were reported in the infliximab 5 mg/kg group and 1 herpes zoster was reported in the placebo group (23).

Herpes Zoster

As mentioned, the safety profile of tofacitinib has been evaluated overall to be comparable to the approved biological therapies for treatment of moderate to severe UC patients except for the HZ. During induction, 0.6% of tofacitinib 10 mg BID treated patients experienced a HZ event in comparison to 0.4% (1 patient) in the placebo group. During maintenance, 1.5% (3 patients) in the tofacitinib 5 mg BID group compared to 0.5% (1 patient) experienced a HZ event. This corresponds to IRs of 2.05 (95% CI 0.42;6.0) and 0.97 (95% CI 0.02;5.42) respectively and a non-significant IR difference of 1.08 (95% CI -1.93; 4.09) between tofacitinib 5 mg BID and placebo. However in patients receiving tofacitinib 10 mg BID during maintenance, the incidence of HZ is increased significantly (IR difference from placebo: 5.67 (95%CI 1.13;10.21)) over placebo suggesting a dose- dependent increased risk of HZ. Accordingly, the risk of HZ with tofacitinib 10 mg BID may be higher than that associated with 5 mg BID. The IR in the long term for patients treated with tofacitinib (all doses) (cohort 3) is 4.07. Despite dose-dependent increase in the risk of HZ, the majority (95.7%) of HZ events were limited to cutaneous involvement and resulted in discontinuation in a minority of cases (5 cases (7.7%)). In Cohort 3 (tofacitinib all doses), a total of 69 events of HZ occurred in 65 subjects. Among these events, 3 were severe AEs, and 4 were SAEs. Post-herpetic neuralgia was reported by 3 (4.6%) subjects who developed HZ. Visceral HZ was reported in 1 subject (a case of HZ meningitis/encephalitis), which was reported as resolved without neurological sequelae after anti-viral treatment. There were higher incidence rates for subjects aged 65 years or older, patients with Diabetes mellitus at baseline, those with TNFi experience and Asian ethnicity. As mentioned above, the reported occurrence of HZ for Infliximab 5 mg/kg was 5 cases during the induction and maintenance period and for vedolizumab the number is not provided in the EPAR. In a recent integrated safety analysis for the vedolizumab clinical program by Colombel and coworkers, the overall IR (all vedolizumab dosing schemes in phase 2, 3 and OL) is reported to be 0.5/100 PY (95% CI 0.2;0.8) for vedolizumab treated patients compared to 0 in the placebo group (24).

Malignancies

No malignancies (excluding NMSC) were reported in the induction and maintenance phase for tofacitinib. In the open label phase of the OCTAVE program and with no pattern in types of malignancies, 12 cases were reported during 4.4 years follow-up- all in the group of subjects that predominantly received 10 mg BID. 8 patients had previous TNFi experience and all were previously treated with thiopurines which has been shown to increase lymphoma risk (25). The overall IR for malignancies was 0.48 (tofacitinib all doses), 0.06 for colorectal cancer and 0.06 for lymphoma/lymphoproliferative disease which is similar to those reported for the tofacitinib RA program (all exposure) and for biologic agents in UC patients in external

observational data. For Infliximab, 2 malignancies were reported in the 54 weeks follow-up of the pivotal ACT studies and in the vedolizumab pivotal trial, 3 subjects reported colon cancer (22, 23).

2 NMSC events were reported in the induction phase for tofacitinib 10 mg BID and none was reported for tofacitinib 5 mg BID in the maintenance phase. In the long term- follow- up (cohort 3), 11 subjects were reported to have NMSC and of these 10 subjects were in the predominantly 10 mg tofacitinib BID group. Base on the NMSC data, the EPAR concludes that The IRs of NMSC observed for tofacitinib 5 mg BID and 10 mg BID in Cohort 2 are similar to the IRs reported in the RA study programs and that the IR of NMSC for tofacitinib 5 mg BID is similar to those of biologic agents in UC patients in published randomized controlled trial.

Gastrointestinal (GI) perforations.

During the induction period, GI perforation occurred in 1 (0.1%) subject in the tofacitinib 10 mg BID group compared with 1 (0.4%) subject in the placebo group. In the maintenance phase, GI perforation was reported in 1 subject in the placebo group. Two additional GI perforations were reported in the long term follow-up- both in subjects at high risk of GI perforation. Examination of the clinical details by a gastrointestinal perforation review committee of the reported cases did not suggest a higher risk of GI perforation with tofacitinib treatment in subjects with UC and the rates are comparable to those reported in observational external data for biological therapies (19).

MACE

There were no reported MACE events during induction. In the maintenance phase, 1 subject in the tofacitinib 5 mg BID group experienced a MACE event (IR 0.65/100PY) compared to no subjects in the placebo group. Overall, the IR in cohort 3 (including LTE) was 0.24/100 PY with 4 subjects experiencing a MACE event. Based on clinical history 3 of the 4 patients had pre-existing cardiovascular risk. With this data the EPAR concludes that the IR of MACE in the tofacitinib all group in Cohort 3 is similar to those reported for the RA program (all exposure) and for biologic agents in UC patients in external observational data. For vedolizumab, the reported occurrence of cardiovascular event was higher in the vedolizumab treated group (4%) than the placebo group (1 %). However, the type of cardiovascular events is not specified (22). Likewise for infliximab the EPAR reports on a higher occurrence of cardiovascular disorders (5.4% versus 1.6%) but do not mention MACE events.

Hepatotoxicity, interstitial lung disease and rhabdomyolysis

There were no reports on Hy's law cases or DILI cases that were adjudicated to be probable, highly likely or definite. There were no AEs suggestive of hepatic failure, interstitial lung disease or rhabdomyolysis.

Laboratory changes

Changes in hematological values were comparable to that previously observed in the RA program

Tofacitinib treatment did not appear to be associated with an increased risk of decreased haemoglobin compared with placebo. Small decreases in absolute neutrophil count (ANC), generally similar in magnitude to that observed in the placebo group, were observed in tofacitinib-treated subjects and post baseline confirmed ANC <1.5 ×109/L occurred infrequently. Mean decreases in absolute lymphocyte (ALC) count in tofacitinib-treated subjects were larger than that in the placebo group and the proportion of subjects with post baseline confirmed ALC <1.0 ×109/L was 19.3%. 0.9% of subjects met the criterion of discontinuation related to decreased ALC (2 consecutive ALC <0.5 × 109/L) (19). In comparison, the reported level of ALC<0.5×109/L for vedolizumab in the UC induction/maintenance safety population was 3% in the placebo

group and 5% in the combined vedolizumab group (22). No clinical meaningful differences were observed for infliximab treated patients in ACT 1 and 2 (23).

In the RA trial program tofacitinib was found to change the lipid profile and in line with this finding tofacitinib was associated with increases in low-density lipoprotein cholesterol (LDL-c), total-c, high-density lipoprotein cholesterol (HDL-c), and triglyceride levels in a dose dependent manner in the UC clinical program. However, tofacitinib was not associated with clinically relevant changes in the ratios of LDL-c/HDL-c or total-c/HDL-c. As indicated in the section regarding MACE, MACE events were reported infrequently (4 cases) of which most had pre-existing cardiovascular risk. In line with this finding, no increased risk of cardiovascular events has been reported in RA patients treated with tofacitinib 5 mg BID with longer term follow-up (26). Of interest, a study of 111 RA patients treated with tofacitinib showed that tofacitinib induced elevation in lipid level was reduced by treatment with atorvastatin (27). There is no mention of lipid increases for either vedolizumab or infliximab in the respective EPARs.

Treatment with tofacitinib resulted in a dose-dependent increase in mean creatine kinase (CK) levels. The increase in CK began within the first 2 weeks of treatment and continued up to week 8, with little change after week 8. There were no reports of rhabdomyolysis in tofacitinib-treated subjects.

Additional AEs of interest reported for infliximab and vedolizumab

For the comparators, two adverse events- progressive multifocal leukoencephalopathy (PML) (vedolizumab) and infusion-related events (vedolizumab and infliximab)- of special interest is reported which is not reported for tofacitinib. For vedolizumab there were no reports of PML. Infusion related events were reported in 5% for vedolizumab compared to <1% in the placebo treated group during induction and maintenance (22). The majority of reported reactions were mild or moderate in intensity and few resulted in discontinuation of study treatment. For infliximab infusion reactions were reported in 10% of patients treated with 5 mg/kg. This rate was comparable to placebo and none were serious.

Summary

In summary, the safety profile of tofacitinib is comparable to the safety profile for infliximab and vedolizumab with a few exceptions. HZ is reported in a dose-dependent manner at higher rates in tofacitinib treated patients. Accordingly the rate is not significantly increased in patients receiving tofacitinib 5 mg BID maintenance therapy for up to 52 weeks but higher doses of 10 mg BID do significantly increase the risk of Herpes Zoster and overall incidence rates (all doses) is 4.07 on long-term follow up in a global population, which is higher compared to available data for biologics. The majority of HZ cases were mild to moderate and rarely required discontinuation of study drug. Also lipid increase is reported specifically for tofacitinib and lipid monitoring at week 8 after initiation of treatment is recommended. Infusion related events were reported only for infliximab and vedolizumab.

7 Other considerations

In this application, tofacitinib efficacy and safety data for the treatment of moderate to severe UC has been described and discussed for different outcomes in relation to 2 comparators, vedolizumab and infliximab in bio-naïve patients and vedolizumab 300 mg in bio-experienced patients.

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

Tofacitinib is a therapy with a new mode of action and may enable treatment of patients who would not respond to or tolerate current available treatments. It is noteworthy that in this respect, a recent study from a Danish hospital setting estimate loss of response to TNFi therapy (infliximab or adalimumab) and show that in total 12% of screened patients are primary non-responders and 44% of 210 patients experienced loss of response (28). Similarly a recent meta-analysis showed that loss of response to vedolizumab is estimated to be 39.8/100 PY of which only approximately half obtain a response again through dose intensification (29).

Additionally, the pharmacokinetics for tofacitinib differ from the comparators, with for example a short half-life which could potentially be of value for some patients.

Finally, as discussed in the early application, tofacitinib is an oral drug- a route of administration that may be a preference to some patients such as those that are not interested in going to hospital for infusions or perform sc injections (30).

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9 Appendices

9.1 Literature search

Table A1 Inclusion and exclusion criteria

Inclusion criteria	Population: bio-naïve or bio-experienced patients with moderate to severe UC Intervention(s): tofacitinib 10 mg BID for 8 weeks induction then 5 mg BID for maintenance Comparator(s): Infliximab iv 5 mg/kg week 0, 2, 6 and thereafter every 8 weeks or Vedolizumab iv 300 mg week 0,2, 6 and thereafter every 8 weeks Outcomes: Clinical remission week 8, steroid free remission week 52, SAEs, mucosal healing week 8 and 52, IBDQ change and remission in bio-naïve and bio-experienced patients Settings (if applicable): NA Study design: randomised controlled trials Language restrictions: English/Danish Other search limits or restrictions applied: focus on peer-reviewed fully published papers
Exclusion criteria	Population: others than those described in inclusion criteria Intervention(s): other than those described in inclusion criteria Comparator(s): other than those described in inclusion criteria Outcomes: outcomes other than those described in inclusion Settings (if applicable): NA Study design: other study designs than randomised controlled trials and phase 1 and 2a studies Language restrictions: Other search limits or restrictions applied: NA

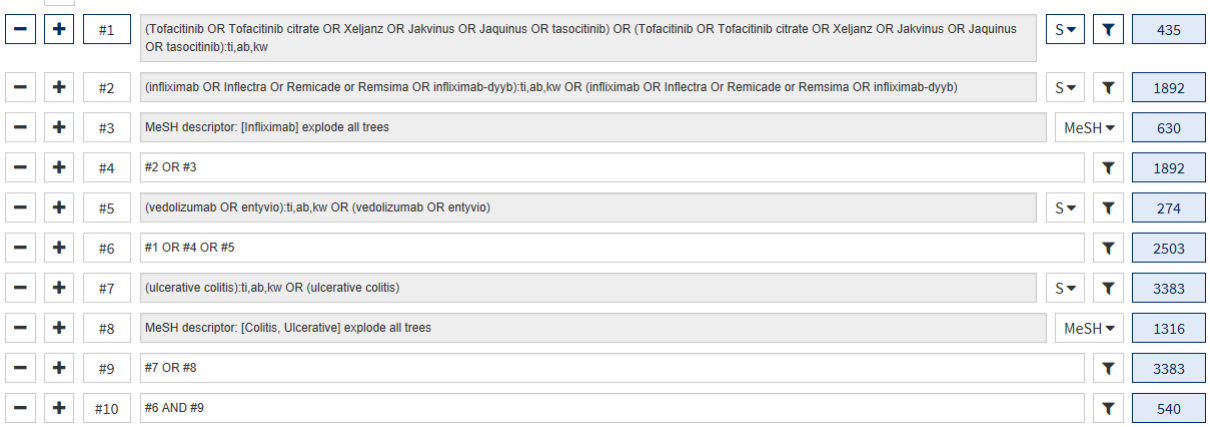
Literature search string for clinical question 1 og 2: What is the clinical added value of tofacitinib for bio-naïve (question 1) and bio-experienced (question 2) patients with moderate to severe UC compared to Infliximab and Vedolizumab respectively?

Pubmed search November 2nd 2018:

Search string:

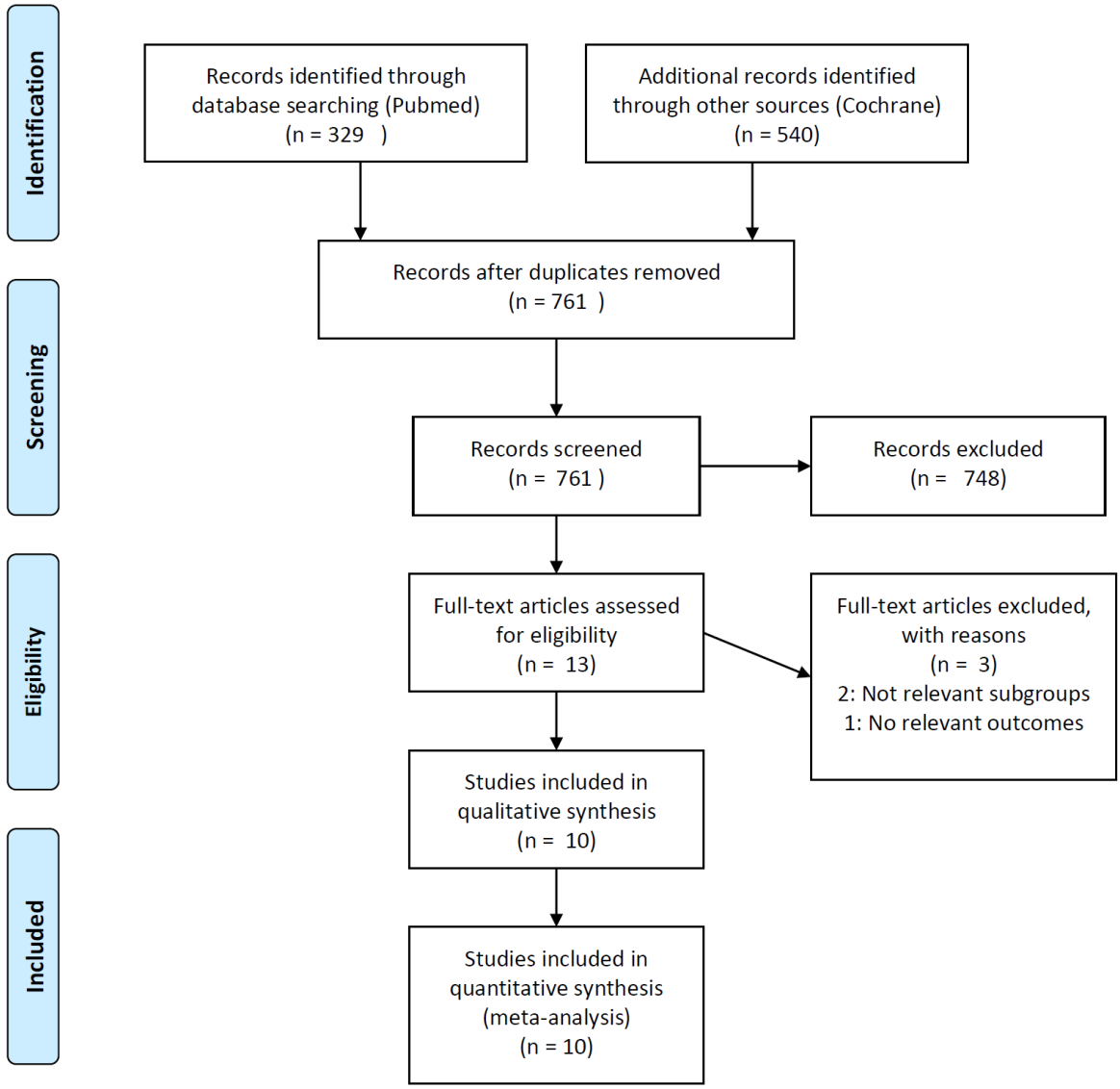
(((((((((Tofacitinib OR Tofacitinib citrate OR Xeljanz OR Jakvinus OR Jaquinus OR tasocitinib)) OR (Tofacitinib OR Tofacitinib citrate OR Xeljanz OR Jakvinus OR Jaquinus OR tasocitinib[MeSH Terms])) OR (Tofacitinib[Supplementary Concept] OR Tofacitinib citrate[Supplementary Concept] OR Xeljanz[Supplementary Concept] OR Jakvinus[Supplementary Concept] OR Jaquinus[Supplementary Concept] OR tasocitinib[Supplementary Concept]))) OR ((((infliximab OR Inflectra Or Remicade or Remsima OR infliximab-dyyb)) OR (infliximab OR Inflectra Or Remicade or Remsima OR infliximab-dyyb[MeSH Terms])) OR (infliximab[Supplementary Concept] OR Inflectra[Supplementary Concept] OR Remicade[Supplementary Concept] OR Remsima[Supplementary Concept] OR infliximab-dyyb[Supplementary Concept]))) OR ((((vedolizumab OR entyvio)) OR (vedolizumab OR entyvio[MeSH Terms])) OR (vedolizumab[Supplementary Concept] OR entyvio[Supplementary Concept])))) AND ((((ulcerative colitis) OR colitis, ulcerative[MeSH Terms]) OR ulcerative colitis[MeSH Terms]) OR ulcerative colitis[Supplementary Concept])) AND ((((randomized controlled trial[pt] OR randomised controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti] NOT (animals[mh] NOT humans [mh])))))

Cochrane search performed November 13th 2018



#1	(Tofacitinib OR Tofacitinib citrate OR Xeljanz OR Jakvinus OR Jaquinus OR tasocitinib) OR (Tofacitinib OR Tofacitinib citrate OR Xeljanz OR Jakvinus OR Jaquinus OR tasocitinib):ti,ab,kw	S	435
#2	(infliximab OR Inflectra Or Remicade or Remsima OR infliximab-dyyb):ti,ab,kw OR (infliximab OR Inflectra Or Remicade or Remsima OR infliximab-dyyb)	S	1892
#3	MeSH descriptor: [Infliximab] explode all trees	MeSH	630
#4	#2 OR #3		1892
#5	(vedolizumab OR entyvio):ti,ab,kw OR (vedolizumab OR entyvio)	S	274
#6	#1 OR #4 OR #5		2503
#7	(ulcerative colitis):ti,ab,kw OR (ulcerative colitis)	S	3383
#8	MeSH descriptor: [Colitis, Ulcerative] explode all trees	MeSH	1316
#9	#7 OR #8		3383
#10	#6 AND #9		540

PRISMA 2009 Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

List of excluded papers after full review

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2. Tofacitinib, an oral Janus kinase inhibitor, in active ulcerative colitis. Sandborn WJ, Ghosh S, Panes J, Vranic I, Su C, Rousell S, Niezychowski W; Study A3921063 Investigators. N Engl J Med. 2012 Aug 16;367(7):616-24. doi: 10.1056/NEJMoa1112168. Not relevant subgroups and outcomes
3. Clinical trial: benefits and risks of immunomodulators and maintenance infliximab for IBD-subgroup analyses across four randomized trials. Lichtenstein GR, Diamond RH, Wagner CL, Fasanmade AA, Olson AD, Marano CW, Johanns J, Lang Y, Sandborn WJ. Aliment Pharmacol Ther. 2009 Aug;30(3):210-26. doi: 10.1111/j.1365-2036.2009.04027.x. Epub 2009 Apr 21. Not relevant Not relevant outcome

Updated literature search (08 Feb 2019)

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2. Advances in Therapeutic Drug Monitoring for Small-Molecule and Biologic Therapies in Inflammatory Bowel Disease. Ma C, Battat R, Jairath V, Vande Casteele N. Curr Treat Options Gastroenterol. 2019 Jan 25. doi: 10.1007/s11938-019-00222-9. [Epub ahead of print] Review.
3. Systematic review and network meta-analysis of treatment for moderate-to-severe ulcerative colitis. Trigo-Vicente C, Gimeno-Ballester V, García-López S, López-Del Val A. Int J Clin Pharm. 2018 Dec;40(6):1411-1419. doi: 10.1007/s11096-018-0743-4. Epub 2018 Nov 26.
4. Safety of Tofacitinib for Treatment of Ulcerative Colitis, Based on 4.4 Years of Data From Global Clinical Trials. Sandborn WJ, Panés J, D'Haens GR, Sands BE, Su C, Moscariello M, Jones T, Pedersen R, Friedman GS, Lawendy N, Chan G. Clin Gastroenterol Hepatol. 2018 Nov 23. pii: S1542-3565(18)31278-3. doi: 10.1016/j.cgh.2018.11.035. [Epub ahead of print]
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6. Systematic review: efficacy and safety of switching patients between reference and biosimilar infliximab. Feagan BG, Lam G, Ma C, Lichtenstein GR. Aliment Pharmacol Ther. 2019 Jan;49(1):31-40. doi: 10.1111/apt.14997. Epub 2018 Nov 8. Review.
7. Etrolizumab versus infliximab in the treatment of induction phase of ulcerative colitis: A systematic review and indirect comparison. Motaghi E, Ghasemi-Pirbaluti M, Zabihi M.Pharmacol Res. 2019 Jan;139:120-125. doi: 10.1016/j.phrs.2018.11.003. Epub 2018 Nov 3. Review.
8. Systematic review with network meta-analysis: the impact of medical interventions for moderate-to-severe ulcerative colitis on health-related quality of life. Paschos P, Katsoula A, Salanti G, Giouleme O, Athanasiadou E, Tsapas A. Aliment Pharmacol Ther. 2018 Dec;48(11-12):1174-1185. doi: 10.1111/apt.15005. Epub 2018 Oct 30. Review.
9. Deep Remission With Vedolizumab in Patients With Moderately to Severely Active Ulcerative Colitis: A GEMINI 1 post hoc Analysis. Sandborn WJ, Colombel JF, Panaccione R, Dulai PS, Rosario M, Cao C, Barocas M, Lasch K. J Crohns Colitis. 2019 Feb 1;13(2):172-181. doi: 10.1093/ecco-jcc/jjy149.
10. Incidence of Arthritis/Arthralgia in Inflammatory Bowel Disease with Long-term Vedolizumab Treatment: Post Hoc Analyses of the GEMINI Trials. Feagan BG, Sandborn WJ, Colombel JF, Byrne SO, Khalid JM, Kempf C, Geransar P, Bhayat F, Rubin DT. J Crohns Colitis. 2019 Jan 1;13(1):50-57. doi: 10.1093/ecco-jcc/jjy125.
11. Tofacitinib Induction Therapy Reduces Symptoms Within 3 Days for Patients With Ulcerative Colitis. Hanauer S, Panaccione R, Danese S, Cheifetz A, Reinisch W, Higgins PDR, Woodworth DA, Zhang H, Friedman GS, Lawendy N, Quirk D, Nduaka CI, Su C. Clin Gastroenterol Hepatol. 2019 Jan;17(1):139-147. doi: 10.1016/j.cgh.2018.07.009. Epub 2018 Sep 10.
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Borren NZ, Avalos D, Luther J, Colizzo F, Garber J, Khalili H, Melia J, Bohm M, Ananthakrishnan AN. Clin Gastroenterol Hepatol. 2019 Feb;17(3):502-509.e1. doi: 10.1016/j.cgh.2018.06.031. Epub 2018 Jun 23.

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9.2 Main characteristics of included studies

Study characteristics

Table A2. Main study characteristics

Trial name	*OCTAVE induction 1*
NCT number	*NCT01465763*
Objective	*Evaluation of the efficacy and safety of tofacitinib versus placebo for induction treatment of TNFi naive and experienced patients with moderate to severe UC*
Publications – title, author, journal, year	• *Tofacitinib as induction and maintenance therapy for Ulcerative colitis, Sandborn WJ.et al., NEJM, 2017* • *Tofacitinib in patients with Ulcerative Colitis: Health-related quality of life in phase 3 randomised controlled induction and maintenance studies, Pánes J.et al., 2017*
Study type and design	*Completed multicenter, double-blinded, placebo-controlled phase 3 study. Eligible patients were randomly assigned, in a 4:1 ratio, to receive induction therapy with oral tofacitinib at a dose of 10 mg twice daily or placebo for 8 weeks. Randomization was performed centrally with the use of a telerandomization system and was stratified according to previous treatment with TNF antagonists, glucocorticoid use at baseline, and geographic region. Participant, Care Provider, Investigator, Outcomes Assessor were all blinded.*
Follow-up time	*8 weeks*

Population (inclusion and exclusion criteria)	Inclusion Criteria:
	• Subject must be at least 18 years of age.
	• Males and females with a documented diagnosis of UC at least 4 months prior to entry into the study.
	• Subjects with moderately to severely active UC based on Mayo score criteria.
	• Subjects must have failed or be intolerant of at least one of the following treatments for UC:
	  ○ Corticosteroids (oral or intravenous).
	  ○ Azathioprine or 6 mercaptopurine (6 MP).
	  ○ Anti TNF-alpha therapy.
	Exclusion Criteria:
	• Presence of indeterminate colitis, microscopic colitis, ischemic colitis, infectious colitis, or clinical findings suggestive of Crohn's disease.
	• Subjects with disease limited to distal 15 cm.
	• Subjects without previous treatment for UC (ie, treatment naïve).
	• Subjects displaying clinical signs of fulminant colitis or toxic megacolon.

Intervention	*Placebo (with optional background oral aminosalicylates and oral glucocorticoids at max dose of 25 mg/day prednisone or an equivalent): n=122* *Tofacitinib 10 mg BID ((with optional background oral aminosalicylates and oral glucocorticoids at max dose of 25 mg/day prednisone or an equivalent): n=476*
Baseline characteristics	*- Mean (± SD) age: 41.3(14.1)-41.8(15.3)* *- % males: 58.2-63.1* *- Mean duration of disease (years ±SD) : 8.3 (7.2)* *-Extend of disease: 13.7-15.6% proctosigmoiditis; 30.3-33.3% left sided colitis and 53.1-*

	54.1% extensive/pancolitis *- total Mayo score (±SD): 9.0 (1.4) - 9.1 (1.4)* *- previous treatments: 53.3-53.4% previous TNFi treatment* *-% using glucocorticoid: 45-47.5%*
Primary and secondary endpoints	*The primary efficacy end point was remission (a total Mayo score of ≤2, with no subscore >1 and a rectal bleeding subscore of 0) at 8 weeks.* *The key secondary end point was mucosal healing (a Mayo endoscopic subscore of ≤1) at 8 weeks. Additionally secondary endpoints at week 8 included clinical response, endoscopic remission as well as symptomatic remission and deep remission. HRQoL outcomes included IBDQ change and remission at week 8.*
Method of analysis	*The efficacy analyses were based on data from all patients who underwent randomization. The safety analyses were based on data from all patients who underwent randomization and received at least one dose of the assigned treatment* *Binary end points, including the primary efficacy end points were compared between the tofacitinib and placebo group with the use of a stratified Cochran–Mantel–Haenszel chi-square test. Patients with missing data were considered as not having had a response. The family-wise type 1 error rate was controlled at 0.05 for the primary and key secondary end points with the use of a fixed-sequence testing Procedure.* *The change from baseline in the total Mayo score was analyzed with the use of an analysis of covariance model with observed case data. For other continuous end points, change from baseline was analyzed with the use of a linear mixed-effects model*
Subgroup analyses	*Pre-specified analysis of primary and secondary endpoints were performed on subgroups including the TNFi naïve subpopulation and the TNFi experienced subpopulation*

Trial name	*OCTAVE induction 2*
NCT number	*NCT01458951*
Objective	*Evaluation of the efficacy and safety of tofacitinib versus placebo for induction treatment of bio-naïve and experienced patients with moderate to severe UC*
Publications – title, author, journal, year	• *Tofacitinib as induction and maintenance therapy for Ulcerative colitis, Sandborn WJ.et al., NEJM, 2017* • *Tofacitinib in patients with Ulcerative Colitis: Health-related quality of life in phase 3 randomised controlled induction and maintenance studies, Pánes J.et al., 2017*
Study type and design	*Completed multicenter, double-blinded, placebo-controlled phase 3 study. Eligible patients were randomly assigned, in a 4:1 ratio, to receive induction therapy with oral tofacitinib at a* *dose of 10 mg twice daily or placebo for 8 weeks. Randomization was performed centrally with the use of a telerandomization system and was stratified according to previous treatment with TNF antagonists, glucocorticoid use at baseline, and geographic region. Participant, Care Provider, Investigator, Outcomes Assessor were all blinded.*

Follow-up time	*8 weeks*

Population (inclusion and exclusion criteria)	Inclusion Criteria:
	• Subject must be at least 18 years of age.
	• Males and females with a documented diagnosis of UC at least 4 months prior to entry into the study.
	• Subjects with moderately to severely active UC based on Mayo score criteria.
	• Subjects must have failed or be intolerant of at least one of the following treatments for UC:
	  ○ Corticosteroids (oral or intravenous).
	  ○ Azathioprine or 6 mercaptopurine (6 MP).
	  ○ Anti TNF-alpha therapy.
	Exclusion Criteria:
	• Presence of indeterminate colitis, microscopic colitis, ischemic colitis, infectious colitis, or clinical findings suggestive of Crohn's disease.
	• Subjects with disease limited to distal 15 cm.
	• Subjects without previous treatment for UC (ie, treatment naïve).
	• Subjects displaying clinical signs of fulminant colitis or toxic megacolon.

Intervention	*Placebo (with optional background oral aminosalicylates and oral glucocorticoids at max dose of 25 mg/day prednisone or an equivalent): n=112* *Tofacitinib 10 mg BID ((with optional background oral aminosalicylates and oral glucocorticoids at max dose of 25 mg/day prednisone or an equivalent): n=429*
Baseline characteristics	*- Mean (± SD) age: 40.4(13.2)-41.1(13.5)* *- % males: 49.1-60.4* *- duration of disease (Mean (± SD)) : 7.9 (6.8)* *-Extend of disease: 14.4-15.7% proctosigmoiditis; 34.8-35.1% left sided colitis and 49.3-50.5% extensive/pancolitis* *- total Mayo score (±SD): 8.9 (1.5) - 9.0 (1.5)* *- previous treatments: 54.5-58.0% previous TNFi treatment* *-% using glucocorticoid: 46.2-49.1%*
Primary and secondary endpoints	*The primary efficacy end point was remission (a total Mayo score of ≤2, with no subscore >1 and a rectal bleeding subscore of 0) at 8 weeks.* *The key secondary end point was mucosal healing (a Mayo endoscopic subscore of ≤1) at 8 weeks. Additionally secondary endpoints at week 8 included clinical response, endoscopic remission as well as symptomatic remission and deep remission. HRQoL outcomes included IBDQ change and remission at week 8.*
Method of analysis	*The efficacy analyses were based on data from all patients who underwent randomization. The safety analyses were based on data from all patients who underwent randomization and received at least one dose of the assigned treatment* *Binary end points, including the primary efficacy end points were compared between the tofacitinib and placebo group with the use of a stratified Cochran–Mantel–Haenszel chi-square test. Patients with missing data were considered as not having had a response. The family-wise type 1 error rate was controlled at 0.05 for the primary and key secondary end points with the use of a fixed-sequence testing Procedure.* *The change from baseline in the total Mayo score was analyzed with the use of an analysis of covariance model with observed case data. For other continuous end points, change from baseline was analyzed with the use of a linear mixed-effects model*

Subgroup analyses	*Pre-specified analysis of primary and secondary endpoints were performed as described above on subgroups including the TNFi naïve subpopulation and the TNFi experienced subpopulation* *.*

Trial name	*OCTAVE Sustain*
NCT number	*NCT01458574*
Objective	*Evaluation of the efficacy and safety of tofacitinib versus placebo for maintenance treatment of bio-naïve and experienced patients with moderate to severe UC*
Publications – title, author, journal, year	• *Tofacitinib as induction and maintenance therapy for Ulcerative colitis, Sandborn WJ.et al., NEJM, 2017* • *Tofacitinib in patients with Ulcerative Colitis: Health-related quality of life in phase 3 randomised controlled induction and maintenance studies, Pánes J.et al., 2017*
Study type and design	*Completed multicenter, double-blinded, placebo-controlled phase 3 study.* *Patients from OCTAVE induction 1 and 2 who obtained a clinical response in the induction phase were eligible for entering OCTAVE sustain. Patients were randomly assigned in a 1:1:1 ratio, to receive maintenance therapy with tofacitinib at a dose of 5 mg twice daily, tofacitinib at a dose of 10 mg twice daily, or placebo for 52 weeks.* *Randomization was performed centrally with the use of a telerandomization system and was stratified according to previous treatment with TNF antagonists, glucocorticoid use at baseline, and geographic region.* *Participant, care provider, investigator and outcomes assessor were all blinded.*
Follow-up time	*52 weeks*
Population (inclusion and exclusion criteria)	*Inclusion Criteria:* • *Subjects who met study entry criteria and completed 8-week induction treatment from Study A3921094 or A3921095* • *Subjects who achieved clinical response in Study A3921094 or A3921095* • *Women of childbearing potential must test negative for pregnancy prior to study enrollment* • *Subjects who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures* • *Evidence of a personally signed and dated informed consent document(s) indicating that the subject (or a legally acceptable representative) has been informed of all pertinent aspects of the study.* *Exclusion Criteria:* • *Subjects who had major protocol violation (as determined by the Sponsor) in Study A3921094 or A3921095* • *Presence of indeterminate colitis, microscopic colitis, ischemic colitis, infectious colitis, or clinical findings suggestive of Crohn's disease* • *Subjects who have had surgery for UC or in the opinion of the investigator, are likely to require surgery for UC during the study period.*

Intervention	*Placebo (with optional 5-ASA background. Glucocorticoids to be tapered): n=198* *Tofacitinib 5 mg BID (with optional 5-ASA background. Glucocorticoids to be tapered): n=198* *Tofacitinib 10 mg BID (with optional 5-ASA background. Glucocorticoids to be tapered): n=197*
Baseline characteristics	*- Mean (± SD) age: 41.9(13.7)-43.4(14.0)* *- % males: 52.0-58.6* *- Duration of disease (Mean (± SD)) : 8.6 (7.2)* *-Extend of disease: 10.6-16.8% proctosigmoiditis; 30.6-34.3% left sided colitis and 52.0-54.5% extensive/pancolitis* *- total Mayo score (±SD): 3.3 (1.8) – 3.4 (1.8)* *- previous treatments: 45.5-51.3% previous TNFi treatment* *-% using glucocorticoid: 44.2-51.0%*
Primary and secondary endpoints	*The primary efficacy end point was remission (a total Mayo score of ≤2, with no subscore >1 and a rectal bleeding subscore of 0) at 52 weeks with endoscopy centrally read.* *Key secondary end points were mucosal healing at 52 weeks and remission that was sustained (i.e., occurring at both 24 and 52 weeks) and glucocorticoid-free (i.e., occurring without the administration of glucocorticoids for ≥4 weeks before the assessment) among patients who were in remission at maintenance-trial entry.* *Additional secondary endpoints included % patients in remission at Week 24, sustained remission at both Week 24 and Week 52. Percentage of Participants With Mucosal Healing at Week 24, Sustained Mucosal Healing at both Week 24 and Week 52, Clinical Response at Week 24 and 52, Sustained Clinical Response at both Week 24 and Week 52, Deep Remission at Week 24 and 52, Sustained Deep Remission at both Week 24 and Week 52, Symptomatic Remission at Week 24 and 52, Sustained Symptomatic Remission at both Week 24 and Week 52, Endoscopic Remission at Week 24 and 52, sustained Endoscopic Remission at both Week 24 and Week 52, Total Mayo Score at Baseline, Week 24 and 52, change From Baseline in Total Mayo Score at Week 24 and 52 and patients in Steroid-Free Remission, Among Participants Receiving Steroids at Baseline.* *HRQoL outcomes included IBDQ change and remission at week 52.*
Method of analysis	*The efficacy analyses were based on data from all patients who underwent randomization. The safety analyses were based on data from all patients who underwent randomization and received at least one dose of the assigned treatment* *Binary end points, including the primary efficacy end points were compared between the tofacitinib and placebo group with the use of a stratified Cochran–Mantel–Haenszel chi-square test. Patients with missing data were considered as not having had a response. The family-wise type 1 error rate was controlled at 0.05 for the primary and key secondary end points with the use of a sequentially rejective, Bonferroni-based, iterative multiple test procedure* *For continuous end points, change from baseline was analyzed with the use of a linear mixed-effects model*
Subgroup analyses	*Pre-specified analysis of primary and secondary efficacy endpoints were performed as described above on subgroups including the TNFi naïve subpopulation and the TNFi experienced subpopulation. HRQoL subgroup analyses were performed post-hoc.*

Trial name	*GEMINI 1*
NCT number	*NCT00783718*
Objective	*Evaluation of the efficacy and safety of Vedolizumab for treatment of patients with moderate to severe UC*
Publications – title, author, journal, year	• *Vedolizumab as Induction and Maintenance Therapy for Ulcerative Colitis, Feagan BG et al, NEJM, 2013* • *Efficacy of vedolizumab induction and maintenance therapy in patients with ulcerative colitis, regardless of prior exposure to tumor necrosis factor antagonists, Feagan BG et al., Clin Gastro Hep, 2017* • *Effects of Vedolizumab on helath-related quality of life in patients with ulcerative colitis: results from the randomized GEMINI 1 trial*
Study type and design	*Completed multicenter, double-blinded, placebo-controlled phase 3 study.* *For induction therapy, patients were randomly assigned, in a 3:2 ratio, to receive iv vedolizumab (300 mg) or placebo (cohort 1). The proportion of patients with previous exposure to TNF antagonists was limited to 50%. To fulfill sample-size requirements for the maintenance trial, additional patients were enrolled in an open-label group (cohort 2), which received the same active induction regimen given in the blinded study.* *In the Maintenance Phase vedolizumab-treated participants from both Cohort 1 and Cohort 2 who demonstrated a clinical response were randomized in a 1:1:1 ratio to double-blind treatment with vedolizumab administered every 4 weeks (Q4W), vedolizumab administered every 8 weeks (Q8W), or placebo. Vedolizumab-treated participants who did not demonstrate response at Week 6 continued treatment with open-label vedolizumab, administered Q4W. Participants treated with double-blind placebo in the Induction Phase continued on double-blind placebo during the Maintenance Phase, regardless of treatment response during induction. The Maintenance Phase began at Week 6 and concluded with Week 52 assessments.* *Participant, care provider and investigator were blinded.* *.*
Follow-up time	*52 weeks*

Population (inclusion and exclusion criteria)	*Inclusion Criteria:*
	1. *Diagnosis of moderately to severely active ulcerative colitis*
	2. *Demonstrated, over the previous 5 year period, an inadequate response to, loss of response to, or intolerance at least 1 of the following agents:*
	  1. *Immunomodulators*
	  2. *Tumor necrosis factor-alpha (TNFα) antagonists*
	  3. *Corticosteroids*
	3. *May be receiving a therapeutic dose of conventional therapies for inflammatory bowel disease (IBD) as defined by the protocol*
	Exclusion Criteria:
	1. *Evidence of abdominal abscess at the initial screening visit*
	2. *Extensive colonic resection, subtotal or total colectomy*
	3. *Ileostomy, colostomy, or known fixed symptomatic stenosis of the intestine*
	4. *Have received non permitted IBD therapies within either 30 or 60 days,*

	depending on the medication, as stated in the protocol *5. Chronic hepatitis B or C infection* *6. Active or latent tuberculosis* *.*
Intervention	• *Placebo (with optional mesalamine and/or immunnosuppressors and background Glucocorticoids up to 30 mg/day prednisone or equivalent. The latter to be tapered after week 6): n=149* • *Vedolizumab 300 mg iv induction on day 1, 15 (with optional mesalamine and/or immunnosuppressors and background Glucocorticoids up to 30 mg/day prednisone or equivalent. cohort 1: n=225 + cohort 2(OL): n= 521* • *Vedolizumab 300 mg iv maintenance every 4 weeks (with optional mesalamine and/or immunnosuppressors and background Glucocorticoids to be tapered) : n=125* • *Vedolizumab 300 mg iv maintenance every 8 weeks (with optional mesalamine and/or immunnosuppressors and background Glucocorticoids to be tapered) : n= 122*
Baseline characteristics	*- Mean (± SD) age: 40.3(13.1)* *- % males: 58.7* *- Mean Duration of disease (years (± SD)) : 6.9 (6.4)* *-Extend of disease: 13.0% proctosigmoiditis; 37.9% left sided colitis, 12.2% proximal to the splenic flexure, 37% all colon* *- Mayo clinic score (±SD): 8.6 (1.8)* *- previous treatments: 48.2% previous TNFi treatment* *-% using glucocorticoid: 37.1 + 16.6%* *-% using immunosuppressants 17.8 +16.6%:*
Primary and secondary endpoints	*The primary outcome for induction therapy was a clinical response at week 6, defined as a reduction in the Mayo Clinic score of at least 3 points and a decrease of at least 30% from the baseline score, with a decrease of at least 1 point on the rectal bleeding subscale or an absolute rectal bleeding score of 0 or 1.* *Secondary outcomes at week 6 were clinical remission, defined as a Mayo Clinic score of 2 or lower and no subscore higher than 1, and mucosal healing, defined as an endoscopic subscore of 0 or 1. The primary outcome for maintenance therapy was clinical remission at week 52. Secondary measures, in ranked order, were durable clinical response (response at both weeks 6 and 52), durable clinical remission (remission at both weeks 6 and 52), mucosal healing at week 52, and glucocorticoid-free remission at week 52 in patients receiving glucocorticoids at baseline. Health-related quality of life was evaluated with the use of the IBDQ.*
Method of analysis	*For the primary analysis of induction therapy, proportions of patients with a clinical response were compared with the use of the Cochran–Mantel–Haenszel chi-square test, with adjustment for stratification factors. Treatment was considered to have failed in patients who withdrew prematurely. Rates of clinical remission and endoscopic healing were compared in a similar fashion. To control for multiple comparisons, a closed sequential procedure was used for primary and secondary outcomes, and a P value of 0.05 or lower was required to proceed to the analysis of each subsequent outcome.* *A similar procedure was used to analyze data from the trial of maintenance therapy. Given the comparisons of two vedolizumab doses with placebo, a Hochberg procedure was used to control the overall alpha error at 5% for testing of both dose regimens for each outcome.*

	Changes from baseline in the partial Mayo Clinic score, IBDQ score, and fecal calprotectin concentration was analyzed separately for induction therapy and maintenance therapy, using analysis of covariance with adjustment for stratification variables. *Analyses were performed according to an intention-to-treat principle.*
Subgroup analyses	*In prespecified exploratory and post-hoc analyses, efficacy outcomes were evaluated in the TNFi failure and TNFi naïve intention-to-treat populations.*

Trial name	*ACT 1*
NCT number	*NCT00036439*
Objective	*Evaluation of the efficacy and safety of Infliximab for treatment of adult patients with moderate to severe UC*
Publications – title, author, journal, year	• *Infliximab for Induction and Maintenance Therapy for Ulcerative Colitis, Rutgeerts P. et al, NEJM, 2005* • *The effects of Infliximab therapy on health-related quality of life in Ulcerative colitis patients, Feagan BG., Am J Gastroenterol, 2007*
Study type and design	*Completed multicenter, double-blinded, placebo-controlled phase 3 study.* *Eligible patients were randomly assigned in a 1:1:1 ratio to receive intravenous infusions of infliximab at a dose of 5 mg/kg or 10 mg/kg or placebo at weeks 0, 2, and 6 and then every eight weeks through week 46. Patients were followed through week 54 ACT 1.* *Each study used central randomization with a dynamic treatment allocation stratified according to the investigational site and whether patients had ulcerative colitis that was refractory to corticosteroid therapy* *Participant and investigator were blinded.* *.*
Follow-up time	*54 weeks*
Population (inclusion and exclusion criteria)	*Inclusion Criteria:* • *Patients who have had ulcerative colitis of at least 3 months' duration at screening* • *Patients who have ulcerative colitis confirmed by the biopsy taken at screening* • *Patients must have active colitis confirmed during the screening sigmoidoscopy* • *Patients must have active disease.* *Exclusion Criteria:* • *Patients must not be likely to require surgical removal of all or part of the colon within 12 weeks of beginning the study*

	• *Patients must not require, or required within the 2 months prior to beginning the study, surgery for active gastrointestinal bleeding, peritonitis, intestinal obstruction, or intra-abdominal or pancreatic abscess requiring surgical drainage.*
Intervention	• *Placebo (with optional 5-ASA, immunnosuppressors and background Glucocorticoids. The latter to be tapered after week 8): n=121* • *Infliximab 5 mg/kg iv at week 0, 2, 6 and then every 8 weeks (with optional 5-ASA, immunnosuppressors and background Glucocorticoids. The latter to be tapered from week 8). n=121* • *Infliximab 10 mg/kg iv at week 0, 2, 6 and then every 8 weeks (with optional 5-ASA, immunnosuppressors and background Glucocorticoids. The latter to be tapered from week 8) : n=122*
Baseline characteristics	*- Mean (± SD) age: 41.4(13.7)- 42.4 (14.3)* *- % males: 59.0-64.5* *- Mean Duration of disease (years (± SD)) : 5.9(5.4)- 8.4 (8.1)* *-Extend of disease: 52.9-55.4% left sided colitis, 44.6-47.1% extensive* *- Mayo clinic score (±SD): 8.4 (1.4)-8.5 (1.7)* *- previous treatments: 0% previous TNFi treatment* *-% using glucocorticoid: 57.9 – 65.3%* *-% using immunosuppressants 43.8-54.5%:*
Primary and secondary endpoints	*The primary end point was a clinical response (defined as a decrease from baseline in the Mayo score by = 30% and = 3 points, with a decrease in the rectal bleeding subscore of = 1 or a rectal bleeding subscore of 0 or 1) at week 8.* *Secondary end points were a clinical response or clinical remission (defined as a Mayo score of = 2 points, with no individual subscore > 1) with discontinuation of corticosteroids at week 30 and at week 54, a clinical remission and mucosal healing at weeks 8 ,30 and at week 54, and a clinical response at week 8 in patients with a history of disease refractory to corticosteroids.*
Method of analysis	*A two-sided Cochran–Mantel–Haenszel chi-square test, at a significance level of 0.05, stratified according to corticosteroid-refractory status and the location of the study center, was used to compare dichotomous end points (i.e., clinical response, clinical remission, mucosal healing, and clinical remission with discontinuation of corticosteroids) among treatment groups.* *All efficacy analyses used intention-to-treat methods.* *Safety comparisons were performed with the use of Fisher's exact test and were based on the combination of the two groups receiving infliximab as compared with the placebo group.*
Subgroup analyses	*NA*

Trial name	*ACT 2*
NCT number	*NCT00096655*
Objective	*Evaluation of the efficacy and safety of Infliximab for treatment of adult patients with moderate to severe UC*
Publications – title, author, journal, year	• *Infliximab for Induction and Maintenance Therapy for Ulcerative Colitis, Rutgeerts P. et al, NEJM, 2005* • *The effects of Infliximab therapy on health-related quality of life in Ulcerative colitis patients, Feagan BG., Am J Gastroenterol, 2007*
Study type and design	*Completed multicenter, double-blinded, placebo-controlled phase 3 study.* *Eligible patients were randomly assigned in a 1:1:1 ratio to receive intravenous infusions of infliximab at a dose of 5 mg/kg or 10 mg/kg or placebo at weeks 0, 2, and 6 and then every eight weeks through week 30. Patients were followed through week 30.* *The study used central randomization with a dynamic treatment allocation stratified according to the investigational site and whether patients had ulcerative colitis that was refractory to corticosteroid therapy* *Participant and investigator were blinded.* *.*
Follow-up time	*30 weeks*
Population (inclusion and exclusion criteria)	*Inclusion Criteria:* • *Patients must have had ulcerative colitis of at least 3 months' duration at screening, confirmed by the biopsy taken at screening* • *Patients must have active colitis confirmed during the screening sigmoidoscopy* • *Patients must have active disease.* *Exclusion Criteria:* • *Patient must not be likely to require surgical removal of all or part of the colon within 12 weeks of beginning the study* • *Patient must not require, or required within the 2 months prior to beginning the study, surgery for active gastrointestinal bleeding, peritonitis, intestinal obstruction, or intra-abdominal or pancreatic abscess requiring surgical drainage*
Intervention	• *Placebo (with optional 5-ASA, immunnosuppressors and background Glucocorticoids. The latter to be tapered after week 8): n=123* • *Infliximab 5 mg/kg iv at week 0, 2, 6 and then every 8 weeks (with optional 5-ASA, immunnosuppressors and background Glucocorticoids. The latter to be tapered from week 8). n=121* • *Infliximab 10 mg/kg iv at week 0, 2, 6 and then every 8 weeks (with optional 5-ASA, immunnosuppressors and background Glucocorticoids. The latter to be tapered from week 8) : n=120*

Baseline characteristics	*- Mean (± SD) age: 39.3(13.5)- 40.5 (13.1)* *- % males: 56.7-62.8* *- Mean Duration of disease (years (± SD)) : 6.5(6.7)- 6.7 (5.3)* *-Extend of disease: 58.3-62.5% left sided colitis, 37.5-41.7% extensive* *- Mayo clinic score (±SD): 8.3 (1.5)-8.5 (1.5)* *- previous treatments: 0% previous TNFi treatment* *-% using glucocorticoid: 48.8 – 55.0%* *-% using immunosuppressants 41.7-43.9%:*
Primary and secondary endpoints	*The primary end point was a clinical response (defined as a decrease from baseline in the Mayo score by = 30% and = 3 points, with a decrease in the rectal bleeding subscore of = 1 or a rectal bleeding subscore of 0 or 1) at week 8.* *Secondary end points were a clinical response or clinical remission (defined as a Mayo score of = 2 points, with no individual subscore > 1) with discontinuation of corticosteroids at week 30, a clinical remission and mucosal healing at weeks 8 and 30, and a clinical response at week 8 in patients with a history of disease refractory to corticosteroids.* *HRQoL was measured using IBDQ and SF-36*
Method of analysis	*A two-sided Cochran–Mantel–Haenszel chi-square test, at a significance level of 0.05, stratified according to corticosteroid-refractory status and the location of the study center, was used to compare dichotomous end points (i.e., clinical response, clinical remission, mucosal healing, and clinical remission with discontinuation of corticosteroids) among treatment groups.* *Changes from baseline in the IBDQ scores were compared between each infliximab maintenance group and the placebo group by using contrasts in analysis of variance based on van der Waerden normal scores. χ2 tests were used for between-group comparisons of the proportions of patients who achieved clinically meaningful improvement. These analyses used increases of 16 and 32 points for the IBDQ questionnaire* *All efficacy analyses used intention-to-treat methods.* *Safety comparisons were performed with the use of Fisher's exact test and were based on the combination of the two groups receiving infliximab as compared with the placebo group.*
Subgroup analyses	NA- only TNFi naïve patients are included in the study

Trial name	*UC-SUCCESS*
NCT number	*NCT00537316*
Objective	*Evaluation of the efficacy and safety of Infliximab monotherapy or in combination with azathioprine for treatment of adult patients with moderate to severe UC*
Publications – title, author, journal, year	• *Combination therapy with Infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis, Panaccione R., Gastroenterology, 2014*
Study type and design	*Terminated multicenter, double-blinded, double dummy trial.* *Patients were randomized in a 1:1:1 ratio to receive infliximab, azathioprine, or combination infliximab/azathioprine treatment. Patients in the infliximab group received 5 mg/kg intravenous at weeks 0, 2, 6, and 14 plus daily oral placebo (PBO) capsules. Patients in the infliximab group who were nonresponders at week 8 (partial Mayo score improvement from baseline of <1) also received PBO infusions at weeks 8 and 10. Patients in the azathioprine group received 2.5 mg/kg azathioprine oral capsules daily plus intravenous PBO infusions at weeks 0, 2, and 6. For patients who responded to azathioprine at week 8, a PBO infusion also was received at week 14. For patients who were non-responders to AZA at week 8 (partial Mayo score improvement from baseline of <1), infliximab rescue infusions were administered at weeks 8, 10, and 14 while continuing azathioprine therapy. Patients in the combination group received infliximab 5 mg/kg at weeks 0, 2, 6, and 14 and also received 2.5 mg/kg azathioprine capsules daily. Patients in this group who were non-responders at week 8 also received PBO infusions at weeks 8 and 10.* *Randomization was performed centrally using an adaptive randomization procedure stratified by whether patients previously used immunomodulators such as AZA and cyclosporine.* *Participant and investigator were blinded.* *.*
Follow-up time	*16 weeks*
Population (inclusion and exclusion criteria)	*Inclusion Criteria:* • *must be >=21 years of age at the time of informed consent, of either sex, and of any race;* • *must have endoscopic evidence of UC, as determined by sigmoidoscopy, within 14 days prior to Baseline;* • *must have a total Mayo score of 6 to 12 points at Baseline;* • *must have responded inadequately to corticosteroid treatment (ie, the last or current UC flare did not respond adequately to a standard course of corticosteroids) with or without 5 aminosalicylic acid (5-ASA);* • *must be off corticosteroids or on a stable dose of corticosteroid for at least 2 weeks prior to enrollment. The maximal daily dose of corticosteroid at Baseline must not exceed the equivalent of 30 mg of prednisone;* • *must be naïve to infliximab and other tumor necrosis factor-alpha (TNF-α) antagonists;*

	• *must be either naïve to AZA/6-MP or have not received AZA/6-MP for at least 3 months before enrollment in the study;*
	• *considered eligible according to the following tuberculosis (TB) screening criteria:*
	  ○ *have no history of latent or active TB prior to Screening;*
	  ○ *have no signs or symptoms suggestive of active TB upon medical history and/or physical examination;*
	  ○ *have had no recent close contact with a person with active TB or, if there has been such contact, will be referred to a physician specializing in TB to undergo additional evaluation and, if warranted, receive appropriate treatment for latent TB prior to or simultaneously with the first administration of IFX;*
	  ○ *within 1 month prior to the first administration of infliximab, either have negative tuberculin skin test OR have a newly identified positive tuberculin test during Screening in which active TB has been ruled out, and for which appropriate treatment for latent TB has been initiated either prior to or simultaneously with the first administration of IFX.*
	  ○ *must have a chest X-ray (posterior-anterior and lateral views), taken within 3 months prior to the first administration of study agent and read by a qualified radiologist, with no evidence of current active TB or old active TB;*
	• *have had UC for more than 10 years should have had a full colonoscopy within 2 years prior to Screening for the surveillance of dysplasia;*
	• *screening and Baseline clinical laboratory tests (complete blood count [CBC] and blood chemistries) must be within predetermined parameters*
	• *had been on antibiotics for the treatment of UC (eg, ciprofloxacin and metronidazole) must have been discontinued from them at least 3 weeks prior to Screening;*
	• *must be free of any clinically significant condition or situation, other than UC that, in the opinion of the investigator, would interfere with the study evaluations or optimal participation in the study;*
	• *willing and able to adhere to the study visit schedule and other protocol requirements;*
	• *capable of providing written informed consent, which must be obtained prior to conducting any protocol-specified procedures;*
	• *women of child-bearing potential and all men must agree to use a medically accepted method of contraception prior to screening, while receiving protocol-specified medication, and for 6 months after stopping the medication. Acceptable methods of contraception include condoms (male or female) with or without a spermicidal agent, diaphragm or cervical cap with spermicide, medically prescribed intrauterine device (IUD), oral or injectable hormonal contraceptive, and surgical sterilization (eg, hysterectomy or tubal ligation). Women of child-bearing potential who are not currently sexually active must agree to use a medically accepted method of contraception should they become sexually active while participating in the study;*
	• *female participants of childbearing potential must have a negative serum*

	pregnancy test (beta-human chorionic gonadotropin) at Screening and a negative urine pregnancy test at Baseline.
	
	Exclusion Criteria:
	
	• *have severe extensive colitis as evidenced by:*
	  ○ *investigator judgment that the participant is likely to require colectomy within 12 weeks of Baseline*
	
	OR
	
	• *at least 4 of these symptoms at Screening or Baseline visits, as follows:*
	  ○ *diarrhea with >=6 bowel movements/day with macroscopic blood in stool;*
	  ○ *focal severe or rebound abdominal tenderness;*
	  ○ *persistent fever (>=37.5 degrees C) for at least 3 days prior to baseline;*
	  ○ *tachycardia (>100 beats/minute);*
	  ○ *hemoglobin <8.5 g/dL (5.3 mM/L).*
	  ▪ *require, or are required within the 2 months prior to baseline, surgery for active gastrointestinal bleeding, peritonitis, intestinal obstruction, or intra-abdominal or pancreatic abscess requiring surgical drainage or other conditions possibly confounding the evaluation of disease activity;*
	  ▪ *have severe, fixed symptomatic stenosis of the large or small intestine;*
	  ▪ *have current evidence of colonic obstruction or history within the 6 months prior to baseline, confirmed with objective radiographic or endoscopic evidence of a stricture with resulting obstruction (dilation of the colon proximal to the stricture on barium radiograph or an inability to traverse the stricture at endoscopy);*
	  ▪ *have a history of colonic mucosal dysplasia;*
	  ▪ *presence on screening endoscopy of adenomatous colonic polyps, if not removed prior to study entry, or history of adenomatous colonic polyps that were not removed;*
	  ▪ *have the presence of a stoma;*
	  ▪ *have a history of extensive colonic resection that would prevent adequate evaluation of clinical disease activity (eg, less than 30 cm of colon remaining);*
	  ▪ *have had a positive stool culture for enteric pathogens, pathogenic ova or parasites within 4 months prior to Baseline unless participant has received treatment and had a negative stool examination 1 week or longer after the end of treatment;*
	  ▪ *have a concomitant diagnosis of congestive heart failure (CHF), including medically controlled asymptomatic subjects;*
	  ▪ *have had serious infections (eg, active hepatitis, pneumonia, or pyelonephritis) within 2 months of Screening. Less serious infections (such as acute upper respiratory tract infection [colds] or a simple urinary tract infection) need not be considered as an exclusion at the discretion of the investigator;*
	  ▪ *have had a nontuberculous mycobacterial infection or opportunistic infection (eg, cytomegalovirus, Pneumocystis carinii, aspergillosis) within 6 months prior to Screening;*
	  ▪ *have a known infection with human immunodeficiency virus (HIV) and/or*

	hepatitis B or hepatitis C; ▪ *have a history of a known allergy to murine proteins or allergy/sensitivity to study drug or its excipients;* ▪ *have current signs and symptoms of systemic lupus erythematosus, or severe, progressive, or uncontrolled renal, hepatic, hematologic, endocrine, pulmonary, cardiac, neurologic, or cerebral diseases;* ▪ *have a known history of demyelinating disease suggestive of multiple sclerosis or optic neuritis;* ▪ *presence of a transplanted organ (with the exception of a corneal transplant >3 months prior to Screening);* ▪ *have a history of lymphoproliferative disease including lymphoma, or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy of unusual size or location (eg, nodes in the posterior triangle of the neck, infra-clavicular, epitrochlear, or periaortic areas), or splenomegaly;* ▪ *have any current known malignancy or malignancy within 5 years prior to Screening (except for squamous or basal cell carcinoma of the skin that has been treated with no evidence of recurrence);* ▪ *have poor tolerability of venipuncture or lack of adequate venous access for required blood sampling and infusion of study drug during the study period;* ▪ *have had a known substance abuse or dependency (drug or alcohol) within 3 years of Screening;* ▪ *require chronic (>=1 month) and frequent use (>=3 days per week)of nonsteroidal anti-inflammatory drugs (NSAIDs) except low-dose aspirin for prevention of heart attacks, unstable angina, or transient ischemic attacks;* ▪ *have other inflammatory diseases that might interfere with the evaluation of the ulcerative colitis;* ▪ *have a history of latent or active granulomatous infection, including TB, histoplasmosis, or coccidioidomycosis, prior to Screening.* ▪ *have had a Bacille Calmette-Guerin (BCG) vaccination within 12 months of Screening.* ▪ *have had a chest X-ray within the 3 months prior to the first administration of study agent that shows an abnormality suggestive of malignancy or current active infection, including TB.* ▪ *have received any specified prohibited treatment more recently than the indicated washout period prior to Screening;* ▪ *who are participating in any other clinical study or who have received treatment with any investigational drug or device within 3 months prior Screening;* ▪ *who is part of the staff or a family member of the staff personnel directly involved with this study.*
Intervention	• *Azathioprine 2.5 mg/kg daily ((with optional oral 5-ASA, and background Glucocorticoids. The latter to be tapered unless contraindicated). N=79* • *Infliximab 5 mg/kg iv at week 0, 2, 6 and 14 (with optional oral 5-ASA, and background Glucocorticoids. The latter to be tapered unless contraindicated). n=78* • *Infliximab 5mg/kg iv at week 0, 2, 6 and 14 + azathioprine 2.5 mg/kg daily (with optional oral 5-ASA, and background Glucocorticoids. The latter to be tapered unless contraindicated) : n=80*

Baseline characteristics	*- Mean (± SD) age: 38.0(12.2)- 40.7 (13.2)* *- % males: 42-60* *- Mean Duration of disease (years (± SD)) : 5.2(5.1)- 6.6 (7.8)* *-Extend of disease: NA* *- Total Mayo score (±SD): 8.31 (1.4)-8.6 (1.3)* *- previous treatments: 0% previous TNFi treatment* *-% using glucocorticoid: 34.2 – 47.5%* *-% using immunosuppressants: NA*
Primary and secondary endpoints	*The primary end point of the study was the proportion of patients in CS-free remission, defined as a total Mayo score of 2 points or less, with no individual subscore exceeding 1 point, without the use of CSs at week 16.* *Secondary end points included the percentage of patients with partial Mayo response at week 8 (defined as a decrease from baseline in partial Mayo score [ie, Mayo score without endoscopy subscore] of _1 point); the percentage of patients with total Mayo response at week 16 (defined as a decrease in the total Mayo score of _3 points and at least a 30% decrease from baseline Mayo score); the percentage of patients with mucosal healing (Mayo endoscopy subscore of 0 or 1) at week 16; and changes in mean Mayo, IBDQ, and SF-36 scores from baseline to weeks 8 and 16. A more lenient definition of Mayo response was used at week 8 than week 16 to provide an earlier rescue treatment for patients with poor response.*
Method of analysis	*The treatment group comparisons for the primary end point of CS-free remission were evaluated using chi-square tests. Treatment group differences in Mayo response at weeks 8 and 16 and mucosal healing at week 16 also were evaluated using chi-square tests. The changes from baseline in Mayo, IBDQ, and SF-36 scores at weeks 8 and 16 were evaluated using the Mann–Whitney U tests.* *The study had planned to enroll 600 patients in the initial randomized treatment phase to adequately power the maintenance portion of the study. With 200 patients per group, the study had more than 90% power to detect a 15% difference in remission rate between the azathioprine and infliximab/azathioprine combination arms with α = .05 (2-sided test), assuming a remission rate of 15% in the azathioprine arm. Because the study was terminated early, only 239 patients (w80/group) were available for analysis; therefore, the study had approximately 54% power to detect a 15% difference in remission rates between groups at a P value of less than .05.* *Hochberg's step-down approach was used to control type 1 error during treatment group comparisons for the primary end point and secondary end point comparisons.* *The full analysis set consisted of all patients who were randomized, received at least 1 dose of study treatment, and had data available at baseline and at least 1 postbaseline evaluation. The full analysis set was used for analysis of efficacy.*
Subgroup analyses	NA- only TNFi naïve patients are included in the study

Trial name	*Kobayashi et al*
Japic number	*CTI-060298*
Objective	*Evaluation of the trough levels and efficacy and safety of Infliximab for treatment of adult Japanese patients with moderate to severe UC*

Publications – title, author, journal, year	• *First trough level of infliximab at week 2 predicts future outcomes of induction therapy in ulcerative colitis- results from a multicenter prospective randomized controlled trial and its post-hoc analysis, Kobayashi T., et al, J. Gastroenterol, 2016*
Study type and design	*Completed multicenter, double-blinded, placebo-controlled phase 3 study.* *Eligible patients were randomly assigned in a 1:1 ratio to receive an intravenous infusion of IFX at a dose of 5 mg/kg or placebo at weeks 0, 2, and 6.* *Randomization was performed centrally with the use of computer-generated randomization schedules stratified according to the investigational site and concomitant use or nonuse of corticosteroids (prednisolone equivalent of 0, \20, or C20 mg/day). Patients with a significantly lower Mayo score at week 8 (defined as a decrease in the total Mayo baseline score of at least 3 points and at least 30 %, with an accompanying decrease in the rectal bleeding subscore of at least 1 point or an absolute subscore of 0 or 1, i.e., 8-week responders) then received IFX or placebo at weeks 14 and 22. Conversely, 8-week non-responders were discontinued from IFX or placebo treatment.* *Eight-week responders were followed through week 38. 8-week non-responders and other patients who discontinued treatment with IFX or placebo were followed until* *16 weeks after the last administration.*
Follow-up time	*38 weeks*
Population (inclusion and exclusion criteria) (extracted from NIPH clinical trial search of Japan, https://rctportal.niph.go.jp/en/) + kobayashi et al 2016	*[Inclusion criteria]* *Patients with active ulcerative colitis (Mayo score 6-12), who have failed to response, have failed to successfully taper or have medical complications to other existing medications, 16 years and above, male and female.* *[Exclusion criteria]* *Patients who have received infliximab in the past, have a history of serious infection which caused hospitalization within 6 months before the registration, have an active tuberculosis, have a complication or a history of malignancy within 5 years before the registration.*
Intervention	• *Placebo (with optional oral 5-ASA, immunnosuppressors and background corticosteroids. The latter to be tapered after week 8): n=104* • *Infliximab 5 mg/kg iv at week 0, 2, 6 and then every 8 weeks (with optional 5-ASA, immunnosuppressors and background corticosteroids. The latter to be tapered from week 8). n=104*
Baseline characteristics	*- Mean (± SD) age: 37.8(12.9)- 40.0 (12.7)* *- % males: 63.5-64.4* *- Mean Duration of disease (years (± SD)) : 7.1(6.6)- 8.1 (7.2)* *-Extend of disease: 19.2-20.2% left sided colitis, 79.8-80.8% extensive* *- Mayo clinic score (±SD): 8.5(1.4) - 8.6(1.4)* *- previous treatments: 0% previous TNFi treatment* *-% using glucocorticoid: 65.4 – 66.3%* *-% using immunosuppressants 47.1-48.1%:*
Primary and secondary endpoints	*The primary end point was a clinical response (a decrease in the total Mayo baseline score of at least 3 points and at least 30 %, with an accompanying*

	decrease in the rectal bleeding subscore of at least 1 point or an absolute subscore of 0 or 1.) at week 8. *Secondary end points were clinical remission or mucosal healing. Response at week 8 as well as clinical response or clinical remission at week 30. The Mayo score was determined at weeks 0, 8, and 30. Clinical remission was defined as a total Mayo score of 2 points or lower, with no individual subscore exceeding 1 point. Mucosal healing was defined as an endoscopic subscore of 0 or 1. The clinical activity index (CAI) was determined at all visits. CAI remission was defined as a CAI score of 4 or lower.* *Trough levels at weeks 0, 2, 6, and every 8 weeks thereafter and development of antibodies against infliximab at weeks 0, 14, and 30 were measured using an enzyme-linked immunosorbent assay*
Method of analysis	*Efficacy was assessed in the full analysis set. Patients who took prohibited medication because of worsening UC (lack of efficacy or loss of response to the study medication), who discontinued the study medication because of worsening UC, including 8-week non-responders, or who underwent colectomy or colostomy were not considered to have had a clinical response, clinical remission, or MH, and their post-procedure CAI score was used as the baseline value from the time of the procedure onward. For other patients who withdrew prematurely, the last observation was carried forward. Statistical tests were two-sided, with p 0.05 considered to indicate statistical significance.* *Proportions of patients with a clinical response, clinical remission, and MH were compared using logistic regression analysis [explanatory variables: treatment group, corticosteroid use (except for analysis in severe cases)].*
Subgroup analyses	NA- only TNFi naïve patients are included in the study

Trial name	*Jiang*
NCT number	*NA*
Objective	*Evaluation of the efficacy and safety and dosage of infliximab in Chinese patients with moderate to severe ulcerative colitis*
Publications – title, author, journal, year	*Low-dose Infliximab for Induction and Maintenance treatment in Chinese Patients With Moderate to Severe Active Ulcerative Colitis, Jiang X-L et al, J Clin Gastroenterol 2015*
Study type and design	*Completed multicenter, double-blinded, placebo-controlled phase 3 study. Eligible patients were randomly assigned in a 1:1:1 ratio to receive intravenous infusions of infliximab at a low dose of 3.5mg/kg or a standard dose of 5mg/kg or placebo at weeks 0, 2, and 6 and then every 8 weeks through week 22. Patients were followed up through week 30. Central randomization with a dynamic treatment allocation stratification was used based on the investigational site and whether patients had ulcerative colitis that was refractory to treatment with corticosteroid.*
Follow-up time	*30 weeks*
Population (inclusion and exclusion criteria)	Inclusion Criteria: • subjects' participation in the study was voluntary, and all subjects had to sign

(extracted from publication)	the informed consent form before the enrollment • subjects should be aged between 18 and 65 years, irrespective • of sex • moderate to severe active ulcerative colitis was diagnosed using endoscopy and biopsy 1 week before treatment • eligible patients had active ulcerative colitis with a Mayo score of 6 to 12 points and an endoscopic score of ≥2 points despite concurrent treatment with corticosteroids only or in combination with azathioprine and drugs containing 5-aminosalicylates. Exclusion Criteria: • patients who had been diagnosed with Crohn's disease (CD), or clinical findings suggestive of CD or indeterminate colitis. • a recent medical history of active infection, chronic infection, or repeated infection • patients with congestive heart failure • children and patients under pregnancy • patients allergic to mouse proteins • patients with demyelinating diseases of the nervous system • patients with malignancy (both present and previous) • patients with severe ulcerative colitis requiring intravenous steroids • patients who received corticosteroids or drugs containing 5-aminosalicylates rectally within 2 weeks before screening • patients who were previously exposed to infliximab or any other anti–tumor necrosis factor (TNF) • patients who did not respond to corticosteroids within the preceding 18 months or who could not tolerate corticosteroids • patients who did not respond to azathioprine or mercaptopurine within the preceding 5 years or who could not tolerate these drugs, and patients who did not respond to drugs containing 5-aminosalicylates within the preceding 18 months or who could not tolerate such drugs • patients with cytomegalovirus colitis.
Intervention	*Placebo (with optional background of aminosalicylate, glucocorticoids and/or azathioprine): n=41* *Infliximab 3.5 mg/kg (with optional background aminosalicylates, glucocorticoids or/and azathioprine: n=41* *Infliximab 5 mg/kg (with optional background aminosalicylates, glucocorticoids or/and azathioprine: n=41*
Baseline characteristics	*- Mean (± SD) age: 34.1(13.8)-34.5(14.9)* *- % males: 58.5-63.4* *- Mean duration of disease (years ±SD) : 4.3 (2.5)-4.4 (2.8)* *-Extend of disease: 36.6-41.5% left sided colitis and 58.5-63.4% pancolitis* *- total Mayo score (±SD):* *- previous treatments: 0% previous TNFi treated* *-% using glucocorticoid: 51.2-53.7%* *-% using immunosuppressants 29.3-31.7%:*
Primary and secondary endpoints	*The primary end point was a clinical response at week 8. Secondary end points were clinical response or clinical remission with discontinuation of corticosteroids at week 30, clinical remission and mucosal healing at weeks 8 and 30, and clinical response at week 8 in patients with a medical history of disease refractory to corticosteroids.* *The primary efficacy end point was remission (a total Mayo score of ≤2, with no*

	subscore >1 and a rectal bleeding subscore of 0) at 8 weeks. The key secondary end point was mucosal healing (a Mayo endoscopic subscore of ≤1) at 8 weeks. Additionally secondary endpoints at week 8 included clinical response, endoscopic remission as well as symptomatic remission and deep remission. HRQoL outcomes included IBDQ change and remission at week 8.
Method of analysis	*All efficacy analyses used intention-to-treat methods.* *Safety comparisons were performed using the Fisher exact test and were based on the combination of the 2 groups receiving infliximab as compared with the placebo group.* *Patients who received prohibited drug because of lack of efficacy or loss of response to the study drug, who discontinued the study drug because of lack of efficacy, or who underwent a colectomy or ostomy were not considered to have had a clinical response, to be in clinical remission, or to have had mucosal healing from the time of the event onward, regardless of their Mayo score. In addition, patients with insufficient data for the assessment of response were not considered to have had a clinical response, to be in clinical remission, or to have had mucosal healing at that visit* *A 2-sided Cochran-Mantel-Haenszel X^2 test, at a significance level of 0.05, stratified according to the corticosteroid-refractory status and the location of the study center, was used to compare dichotomous end points (ie, clinical response, clinical remission, mucosal healing, and clinical remission with discontinuation of corticosteroids) among the treatment groups.*
Subgroup analyses	NA

9.3 Results per study

Table A3a Results of study <OCTAVE INDUCTION 1, bio-naïve population>

Trial name:	*OCTAVE Induction 1*									
NCT number:	*NCT01465763*									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (responders/non responders (n)	Difference (%)	95% CI	*P* value	Risk ratio	95% CI	*P* value	
*Clinical remission week 8** *(central/local*)*	Tofacitinib 10 mg BID Ctl	222 57	56/166 72/151 9/48 11/46	9.4 12.7	-2.5 – 32.1 -1.1 – 36.9		1.598 1.657	0.842-3.033 0.942-2.914		**Central and local : indicates central read endoscopy and local read endoscopy respectively* Remission defined as a total Mayo score of ≤2, no subscore >1 and a rectal bleeding subscore of 0
*steroid free remission week 52**	NA NA	NA NA	NA NA	NA	NA		NA	NA		*See OCTAVE Sustain*
Serious adverse events week 8	Tofacitinib 10 mg BID Ctl	222 57	NA NA	NA	NA		NA	NA		*Published data not available for subgroup of bio-naïve patients.*

Mucosal healing week 8 (central/local)	Tofacitinib 10 mg BID Ctl	222 57	71/151 112/110 9/48 21/36	13.3 13.6	-1.4- 36.7 -1.8- 35.8	1.505 1.369	0.947-2.395 0.952-1.971	
Mucosal healing week 52	NA NA	NA NA	NA NA	NA	NA	NA	NA	*See OCTAVE Sustain*
IBDQ remission Week 52	NA NA	NA NA	NA NA	NA	NA	NA	NA	*See OCTAVE Sustain*
IBDQ change Week 52	NA NA	NA NA	NA	NA	NA	NA	NA	*See OCTAVE Sustain*

Table A3b. Results of study <OCTAVE INDUCTION 1, bio-experienced population>

Trial name:	*OCTAVE Induction 1*									
NCT number:	*NCT01465763*									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result Responders/non-responders (n)	Difference	95% CI	*P* value	Risk ratio	95% CI	*P* value	
Clinical remission week 8 *(central/local*)*	Tofacitinib 10 mg BID	254	32/222 47/207	11.1 13.9	0.2- 89.0 1.3- 52.9		8.189 4.009	1.140-58.818 1.289-12.472		**Central and local : indicates central read endoscopy and local read endoscopy respectively* Remission defined as a total Mayo score of ≤2, no subscore >1 and a rectal bleeding subscore of 0
	Ctl	65	1/64 3/62							
steroid free remission week 52	NA	NA	NA	NA	NA	NA	NA	NA		*See OCTAVE Sustain*
	NA	NA	NA							
Serious adverse events week 8	Tofacitinib 10 mg BID	254	NA	NA	NA		NA	NA		*Published data not available for subgroup of bio-experienced patients.*
	Ctl	65	NA							
Mucosal healing week 8 (central/local)	Tofacitinib 10 mg BID	254	61/193 90/164	17.9 24.7	2.9- 57.5 6.5- 62.0		3.903 3.290	1.473-10.339 1.603-6.754		
	Ctl	65	4/61 7/58							

Mucosal healing week 52	NA	NA	NA	NA	NA	NA	NA	NA	NA	*See OCTAVE Sustain*
IBDQ remission Week 52	NA	NA	NA	NA	NA	NA	NA	NA	NA	*See OCTAVE Sustain*
IBDQ change Week 52	NA	NA	NA	NA	NA		NA	NA	NA	*See OCTAVE Sustain*

Table A3c. Results of study <OCTAVE INDUCTION 1, bio-naïve and bio-experienced population combined>

Trial name:	*OCTAVE Induction 1*									
NCT number:	*NCT01465763*									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result Responders/non-responders (n)	Difference	95% CI	*P* value	Risk ratio	95% CI	*P* value	
Clinical remission week 8 (central/local)*	Tofacitinib 10 mg BID	476	88/388 118/358	10.3 13.3	(1.7-26.3) (3.3-30.1)		2.255 2.160	(1.210-4.206) (1.288-3.623)		**Central and local : indicates central read endoscopy and local read endoscopy respectively* Remission defined as a total Mayo score of ≤2, no subscore >1 and a rectal bleeding subscore of 0
	Ctl	122	10/112 14/108							
steroid free remission week 52	NA	NA	NA	NA	NA	NA	NA	NA		*See OCTAVE Sustain*
	NA	NA	NA							

Serious adverse events week 8	Tofacitinib 10 mg BID Ctl	476 122	16/460 5/117	-0.7	(-2.8-4.9)		0.820	(0.306-2.195)		
Mucosal healing week 8 (central/local)	Tofacitinib 10 mg BID Ctl	476 122	149/327 202/274 19/103 28/94	15.7 19.5	(4.7-32.7) (7.2-36.8)		2.010 1.849	(1.302-3.102) (1.314-2.602)		
Mucosal healing week 52	NA NA	NA NA	NA NA	NA	NA	NA	NA	NA	NA	*See OCTAVE Sustain*
IBDQ remission Week 52	NA NA	NA NA	NA NA	NA	NA	NA	NA	NA	NA	*See OCTAVE Sustain*
IBDQ change Week 52	NA	NA	NA	NA	NA		NA	NA	NA	*See OCTAVE Sustain*

Table A3d Results of study <OCTAVE INDUCTION 2, bio-naïve population>

Trial name:	*OCTAVE Induction 2*									
NCT number:	*NCT01458951*									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result Responders/non-responders (n)	Difference	95% CI	*P* value	Risk ratio	95% CI	*P* value	
Clinical remission week 8 (central/local)*	Tofacitinib 10 mg BID Ctl	195 47	43/152 57/138 4/43 3/44	13.5. 22.8	-0.2- 49.8 3.2- 82.9		2.591 4.579	0.978-6.861 1.499-13.986		**Central and local : indicates central read endoscopy and local read endoscopy respectively* *Remission defined as a total Mayo score of ≤2, no subscore >1 and a rectal bleeding subscore of 0
*steroid free remission week 52**	NA NA	NA NA	NA NA	NA	NA		NA	NA		
Serious adverse events week 8	Tofacitinib 10 mg BID Ctl	195 47	NA NA	NA	NA		NA	NA		*Published data not available for subgroup of bio-experienced patients.*
Mucosal healing week 8 (central/local)	Tofacitinib 10 mg BID Ctl	195 47	71/124 87/108 9/38 9/38	17.3 25.5	0.5- 48.3 5.1- 62.8		1.901 2.330	1.027-3.521 1.269-4.279		

Mucosal healing week 52	NA NA	NA		NA	NA		NA	NA		
IBDQ remission Week 52	NA	NA		NA	NA		NA	NA		
IBDQ change Week 52	NA	NA		NA	NA		NA	NA		

Table A3e Results of study <OCTAVE INDUCTION 2, bio-experienced population>

Trial name:	*OCTAVE Induction 2*									
NCT number:	*NCT01458951*									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result Responders/non-responders (n)	Difference	95% CI	*P* value	Risk ratio	95% CI	*P* value	
*Clinical remission week 8** *(central/local**)*	Tofacitinib 10 mg BID	234	28/206 33/201	NA# 9.5	NA# -0.1- 39.9		16.009 3.056	0.991-258.727 0.968-9.646		*Remission defined as a total Mayo score of ≤2, no subscore >1 and a rectal bleeding subscore of 0. **Central and local : indicates central read endoscopy and local read endoscopy respectively #NB: for central read, data are calculated in SAS due to 0 events in placebo. Absolute
	Ctl	65	0/65 3/62							

									difference can not be calculated from RR. The direct calculation of difference between the two groups is however 12% with 95% CI of 7.8-16.1
*steroid free remission week 52**	NA NA	NA NA	NA NA	NA	NA	NA	NA	NA	
Serious adverse events week 8	Tofacitinib 10 mg BID Ctl	234 65	NA NA	NA	NA	NA	NA	NA	*Published data not available for subgroup of bio-naïve patients.*
Mucosal healing week 8 (central/local)	Tofacitinib 10 mg BID Ctl	234 65	51/183 69/165 4/61 8/57	15.6 17.2	2.0- 51.9 2.7- 45.8		3.542 2.369	1.329-9.436 1.216-4.722	
Mucosal healing week 52	NA NA	NA NA	NA NA	NA	NA		NA	NA	
IBDQ remission Week 52	NA NA	NA NA	NA NA	NA	NA		NA	NA	
IBDQ change Week 52	NA	NA	NA	NA	NA		NA	NA	

Table A3f Results of study <OCTAVE INDUCTION 2, bio-naïve and bio-experienced populations combined>

Trial name:	*OCTAVE Induction 2*									
NCT number:	*NCT01458951*									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result Responders/non-responders (n)	Difference	95% CI	*P* value	Risk ratio	95% CI	*P* value	
Clinical remission week 8 (central/local)*	Tofacitinib 10 mg BID Ctl	429 112	72/357 90/339 4/108 6/106	13.0 15.6	2.6-40.8 4.1-41.3		4.634 3.916	1.730-12.416 1.760-8.714		**Central and local : indicates central read endoscopy and local read endoscopy respectively* Remission defined as a total Mayo score of ≤2, no subscore >1 and a rectal bleeding subscore of 0
steroid free remission week 52	NA NA	NA NA	NA NA	NA	NA	NA	NA	NA		
Serious adverse events week 8	Tofacitinib 10 mg BID Ctl	429 112	18/411 9/103	-3.8	-6.1-1.1		0.522	0.241-1.131		
Mucosal healing week 8 (central/local)	Tofacitinib 10 mg BID Ctl	254 65	61/193 90/164 4/61 7/58	16.8 21.2	5.1-36.8 7.9-42.2		2.450 2.396	1.438-4.174 1.519-3.777		

Mucosal healing week 52	NA NA	NA NA	NA NA	NA	NA	NA	NA	NA	NA	
IBDQ remission Week 52	NA NA	NA NA	NA NA	NA	NA	NA	NA	NA	NA	
IBDQ change Week 52	NA	NA	NA	NA	NA		NA	NA	NA	

Table A3g Results of study <OCTAVE SUSTAIN, bio-naïve population>

Trial name:	*OCTAVE Sustain**									
NCT number:	*NCT01458574*									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result Response/non-response	Difference	95% CI	*P* value	Risk ratio	95% CI	*P* value	
Clinical remission week 8	Tofacitinib 5 mg BID placebo	NA NA	NA NA	NA	NA		NA	NA		** Remission defined as a total Mayo score of ≤2, no subscore >1 and a rectal bleeding subscore of 0.*
Steroid free remission week 52 Central/local	Tofacitinib 5 mg BID placebo	93 89	NA NA	NA	NA		NA	NA		*Published data not available for subgroup of bio-naïve patients.*

Serious adverse events week 52	Tofacitinib 5 mg BID placebo	108 106	NA NA		NA	NA		NA	NA	*Published data not available for subgroup of bio-naïve patients.*
Mucosal healing week 8	Tofacitinib 5 mg BID placebo	NA NA	NA NA		NA	NA	NA	NA	NA	NA	
Mucosal healing week 52	Tofacitinib 5 mg BID placebo	93 89	38/55 47/46 11/78 12/77		28.5 37.1	10.0- 62.5 15.3-75.3		3.306 3.748	1.806-6.053 2.134-6.584	
IBDQ remission Week 52	Tofacitinib 5 mg BID placebo	93 89	NA NA		NA	NA		NA	NA	
IBDQ mean change from baseline week 8 (OCTAVE Induction)	Tofacitinib 10 mg BID (Induction 1 / Induction 2) Placebo (Induction 1 / Induction 2)	205 183 57 43	NA NA		NA			NA		

Table A3h Results of study <OCTAVE SUSTAIN, bio-experienced population>

Trial name:	*OCTAVE Sustain**									
NCT number:	*NCT01458574*									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Results Response/non-response (n)	Difference	95% CI	*P* value	Risk ratio	95% CI	*P* value	
Clinical remission week 8	Tofacitinib 5 mg BID	NA	NA	NA	NA		NA	NA		
	placebo	NA	NA							
Steroid free remission week 52 Central/local*	Tofacitinib 5 mg BID	83	NA	NA	NA		NA	NA		*Published data not available for subgroup of bio-experienced patients.*
	placebo	85	NA							
Serious adverse events week 52	Tofacitinib 5 mg BID	90	NA	NA	NA		NA	NA		*Published data not available for subgroup of bio-experienced patients.*
	placebo	92	10/82							
Mucosal healing week 8	Tofacitinib 5 mg BID	NA	NA	NA	NA	NA	NA	NA	NA	
	placebo	NA	NA							
Mucosal healing week 52	Tofacitinib 5 mg BID	83	25/58 32/51	17.2 24.4	2.9- 44.3 7.2- 55.5		2.327 2.731	1.226-4.420 1.513-4.929		
	placebo	85	11/74 12/73							

IBDQ remission Week 52	Tofacitinib 5 mg BID	83	NA		NA	NA		NA	NA	
	placebo	85	NA							
IBDQ mean change from baseline week 8 (OCTAVE Induction)	Tofacitinib 10 mg BID (Induction 1 / Induction 2)	241 218		NA	NA			NA		
	placebo (Induction 1/Induction 2)	62 56		NA						

*OCTAVE Sustain examined the effect of tofacitinib as maintenance therapy (efficacy evaluated at 52 weeks) in patients with clinical response to 8 week induction treatment (studied in OCTAVE Induction 1 and 2).

Table A3i Results of study <OCTAVE SUSTAIN, bio-naïve and bio-experienced populations combined>

Trial name:	*OCTAVE Sustain**								
NCT number:	*NCT01458574*								
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Results Response/non-response (n)	Difference	95% CI	*P* value	Risk ratio	95% CI	*P* value	
Clinical remission week 8	Tofacitinib 5 mg BID	NA	NA	NA	NA		NA	NA		
	placebo	NA	NA							

Steroid free remission week 52 Central/local	Tofacitinib 5 mg BID placebo	101 101	28/73 33/68 11/90 14/87	16.8 18.8	(3.7-41.7) (4.8-43.4)		2.545 2.357	(1.341-4.830) (1.345-4.131)		
Serious adverse events week 52	Tofacitinib 5 mg BID placebo	198 198	10/188 13/185	-1.5	(-4.3-4.7)		0.769	(0.345-1.713)		
Mucosal healing week 8	Tofacitinib 5 mg BID placebo	NA NA	NA NA	NA	NA	NA	NA	NA	NA	
Mucosal healing week 52	Tofacitinib 5 mg BID placebo	83 85	25/58 32/51 11/74 12/73	23.2 31.1	(10.5-42.8) (16.1-53.6)		2.831 3.254	(1.827-4.386) (2.168-4.884)		
IBDQ remission Week 52	Tofacitinib 5 mg BID placebo	83 85	34/49 16/69	27.8	(14.9-45.4)		2.375	(1.738-3.246)		
IBDQ mean change from baseline week 8 (OCTAVE Induction)	Tofacitinib 10 mg BID (Induction 1 / Induction 2) placebo (Induction 1/Induction 2)	446 401 119 99	40.7 (38.6-44.5) 44.6 (40.6-46.9) 21.0 (16.6-28.2) 25.0 (17.6-30.1)	19.7 19.6	(13.3-26.2) (12.7-26.5)		NA			Data were not available for change from initiation of induction to end of maintenance (week 52). Patients entering OCTAVE Sustain were responders to induction. Analysis showed only a minor further improvement in IBDQ (3.7 points) from week 8 in induction to week 52 maintenance in the 5 mg BID group. Therefore, the data on IBDQ change included in this analysis is from OCTAVE Induction 1 and 2 (change from baseline to 8 weeks), i.e. the populations described in tables A3a-f.

*OCTAVE Sustain examined the effect of tofacitinib as maintenance therapy (efficacy evaluated at 52 weeks) in patients with clinical response to 8 week induction treatment (studied in OCTAVE Induction 1 and 2).

Table A3j Results of study <ACT 1 bio-naïve population>

Trial name:	*ACT 1*									
NCT number:	*NCT00036439*									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Response/non response	Difference	95% CI	*P* value	Risk ratio	95% CI	*P* value	
% Clinical remission week 8	placebo	121	18/103	24.0	9.1- 48.0		2.611	1.614-4.225		*Clinical remission defined as MSC of ≤2 and no subscore >1.* *Local read endoscopy*
	Infliximab	121	47/74							
steroid free remission week 54	Placebo	79	7/72	16.9	2.6- 49.0		2.902	1.289-6.534		
	Infliximab	70	18/52							
Serious adverse events week 54	Placebo	121	31/90	-4.1	-12.0-8.3		0.830	0.531-1.324		
	Infliximab	121	26/95							
Mucosal healing week 8	Placebo	121	41/80	28.1	12.7-48.6		1.829	1.375-2.433		
	Infliximab	121	75/46							
Mucosal healing week 54	Placebo	121	22/99	27.3	11.5- 51.4		2.500	1.634-3.826		
	Infliximab	121	55/66							

IBDQ remission Week 54	Placebo	NA	NA	NA	NA	NA	NA	NA		
	Infliximab	NA	NA							
IBDQ mean change from baseline week 54	Placebo	121	13 (6;18)	20	11.56-28.44	0.0000	NA	NA	Determined from graph. Number of ptts only provided for combined ACT1+2 group but refers back to previous publication	
	Infliximab	121	33 (26;38)							

Table A3k Results of study <ACT 2 bio-naïve population>

Trial name:	*ACT 2*								
NCT number:	*NCT00096655*								
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result Response/non-response	Difference	95% CI	*P* value	Risk ratio	95% CI	*P* value	
Clinical remission week 8	placebo	123	7/116	28.2	10.1- 66.9		5.954	2.781-12.747		**Clinical remission defined as MSC of ≤2 and no subscore >1.*
	Infliximab	121	41/80							
steroid free remission week 30	Placebo	60	2/58	15.0	0.9- 75.9		5.500	1.273-23.767		*All patients continue in long term regardless of response in induction*
	Infliximab	60	11/49							

Serious adverse events week 30	Placebo	123	24/99	-8.8	-13.8-0.6		0.551	0.294-1.030	
	Infliximab	121	13/108						
Mucosal healing week 8	Placebo	123	38/85	29.4	13.7- 50.6		1.953	1.445-2.639	
	Infliximab	121	73/48						
Mucosal healing week 30	Placebo	123	37/86	16.2	3.2- 34.3		1.539	1.105-2.142	
	Infliximab	121	56/65						
IBDQ remission week 30	Placebo	NA	NA	NA	NA		NA	NA	
	Infliximab	NA	NA						
IBDQ mean change from baseline week 30	Placebo	123	18 (11;23)	14	5.20-22.80	0.0019	NA	NA	data read from graph in Feagan et al 2007
	Infliximab	121	32 (24;37)						

Table A3l Results of study <Kobayashi bio-naïve population>

Trial name:	*Kobayashi*									
NCT number:	*NA*									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result Response/non-response	Difference	95% CI	*P* value	Risk ratio	95% CI	*P* value	
Clinical remission week 8	placebo	104	11/93	9.6	-0.3-29.2		1.909	0.970-3.757		
	Infliximab	104	21/83							
steroid free remission week 52	Placebo		NA	NA	NA	NA	NA	NA	NA	
	Infliximab		NA							
Serious adverse events week 14	Placebo	104	13/91	-3.8	-8.6-6.9		0.692	0.309-1.549		
	Infliximab	104	*9/95*							
Serious adverse events week 38	Placebo	104	19/85	-1.0	-8.6-12.8		0.947	0.528-1.7		
	Infliximab	104	18/86							
Mucosal healing week 8	Placebo	104	29/75	18.3	3.9- 39.1		1.655	1.141-2.402		
	Infliximab	104	48/56							

Mucosal healing week 30	Placebo	104	30/74		12.5	-0.5-31.5		1.433	0.981-2.094	
	Infliximab	104	43/61							
IBDQ remission week 38	Placebo	NA	NA		NA	NA		NA	NA	
	Infliximab	NA	NA							
IBDQ mean change from baseline week 38	Placebo	NA		NA	NA	NA		NA	NA	
	Infliximab	NA		NA						

Table A3m Results of study <UC-SUCCESS bio-naïve population>

Trial name:	*UC SUCCESS*									
NCT number:	*NCT00537316*									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result Responders/non-responders	Difference	95% CI	*P* value	Risk ratio	95% CI	*P* value	
Clinical remission week 8	placebo	NA	NA	NA	NA	NA	NA	NA	NA	
	Infliximab	NA	NA							
steroid free remission week 16	Placebo	76	18/58	-1.6	-11.4- 15.8		0.932	0.521-1.669		
	Infliximab	77	17/60							

Serious adverse events week 16	Placebo	79	6/73		-7.7	-7.6-2.7		0.078	0.005-1.36	*Calculated in SAS due to 0 events*
	Infliximab	78	0/78							
Mucosal healing week 8	Placebo	76	42/35		17.7	1.3- 41.2		1.481	1.035-2.118	
	Infliximab	77	28/48							
Mucosal healing week 52	Placebo	NA	NA		NA	NA	NA	NA	NA	
	Infliximab	NA	NA							
IBDQ remission Week 16	Placebo	NA	NA		NA	NA		NA	NA	
	Infliximab	NA	NA							
IBDQ mean change from baseline week 16	Placebo	53		32.5	NA	NA		NA	NA	Missing SD/SE and CI for the mean
	Infliximab	58		38.55						

Table A3n Results of study <Jiang, bio-naïve population>

Trial name:	*Jiang*									
NCT number:	*NA*									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result Response/non-response	Difference	95% CI	*P* value	Risk ratio	95% CI	*P* value	
Clinical remission week 8	placebo	41	9/32	31.7	10.7-49.1		2.444	1.284-4.652		
	Infliximab	41	22/19							
steroid free remission week 30	Placebo	21	1/20	35.9	10.3-56.7		8.591	1.189-62.072		
	Infliximab	22	9/13							
Serious adverse events week 8	Placebo	NA	NA	NA		NA	NA	NA		
	Infliximab	NA	NA							
Serious adverse events week 30	Placebo	41	4/37	-2.4	-16.1-11.0		0.750	0.179-3.143		
	Infliximab	41	3/38							
Mucosal healing week 8	Placebo	41	10/31	34.1	12.8-51.5		2.400	1.321-4.362		
	Infliximab	41	24/17							

Mucosal healing week 30	Placebo	41	9/32	31.7	10.7-49.1	2.444	1.284-4.652	
	Infliximab	41	22/19					
IBDQ remission week 30	Placebo	NA	NA	NA	NA	NA	NA	
	Infliximab	NA	NA					
IBDQ mean change from baseline week 30	Placebo	NA	NA	NA	NA	NA	NA	
	Infliximab	NA	NA					

Table A3o Results of study <GEMINI 1, bio-naïve population>

Trial name:	*GEMINI 1*									
NCT number:	*NCT00783718*									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result Response/non-response	Difference	95% CI	*P* value	Risk ratio	95% CI	*P* value	
Clinical remission week 6	placebo	76	5/71	16.5	2.8- 50.4		3.508	1.421-8.658		**Clinical remission defined as MSC of ≤2 and no subscore >1.* *Note: unadjusted RR and absolute difference is provided*
	Vedolizumab	130	30/100							
steroid free remission week 52	placebo	43	8 /35	17.3	-1.7-57.6		1.929	0.908-4.096		*Note: unadjusted RR and absolute difference is provided*
	Vedolizumab	39	14/25							

Serious adverse events week 8	Placebo Vedolizumab	79 388	8/68 11/377	-7.7	-9.3- -3.7	0.269	0.112-0.647	*Includes both cohort 1 and 2*
Serious adverse events week 52	Placebo Vedolizumab	76 309	12/28	-6.7	-11- 1.2	0.574	0.306-1.075	*Includes both cohort 1 and 2 and both 4 weeks and 8 weeks dosing regimens*
Mucosal healing week 6	placebo Vedolizumab	76 130	19/57 64/66	24.2	7.1- 50.4	1.969	1.285-3.017	*Note: unadjusted RR and absolute difference is provided*
Mucosal healing week 52	placebo Vedolizumab	79 72	19/60 43/29	34.7	13.7-67.1	2.389	1.549-3.684	*Note: unadjusted RR and absolute difference is provided0.80 [0.71, 0.91]*
IBDQ remission week 52	placebo Vedolizumab	NA NA	NA NA	NA	NA NA	NA	NA	
IBDQ change from baseline week 52	placebo Vedolizumab	79		25.9	14.6-37.3	NA	NA	

Table A3p Results of study <GEMINI 1, bio-experienced population>

Trial name:	*GEMINI 1*									
NCT number:	*NCT00783718*									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result Response/non-response	Difference (adjusted difference)	95% CI	*P* value	Risk ratio	95% CI	*P* value	
*Clinical remission week 6**	placebo	63	2/61	6.6	-1.0-41.2		3.073	0.676-13.972		**Clinical remission defined as MSC of ≤2 and no subscore >1.* *Note: unadjusted RR and absolute difference is provided*
	Vedolizumab	82	8/74							
*steroid free remission week 52**	placebo	23	1/22	18.7	-1.4- 173.4		5.308	0.689- 40.874		*Note: unadjusted RR and absolute difference is provided*
	Vedolizumab	26	6/20							
Serious adverse events week 8	placebo	63	3/60	-0.8	-3.6-8.8		0.829	0.241-2.852		*Note: unadjusted RR and absolute difference is provided*
	Vedolizumab	304	12/292							
Serious adverse events week 52	placebo	63	7/56	5.4	-3.3-23.9		1.489	0.704-3.148		*Includes both cohort 1 and 2*
	Vedolizumab	266	44/222							
Mucosal healing week 6	placebo	63	13/50	9.9	-3.6- 34.0		1.477	0.824-2.65		*Note: unadjusted RR and absolute difference is provided*
	Vedolizumab	82	25/57							

Mucosal healing week 52	placebo	38	3/35	34.0	5.5- 123.0		5.302	1.693-16.608		*Note: unadjusted RR and absolute difference is provided*
	Vedolizumab	43	18/25							
IBDQ remission week 52	placebo	NA	NA	NA	NA	NA	NA	NA		
	Vedolizumab	NA	NA							
IBDQ change from baseline week 52	placebo			14.1	-2.5-30.7	ns	NA	NA	NA	
	Vedolizumab									

Table A3q Results of study <GEMINI 1, bio-naïve and bio-experienced populations combined>

Trial name:	*GEMINI 1*									
NCT number:	*NCT00783718*									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result Response/non-response	Difference (adjusted difference)	95% CI	*P* value	Risk ratio	95% CI	*P* value	
*Clinical remission week 6**	placebo	149	8/141	11.5	2.7-29.8		3.146	1.510-6.552		**Clinical remission defined as MSC of ≤2 and no subscore >1.* *Note: unadjusted RR and absolute difference is provided*
	Vedolizumab	225	38/187							
*steroid free remission week 52**	placebo	72	10/62	17.5	2.2-47.6		2.263	1.157-4.428		*Note: unadjusted RR and absolute difference is provided*
	Vedolizumab	70	22/48							

Serious adverse events week 8	placebo	149	10/139	-4.5	-5.9- -0.3		0.331	0.115-0.949		*Note: unadjusted RR and absolute difference is provided*
	Vedolizumab	225	5/220							
Serious adverse events week 52	placebo	126	20/106	-7.7	-11.9-0.9		0.516	0.252-1.059		
	Vedolizumab	122	10/112							
Mucosal healing week 6	placebo	149	37/112	16.1	4.8-31.5		1.647	1.195-2.269		*Note: unadjusted RR and absolute difference is provided*
	Vedolizumab	225	92/133							
Mucosal healing week 52	placebo	126	25/101	31.8	15.1-56.5		2.603	1.761-3.847		*Note: unadjusted RR and absolute difference is provided*
	Vedolizumab	122	63/59							
IBDQ remission week 52	placebo	NA	NA	NA	NA	NA	NA	NA		
	Vedolizumab	NA	NA							
IBDQ change from baseline week 52	placebo	126	27.3 (20.8-33.8)	21.1	11.8-30.4	ns	NA	NA	NA	
	Vedolizumab	122	48.4 (41.7-55.1)							

9.4 Results per PICO

What is the clinically added value of tofacitinib for bio-naïve patients with moderate to severe UC compared to infliximab and vedolizumab respectively?

Table A4a Results referring to <clinical question 1>

Results per outcome	*Attach forest plots and statistical results as a separate file.* *Results from the comparative analysis should be given in the table below, if possible.*							
		Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	Difference (%)	CI	*P* value	Risk ratio	CI	*P* value	
% Clinical remission week 6-8	OCTAVE 1+2 GEMINI 1 Central-local Local-local ACT 1+2 Central-local Local-local Sensitivity ACT1+2+Kobayashi Central-local Local-local Sensitivity ACT 1+2+Jiang	 -10.9 -7.0 -18.3 -12.5 -12.0 -5.7 -16.2 -8.8	 -18.8-11.7 -18.8-37.5 -29.5-10.9 -29.6-47.4 -22.7-11.5 -23.2-48.3 -27.9-8.1 -28.7-50.1		 0.527 0.698 0.496 0.657 0.619 0.819 0,584 0.773	 0.184-1.508 0.186-2.624 0.189-1.299 0.187-2.304 0.280-1.365 0.265-2.533 0.282-1.21 0.261-2.289	 0.233 0.595 0.153 0.512 0.234 0.729 0.148 0.642	Meta-analysis: Inverse variance method was used to combine results from 2 or more studies. Review Manager v5.3 was used for the calculation. 95% Confidence intervals were calculated in SAS or Review Manager v5.3. Indirect comparison: Bucher method was used with input from above meta-analysis. Absolute risk reduction (i) was calculated from Relative Risk (RR): ARR=(RR-1)*comparative event rate. The comparative event rate was determined from the published included comparator studies and were 23.1% for vedolizumab, 36.4% for infliximab, 31.5% and 38.9% for the Kobayashi and Jiang sensitivity analyses respectively. P-values are calculated using Chi-Square.

% Mucosal healing week 6 -8	OCTAVE 1+2 GEMINI 1 Central-local Local-local ACT 1+2 Central-local Local-local Sensitivity analysis ACT1+2+ Kobayashi Central-local Local-local ACT1+2+ UC SUCCESS Central-local Local-local Sensitivity analysis ACT1+2+ Jiang Central-local Local-local	 -8.2 -7.0 -8.1 -6.5 -5.9 -4.3 -4.7 -3.0 -9.4 -7.8	 -25.9-22.9 -27.5-32.9 -26.5-20.0 -29.6-33.7 -23.0-20.0 -26.2-33.0 -23.2-23.3 -26.6-37.5 -27.0-17.3 -30.1-30.6		 0.833 0.858 0.868 0.894 0.896 0.923 0.921 0.949 0.845 0.871	 0.473-1.466 0.441-1.669 0.567-1.327 0.516-1.551 0.594-1.352 0.538-1.585 0.610-1.391 0.553-1.630 0.556-1.285 0.505-1.504	 0.526 0.652 0.513 0.691 0.602 0.773 0.696 0.851 0.432 0.620	As above The comparative event rate was determined from the included and published comparator studies and were 49.2% for vedolizumab, 61.2% for infliximab, 59.6% for the sensitivity analysis with UC-success, 56.6% and 60.8% for Kobayashi and Jiang respectively.
% Mucosal healing week 52	OCTAVE SUSTAIN GEMINI 1 Central-local Local-local ACT 1+2 Central-local Local-local Sensitivity analysis ACT1+2+kobayashi Central-local Local-local Sensitivity analysis ACT1+2+kobayashi Central-local Local-local	 22.9 34.0 33.1 43.7 40.5 51.9 30.3 40.6	 -20.4-114.2 -13.7-131.0 -9.2-124.3 -3.0-141.0 -1.6-123.9 6.0-139.6 -8.6-108.7 -1.9-123.4		 1.384 1.569 1.722 1.952 1.911 2.166 1.645 1.865	 0.658-2.912 0.771-3.193 0.799-3.710 0.936-4.073 0.965-3.784 1.135-4.137 0.816-3.314 0.959-3.626	 0.392 0.214 0.165 0.075 0.063 **0.019** 0.164 0.066	As above The comparative event rate was determined from the included and published comparator studies and were 59.7% for vedolizumab, 45.9% for infliximab, 44.5% and 47% for the Kobayashi and Jiang sensitivity analyses respectively

% IBDQ remission week52	OCTAVE SUSTAIN	NA	NA	NA	NA	NA	NA	
IBDQ change from baseline week 52	OCTAVE SUSTAIN GEMINI ACT 1+2	NA	NA	NA	NA	NA	NA	As above

What is the added clinical value of tofacitinib for bio-experienced patients with moderate to severe UC compared to infliximab and vedolizumab respectively?

Table A4b Results referring to <clinical question 2>

Results per outcome	*Attach forest plots and statistical results as a separate file.* *Results from the comparative analysis should be given in the table below, if possible.*							
		Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	Difference	CI	*P* value	Risk ratio	CI	*P* value	
% Clinical remission week 6-8 Central/local	OCTAVE 1+2 GEMINI 1 Central-local Local-local	 22.8 1.4	 -6.2-286.7 -7.8-52.3		 3.336 1.142	 0.366–30.388 0.205-6.357	 0.285 0.879	Meta-analysis: Inverse variance method was used to combine results from 2 or more studies. Review Manager v5.3 was used for the calculation. 95% Confidence intervals were calculated in SAS or Review Manager v5.3. Indirect comparison: Bucher method was used with input from above meta-analysis. Absolute risk reduction (ARR) was calculated from Relative Risk (RR): ARR=(RR-1)*comparative event rate. The comparative event rate was determined from the included and published comparator study and was

								9.8% for vedolizumab P-values are calculated using Chi-Square.
% Mucosal healing week 6 -8	OCTAVE 1+2 GEMINI 1 Central-local Local-local	46.3 26.9	0.6-159.4 -3.8-92.8		2.519 1.882	1.018-6.228 0.876-4.043	**0.046** 0.105	As above The comparative event rate was determined from the included and published comparator study and was 30.5% for vedolizumab
% Mucosal healing week 52	OCTAVE SUSTAIN GEMINI 1 Central-local Local-local	-23.5 -20.3	-36.9-26.2 -35.9-36.1		0.439 0.515	0.118-1.626 0.142-1.863	0.218 0.312	The comparative event rate was determined from the included and published comparator study and was 41.9% for vedolizumab
% IBDQ remission week 52	OCTAVE SUSTAIN	NA	NA	NA	NA	NA	NA	

What is the added clinical value of tofacitinib for bio-naïve and bio-experienced patients with moderate to severe UC compared to infliximab and vedolizumab respectively?

Table A4c Results referring to <clinical question 3>

Results per outcome	*Attach forest plots and statistical results as a separate file.* *Results from the comparative analysis should be given in the table below, if possible.*							
		Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	Difference (%)	CI	*P* value	Risk ratio	CI	*P* value	
% Clinical remission week 6-8	OCTAVE 1+2 GEMINI 1 Central-local Local-local ACT 1+2 Central-local Local-local	 -1.3 -2.5 -8.0 -10.2	 -11.1-25.5 -11.2-19.4 -26.4-44.4 -26.5-33.0		 0.925 0.852 0.780 0.718	 0.341-2.507 0.338-2.146 0.274-2.221 0.271-1.908	 0.878 0.734 0.642 0.507	Meta-analysis: Inverse variance method was used to combine results from 2 or more studies. Review Manager v5.3 was used for the calculation. 95% Confidence intervals were calculated in SAS or Review Manager v5.3. Indirect comparison: Bucher method was used with input from above meta-analysis. Absolute risk reduction (ARR) was calculated from Relative Risk (RR): ARR=(RR-1)*comparative event rate. The comparative event rate was determined from the published included comparator studies and were16.9% for vedolizumab and 36.4% for infliximab. P-values are calculated using Chi-Square.
% Steroid free remission week 52	OCTAVE SUSTAIN GEMINI 1 Central-local Local-local ACT 1+2 Central-local Local-local	 3.9 1.3 -5.5 -6.7	 -17.4-58.0 -17.8-47.1 -15.8-21.5 -16.0-16-2		 1.124 1.042 0.755 0.699	 0.445-2.845 0.434-2.498 0.290-1.964 0.283-1.728	 0.804 0.927 0.565 0.439	As above The comparative event rate was determined from the included and published comparator studies and were 31.4% for vedolizumab and 22.3% for infliximab.

% Serious adverse events week 8	OCTAVE 1+2 GEMINI 1	1.9	-1.0-11.8		1.872	0.556-6.309	0.311	As above The comparative event rate was determined from the included and published comparator studies and was 2.2% for vedolizumab.
% Serious adverse events week 52	OCTAVE Sustain GEMINI 1 ACT 1 and 2	4.0 1.1	-4.0-27.6 -9.1-26.0		1.490 1.068	0.509-4.364 0.436-2.615	0.467 0.885	The comparative event rate was determined from the included and published comparator studies and was 8.2% for vedolizumab and 16.1% for infliximab.
% Mucosal healing week 6 -8	OCTAVE 1+2 GEMINI 1 Central-local Local-local ACT 1+2 Central-local Local-local	 13.2 9.5 9.4 4.5	 -6.9-45.4 -7.8-36.0 -13.7-43.8 -14.6-31.6		 1.323 1.233 1.153 1.074	 0.830-2.110 0.808-1.881 0.775-1.716 0.761-1.517	 0.238 0.331 0.481 0.685	As above The comparative event rate was determined from the included and published comparator studies and was 40.9% for vedolizumab and 61.2% for infliximab.
% Mucosal healing week 52	OCTAVE SUSTAIN GEMINI 1 Central-local Local-local ACT 1+2 Central-local Local-local	 4.5 12.9 21.8 31.9	 -20.4-49.4 -14.9-61.8 -10.4-83.0 -4.2-99.1		 1.088 1.250 1.474 1.694	 0.605-1.956 0.712-2.197 0.774-2.808 0.909-3.161	 0.779 0.437 0.237 0.097	As above The comparative event rate was determined from the included and published comparator studies and was 51.6% for vedolizumab and 45.9% for infliximab.
% IBDQ remission week 52	OCTAVE SUSTAIN	NA	NA	NA	NA	NA	NA	
IBDQ change from baseline week 52	OCTAVE SUSTAIN GEMINI ACT 1+2	 -1.45 2.52	 -11.9-9.0 --5.2-10.2	 0.785 0.520	NA	NA	NA	As above

9.5 Meta-analyses & Forest plots

Meta- analysis

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

Forest plots

Below forest plots are list for all metaanalyses. Plots are drawn using Review Manager v5.3.

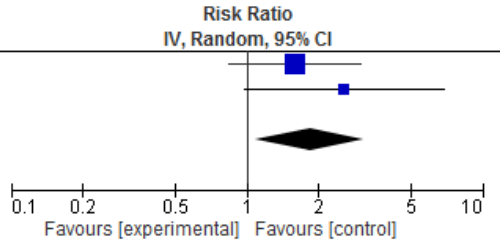
Table of content

TNF naïve patient population

Clinical remission week 8 - tofacitinib (central reading)

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
OCTAVE INDUCTION 1	56	222	9	57	69.8%	1.60 [0.84, 3.03]
OCTAVE INDUCTION 2	43	195	4	47	30.2%	2.59 [0.98, 6.86]
Total (95% CI)		**417**		**104**	**100.0%**	**1.85 [1.08, 3.16]**
Total events	99		13			

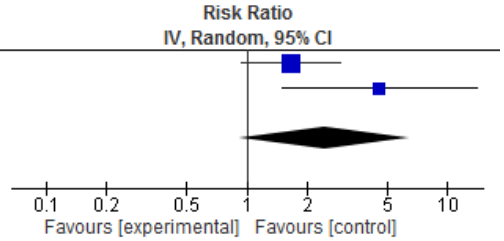
Heterogeneity: Tau² = 0.00; Chi² = 0.66, df = 1 (P = 0.42); I² = 0%
Test for overall effect: Z = 2.25 (P = 0.02)



Clinical remission week 8 - tofacitinib (local reading)

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
OCTAVE INDUCTION 1	71	222	11	57	61.7%	1.66 [0.94, 2.91]
OCTAVE INDUCTION 2	57	195	3	47	38.3%	4.58 [1.50, 13.99]
Total (95% CI)		**417**		**104**	**100.0%**	**2.45 [0.93, 6.44]**
Total events	128		14			

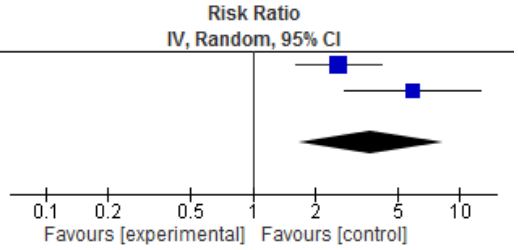
Heterogeneity: Tau² = 0.31; Chi² = 2.54, df = 1 (P = 0.11); I² = 61%
Test for overall effect: Z = 1.81 (P = 0.07)



Clinical remission week 8 infliximab (ACT 1 and 2)

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
ACT1	47	121	18	121	56.7%	2.61 [1.61, 4.23]
ACT2	41	121	7	123	43.3%	5.95 [2.78, 12.75]
Total (95% CI)		**242**		**244**	**100.0%**	**3.73 [1.68, 8.31]**
Total events	88		25			

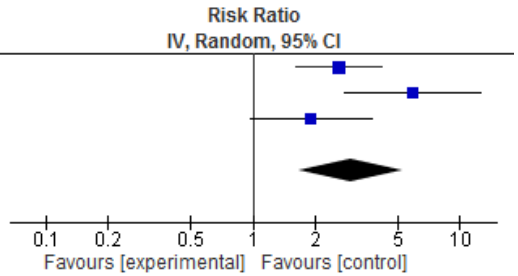
Heterogeneity: Tau² = 0.23; Chi² = 3.22, df = 1 (P = 0.07); I² = 69%
Test for overall effect: Z = 3.22 (P = 0.001)



Clinical remission week 8 infliximab incl Kobayashi (Japan)

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
ACT1	47	121	18	121	40.1%	2.61 [1.61, 4.23]
ACT2	41	121	7	123	28.4%	5.95 [2.78, 12.75]
JAPAN	21	104	11	104	31.6%	1.91 [0.97, 3.76]
Total (95% CI)		**346**		**348**	**100.0%**	**2.99 [1.67, 5.34]**
Total events	109		36			

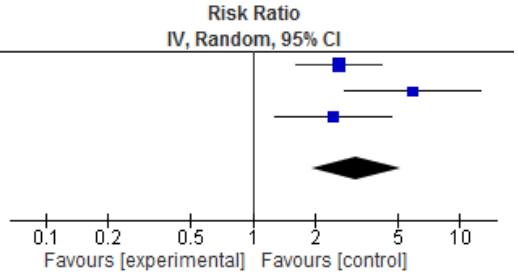
Heterogeneity: Tau² = 0.16; Chi² = 5.07, df = 2 (P = 0.08); I² = 61%
Test for overall effect: Z = 3.69 (P = 0.0002)



Clinical remission week 8 infliximab incl Jiang (KINA)

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
ACT1	47	121	18	121	41.9%	2.61 [1.61, 4.23]
ACT2	41	121	7	123	26.2%	5.95 [2.78, 12.75]
KINA	22	41	9	41	31.9%	2.44 [1.28, 4.65]
Total (95% CI)		**283**		**285**	**100.0%**	**3.17 [1.94, 5.20]**
Total events	110		34			

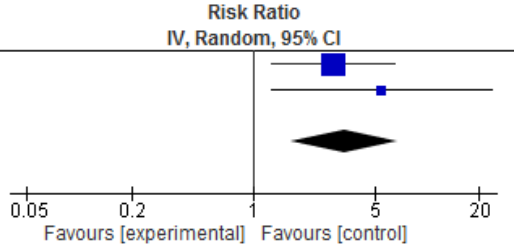
Heterogeneity: Tau² = 0.09; Chi² = 3.82, df = 2 (P = 0.15); I² = 48%
Test for overall effect: Z = 4.59 (P < 0.00001)



Steroid free remission week 30-54 infliximab (ACT 1 and 2)

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
ACT1	18	70	7	79	76.5%	2.90 [1.29, 6.53]
ACT2	11	60	2	60	23.5%	5.50 [1.27, 23.77]
Total (95% CI)		**130**		**139**	**100.0%**	**3.37 [1.66, 6.86]**
Total events	29		9			

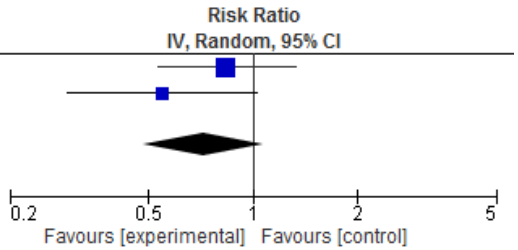
Heterogeneity: Tau² = 0.00; Chi² = 0.56, df = 1 (P = 0.45); I² = 0%
Test for overall effect: Z = 3.36 (P = 0.0008)



Serious adverse events (late) Infliximab

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
ACT1	26	121	31	121	63.6%	0.84 [0.53, 1.32]
ACT2	13	121	24	123	36.4%	0.55 [0.29, 1.03]
Total (95% CI)		**242**		**244**	**100.0%**	**0.72 [0.48, 1.07]**
Total events	39		55			

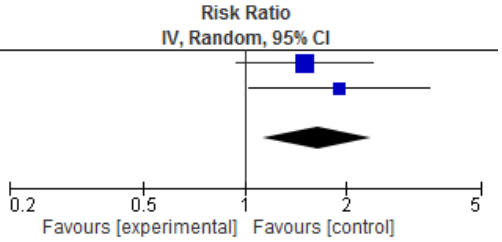
Heterogeneity: Tau² = 0.01; Chi² = 1.13, df = 1 (P = 0.29); I² = 12%
Test for overall effect: Z = 1.63 (P = 0.10)



Mucosal healing week 8 tofacitinib (central reading)

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
OCTAVE INDUCTION 1	88	222	15	57	63.8%	1.51 [0.95, 2.40]
OCTAVE INDUCTION 2	71	195	9	47	36.2%	1.90 [1.03, 3.52]
Total (95% CI)		**417**		**104**	**100.0%**	**1.64 [1.13, 2.37]**
Total events	159		24			

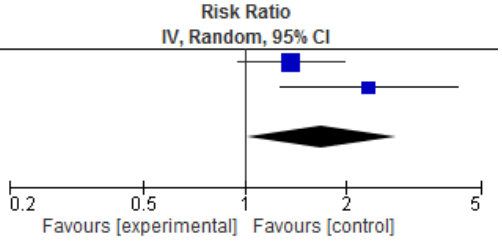
Heterogeneity: Tau² = 0.00; Chi² = 0.35, df = 1 (P = 0.55); I² = 0%
Test for overall effect: Z = 2.61 (P = 0.009)



Mucosal healing week 8 tofacitinib (local reading)

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
OCTAVE INDUCTION 1	112	222	21	57	60.9%	1.37 [0.95, 1.97]
OCTAVE INDUCTION 2	87	195	9	47	39.1%	2.33 [1.27, 4.28]
Total (95% CI)		**417**		**104**	**100.0%**	**1.69 [1.01, 2.80]**
Total events	199		30			

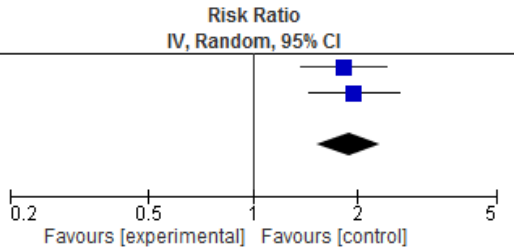
Heterogeneity: Tau² = 0.08; Chi² = 2.16, df = 1 (P = 0.14); I² = 54%
Test for overall effect: Z = 2.01 (P = 0.04)



Mucosal healing week 8 infliximab (ACT 1 and 2)

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
ACT1	75	121	41	121	52.7%	1.83 [1.38, 2.43]
ACT2	73	121	38	123	47.3%	1.95 [1.44, 2.64]
Total (95% CI)		**242**		**244**	**100.0%**	**1.89 [1.53, 2.32]**
Total events	148		79			

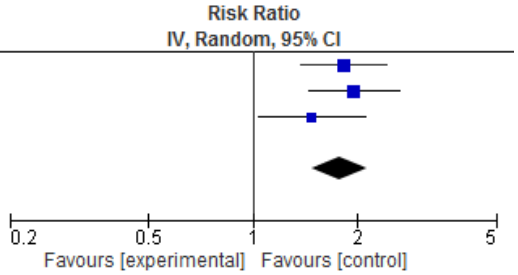
Heterogeneity: Tau² = 0.00; Chi² = 0.10, df = 1 (P = 0.76); I² = 0%
Test for overall effect: Z = 6.01 (P < 0.00001)



Mucosal healing week 8 infliximab INCL UC success

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
ACT1	75	121	41	121	39.5%	1.83 [1.38, 2.43]
ACT2	73	121	38	123	35.4%	1.95 [1.44, 2.64]
UCsuccess	42	77	28	76	25.1%	1.48 [1.03, 2.12]
Total (95% CI)		**319**		**320**	**100.0%**	**1.78 [1.48, 2.12]**
Total events	190		107			

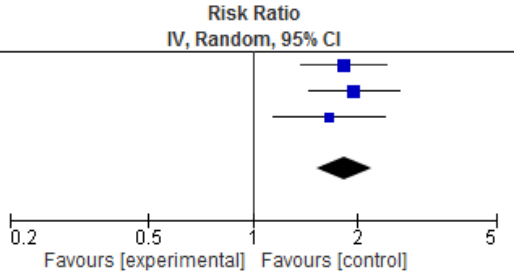
Heterogeneity: Tau² = 0.00; Chi² = 1.41, df = 2 (P = 0.49); I² = 0%
Test for overall effect: Z = 6.27 (P < 0.00001)



Mucosal healing week 8 infliximab INCL Kobayashi (JAPAN)

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
ACT1	75	121	41	121	40.2%	1.83 [1.38, 2.43]
ACT2	73	121	38	123	36.1%	1.95 [1.44, 2.64]
JAPAN	48	104	29	104	23.6%	1.66 [1.14, 2.40]
Total (95% CI)		**346**		**348**	**100.0%**	**1.83 [1.53, 2.19]**
Total events	196		108			

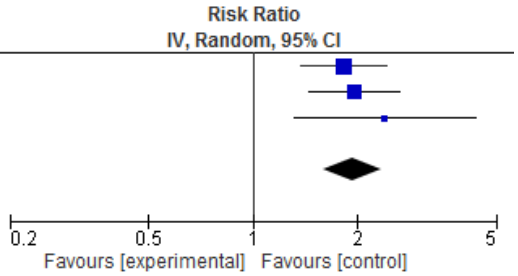
Heterogeneity: Tau² = 0.00; Chi² = 0.46, df = 2 (P = 0.80); I² = 0%
Test for overall effect: Z = 6.54 (P < 0.00001)



Mucosal healing week 8 Infliximab INCL Jiang (KINA)

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
ACT1	75	121	41	121	47.0%	1.83 [1.38, 2.43]
ACT2	73	121	38	123	42.2%	1.95 [1.44, 2.64]
KINA	24	41	10	41	10.7%	2.40 [1.32, 4.36]
Total (95% CI)		**283**		**285**	**100.0%**	**1.94 [1.59, 2.35]**
Total events	172		89			

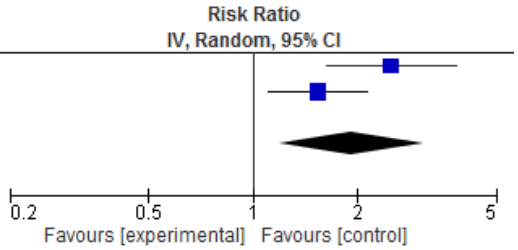
Heterogeneity: Tau² = 0.00; Chi² = 0.65, df = 2 (P = 0.72); I² = 0%
Test for overall effect: Z = 6.62 (P < 0.00001)



Mucosal healing week 30-54 infliximab (ACT 1 and 2)

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
ACT1	55	121	22	121	46.1%	2.50 [1.63, 3.83]
ACT2	56	121	37	123	53.9%	1.54 [1.11, 2.14]
Total (95% CI)		**242**		**244**	**100.0%**	**1.92 [1.20, 3.09]**
Total events	111		59			

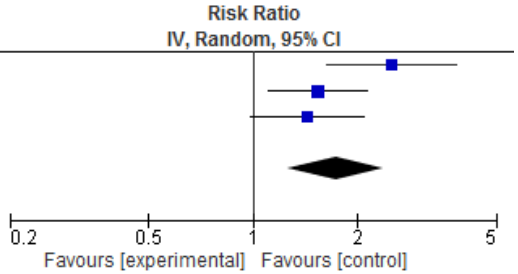
Heterogeneity: Tau² = 0.08; Chi² = 3.12, df = 1 (P = 0.08); I² = 68%
Test for overall effect: Z = 2.70 (P = 0.007)



Mucosal healing week 30-54 infliximab INCL Kobayashi (Japan)

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
ACT1	55	121	22	121	29.5%	2.50 [1.63, 3.83]
ACT2	56	121	37	123	37.3%	1.54 [1.11, 2.14]
JAPAN	43	104	30	104	33.2%	1.43 [0.98, 2.09]
Total (95% CI)		**346**		**348**	**100.0%**	**1.73 [1.26, 2.38]**
Total events	154		89			

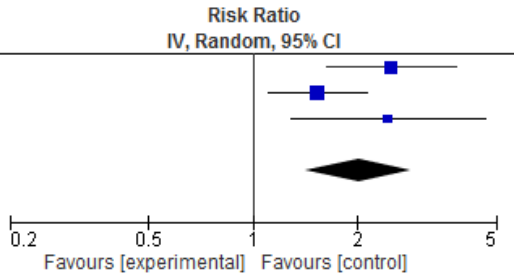
Heterogeneity: Tau² = 0.04; Chi² = 4.29, df = 2 (P = 0.12); I² = 53%
Test for overall effect: Z = 3.39 (P = 0.0007)



Mucosal healing week 30-54 infliximab INCL Jiang (KINA)

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
ACT1	55	121	22	121	35.0%	2.50 [1.63, 3.83]
ACT2	56	121	37	123	43.9%	1.54 [1.11, 2.14]
KINA	22	41	9	41	21.1%	2.44 [1.28, 4.65]
Total (95% CI)		**283**		**285**	**100.0%**	**2.01 [1.41, 2.86]**
Total events	133		68			

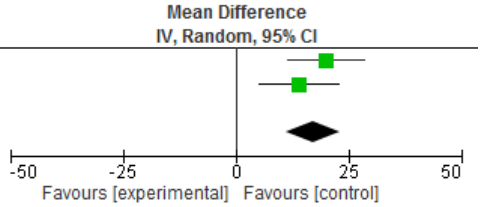
Heterogeneity: Tau² = 0.05; Chi² = 3.74, df = 2 (P = 0.15); I² = 47%
Test for overall effect: Z = 3.89 (P = 0.0001)



IBDQ change week 30-54 infliximab (ACT1 and 2)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
ACT1	33	33.33	121	13	33.33	121	52.1%	20.00 [11.60, 28.40]
ACT2	32	36.11	121	18	33.61	123	47.9%	14.00 [5.24, 22.76]
Total (95% CI)			**242**			**244**	**100.0%**	**17.13 [11.06, 23.19]**

Heterogeneity: Tau² = 0.00; Chi² = 0.94, df = 1 (P = 0.33); I² = 0%
Test for overall effect: Z = 5.54 (P < 0.00001)

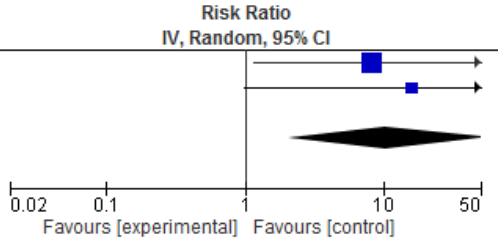


TNF experienced patients

Clinical remission week 8 - tofacitinib (central reading)

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
OCTAVE INDUCTION 1	32	254	1	65	66.6%	8.19 [1.14, 58.82]
OCTAVE INDUCTION 2	28	234	0	65	33.4%	16.01 [0.99, 258.73]
Total (95% CI)		**488**		**130**	**100.0%**	**10.25 [2.05, 51.19]**
Total events	60		1			

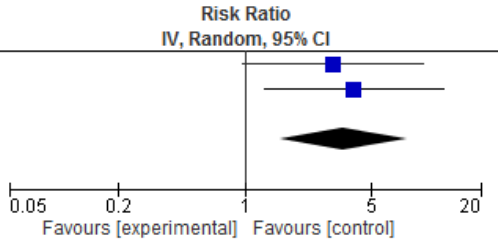
Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 1 (P = 0.70); I² = 0%
Test for overall effect: Z = 2.83 (P = 0.005)



Clinical remission week 8 - tofacitinib (local reading)

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
OCTAVE INDUCTION 2	33	234	3	65	49.4%	3.06 [0.97, 9.65]
OCTAVE INDUCTION 1	47	254	3	65	50.6%	4.01 [1.29, 12.47]
Total (95% CI)		**488**		**130**	**100.0%**	**3.51 [1.56, 7.86]**
Total events	80		6			

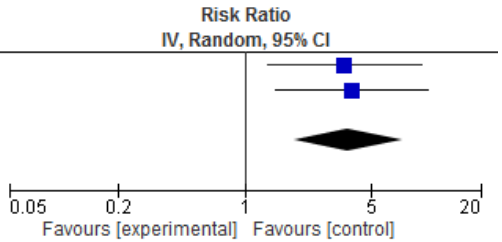
Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 1 (P = 0.74); I² = 0%
Test for overall effect: Z = 3.04 (P = 0.002)



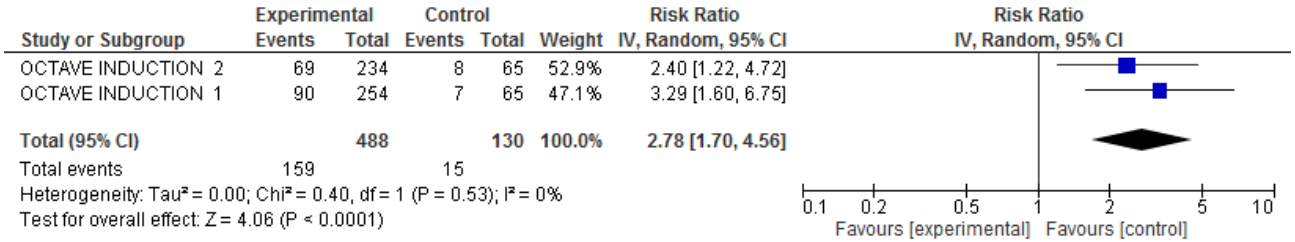
Mucosal healing week 8 tofacitinib (central reading)

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
OCTAVE INDUCTION 2	51	234	4	65	49.7%	3.54 [1.33, 9.44]
OCTAVE INDUCTION 1	61	254	4	65	50.3%	3.90 [1.47, 10.34]
Total (95% CI)		**488**		**130**	**100.0%**	**3.72 [1.86, 7.42]**
Total events	112		8			

Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.89); I² = 0%
Test for overall effect: Z = 3.73 (P = 0.0002)



Mucosal healing week 8 tofacitinib (local reading)

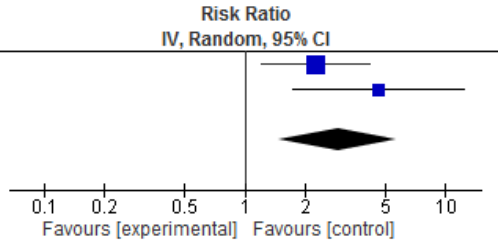


OVERALL POPULATION (excluded Infliximab)

Clinical remission week 8 - tofacitinib (central reading)

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
OCTAVE INDUCTION 1	88	476	10	122	64.6%	2.26 [1.21, 4.21]
OCTAVE INDUCTION 2	71	429	4	112	35.4%	4.63 [1.73, 12.42]
Total (95% CI)		**905**		**234**	**100.0%**	**2.91 [1.48, 5.71]**
Total events	159		14			

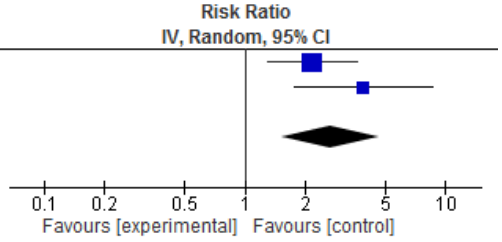
Heterogeneity: Tau² = 0.08; Chi² = 1.47, df = 1 (P = 0.23); I² = 32%
Test for overall effect: Z = 3.10 (P = 0.002)



Clinical remission week 8 - tofacitinib (local reading)

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
OCTAVE INDUCTION 1	118	476	14	122	63.7%	2.16 [1.29, 3.62]
OCTAVE INDUCTION 2	90	429	6	112	36.3%	3.92 [1.76, 8.71]
Total (95% CI)		**905**		**234**	**100.0%**	**2.68 [1.53, 4.70]**
Total events	208		20			

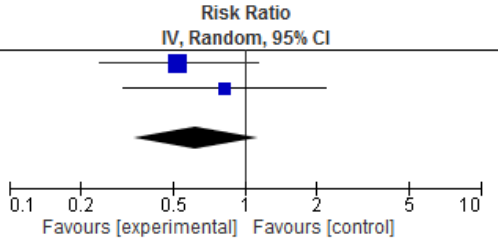
Heterogeneity: Tau² = 0.06; Chi² = 1.50, df = 1 (P = 0.22); I² = 33%
Test for overall effect: Z = 3.45 (P = 0.0006)



Serious adverse events week 8 - tofacitinib

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
OCTAVE INDUCTION 2	18	429	9	112	61.9%	0.52 [0.24, 1.13]
OCTAVE INDUCTION 1	16	476	5	122	38.1%	0.82 [0.31, 2.19]
Total (95% CI)		**905**		**234**	**100.0%**	**0.62 [0.34, 1.14]**
Total events	34		14			

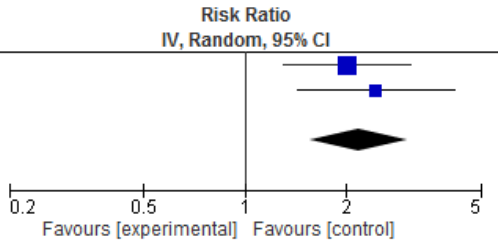
Heterogeneity: Tau² = 0.00; Chi² = 0.50, df = 1 (P = 0.48); I² = 0%
Test for overall effect: Z = 1.54 (P = 0.12)



Mucosal healing week 8 tofacitinib (central reading)

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
OCTAVE INDUCTION 1	149	476	19	122	60.1%	2.01 [1.30, 3.10]
OCTAVE INDUCTION 2	122	429	13	112	39.9%	2.45 [1.44, 4.17]
Total (95% CI)		**905**		**234**	**100.0%**	**2.18 [1.55, 3.05]**
Total events	271		32			

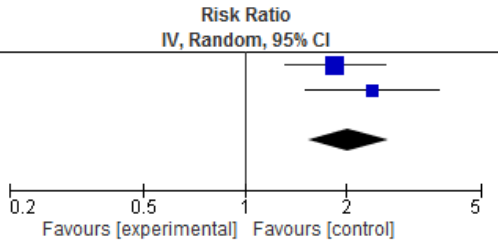
Heterogeneity: Tau² = 0.00; Chi² = 0.32, df = 1 (P = 0.57); I² = 0%
Test for overall effect: Z = 4.53 (P < 0.00001)



Mucosal healing week 8 tofacitinib (local reading)

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
OCTAVE INDUCTION 1	202	476	28	122	64.0%	1.85 [1.31, 2.60]
OCTAVE INDUCTION 2	156	429	17	112	36.0%	2.40 [1.52, 3.78]
Total (95% CI)		**905**		**234**	**100.0%**	**2.03 [1.54, 2.67]**
Total events	358		45			

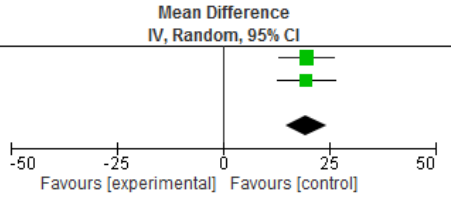
Heterogeneity: Tau² = 0.00; Chi² = 0.80, df = 1 (P = 0.37); I² = 0%
Test for overall effect: Z = 5.08 (P < 0.00001)



IBDQ change week 8 tofacitinib

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
OCTAVE INDUCTION 1	40.7	31.2557	446	21	31.9625	119	53.3%	19.70 [13.27, 26.13]
OCTAVE INDUCTION 2	44.6	32.04	401	25	31.0436	99	46.7%	19.60 [12.73, 26.47]
Total (95% CI)			**847**			**218**	**100.0%**	**19.65 [14.96, 24.35]**

Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.98); I² = 0%
Test for overall effect: Z = 8.20 (P < 0.00001)



Medicinrådet

Medicinrådets protokol for vurdering af klinisk merværdi for tofacitinib til behandling af colitis ulcerosa

Handelsnavn	Xeljanz
Generisk navn	Tofacitinib
Firma	Pfizer ApS
ATC-kode	L04AA29
Virkningsmekanisme	Janus kinase inhibitor
Administration/dosis	Tabletter 10 mg to gange dagligt i otte uger efterfulgt af 5 mg to gange dagligt.
EMA-indikation	Tofacitinib er indiceret til behandling af voksne patienter med moderat til alvorlig aktiv ulcerativ colitis (UC), der har haft et utilstrækkeligt respons, ophørt respons, eller har været intolerante over for enten konventionel behandling eller et biologisk lægemiddel.
Godkendelsesdato Offentliggørelsesdato Dokumentnummer Versionsnummer	24. oktober 2018 24. oktober 2018 25452 1.0

Indhold

Forkortelser

ARR:	Absolut risikoreduktion
CI:	Konfidensinterval
EMA:	Det Europæiske Lægemiddelagentur (*European Medicines Agency)*
EPAR:	*European public assessment report*
GRADE:	System til vurdering af evidens (*Grading of Recommendations Assessment, Development and Evaluation*)
ITT:	*Intention-to-treat*
i.v.:	Intravenøs
HR:	*Hazard ratio*
OR:	*Odds ratio*
ORR:	Objektiv responsrate
PICO:	Population, intervention, komparator og outcome
RADS:	Rådet for Anvendelse af Dyr Sygehusmedicin
RR:	Relativ risiko
SAE:	Alvorlig uønsket hændelse (*Serious Adverse Event)*
s.c.:	Subkutan
SD:	Standarddeviation
SMD:	Standardized Mean Difference
UC:	Colitis ulcerosa (*Ulcerative Colitis)*

1 Formål

Protokollen har til formål at definere de kliniske spørgsmål, der ønskes belyst i vurderingen af tofacitinib som mulig standardbehandling af patienter med colitis ulcerosa (UC). I protokollen angives en definition af populationer, komparatorer og effektmål, der skal præsenteres i den endelige ansøgning, samt de metoder der ønskes anvendt til den komparative analyse. Arbejdet med protokollen er igangsat på baggrund af den foreløbige ansøgning vedrørende tofacitinib modtaget den 22. juni 2018.

Protokollen danner grundlaget for den endelige ansøgning for vurderingen af den kliniske merværdi af tofacitinib sammenlignet med dansk standardbehandling. Alle effektmål, der er opgivet i denne protokol, skal besvares med en sammenlignende analyse mellem tofacitinib og komparator af både absolutte og relative værdier for de udspecificerede populationer i de angivne måleenheder (se tabel 1). Litteratursøgning og databehandling udføres som beskrevet i protokollen.

2 Baggrund

UC er en kronisk, inflammatorisk tarmsygdom med uspecifik inflammation i ende- og tyktarmens slimhinde. Sygdommen påvirker oftest/altid endetarmen og nedre dele af tyktarmen. Efter den første episode af UC oplever patienten ofte skiftende perioder med henholdsvis spontan remission, hvor sygdommen ikke giver symptomer, og tilbagefald.

Patienter med moderat til svær UC har symptomer i form af blodige diarréer og/eller afgang af blodigt slim per rektum ved/imellem defækationer [1,2].

Prævalensen af UC i Danmark er estimeret til ca. 35.000 personer, og incidensen er ca. 18,6 pr. år pr. 100.000 personer. Incidensen i Danmark er blandt den højeste i verden og er stigende [3,4].

2.1 Nuværende behandling

Ved kronisk aktiv UC kan biologisk behandling initieres, hvis sygdommen ikke bliver bragt i remission under streroidbehandling, hvis sygdommen recidiverer under aftrapning af steroidbehandling, hvis sygdommen ikke bliver holdt i remission med immunosuppressiv behandling (azathioprin, 6-mercaptopurin), og hvis kirurgi ikke er at foretrække [2].

Hos cirka en tredjedel af patienterne aftager effekten af den biologiske behandling, hvorefter dosis kan øges, eller intervallerne mellem behandling må afkortes. Ved ophør af behandlingsrespons kan patienterne i 25-35 % af tilfældene opnå en effekt ved at skifte til en anden biologisk behandling [2].

RADS har i 2016 ligestillet de biologiske lægemidler infliximab, golimumab og vedolizumab som 1. og 2. linjebehandling af UC ved bionaive og bioerfarne patienter, mens adalimumab kan overvejes som 3. linjebehandling [5]. Adalimumab, golimumab og infliximab er TNF-alfa hæmmere og vedolizumab er en integrinhæmmer.

2.2 Tofacitinib

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

Den anbefalede dosis er 10 mg to gange dagligt i otte uger efterfulgt af 5 mg to gange dagligt. Tofacitinib gives som en tablet, og patienten kan dermed selv administrere behandlingen.

3 Kliniske spørgsmål

De kliniske spørgsmål skal indeholde specifikation af patientgruppen, interventionen, alternativet/-erne til interventionen og effektmål.

3.1 Klinisk spørgsmål 1

1. *Hvad er den kliniske merværdi af tofacitinib til bionaive patienter med moderat til svær UC sammenlignet med henholdsvis infliximab og vedolizumab?*

Population
Bionaive patienter med moderat til svær UC, der er bionaive og opfylder kriterierne for biologisk behandling (jf. afsnit 2.1).

Intervention
Tofacitinib 10 mg to gange dagligt i otte uger efterfulgt af 5 mg to gange dagligt.

Komparator
Fagudvalget ønsker at sammenligne tofacitinib med to standardbehandlinger med forskellige virkningsmekanismer (en TNF-alfa hæmmer og en integrinhæmmer):

- Infliximab intravenøs (i.v.) infusion 5 mg/kg uge 0, 2 og 6, herefter hver 8. uge.
- Vedolizumab i.v. infusion 300 mg uge 0, 2 og 6, herefter 8. uge.

Effektmål
Kritiske og vigtige effektmål er oplistet i tabel 1.

3.2 Klinisk spørgsmål 2

1. *Hvad er den kliniske merværdi af tofacitinib til bioerfarne patienter med moderat til svær UC sammenlignet med henholdsvis infliximab og vedolizumab?*

Population
Bioerfarne patienter med moderat til svær UC, der opfylder kriterierne for biologisk behandling (jf. afsnit 2.1).

Intervention
Tofacitinib 10 mg to gange dagligt i otte uger efterfulgt af 5 mg to gange dagligt.

Komparator
Fagudvalget ønsker at sammenligne tofacitinib med to standardbehandlinger med forskellige virkningsmekanismer (en TNF-alfa hæmmer og en integrinhæmmer):

- Infliximab intravenøs (i.v.) infusion 5 mg/kg uge 0, 2 og 6, herefter hver 8. uge.
- Vedolizumab i.v. infusion 300 mg uge 0, 2 og 6, herefter 8. uge.

Effektmål
Kritiske og vigtige effektmål er oplistet i tabel 1.

3.3 Valg af effektmål

Tabel 1 summerer de valgte effektmål, deres vigtighed, mindste klinisk relevante forskel og kategori.
For alle effektmål ønskes både absolutte og relative værdier, jævnfør ansøgningsskemaet. For de relative værdier vurderes den klinisk relevans (merværdi), jævnfør væsentlighedskriterierne beskrevet i Medicinrådets metodehåndbog for vurdering af nye lægemidler. De relative effektestimater kan angives i

relativ risiko (RR), odds ratio (OR) eller hazard ratio (HR). Det skal begrundes i ansøgningen, hvis der afviges fra de ønskede effektmål.

Tabel 1. Oversigt over valgte effektmål. For hvert effektmål er angivet deres vigtighed. For kritiske og vigtige effektmål er desuden angivet den mindste klinisk relevante forskel samt indplacering i de fire kategorier (overlevelse, alvorlige symptomer og bivirkninger, livskvalitet og ikkealvorlige symptomer og bivirkninger).

Effektmål*	Vigtighed	Kategori	Måleenhed	Mindste klinisk relevante forskelle (absolutte værdier)
Klinisk remission, uge 8	Kritisk	Alvorlige symptomer og bivirkninger	Andel patienter med total Mayo score ≤ 2, ingen subscore > 1 og rektal blødning score = 0	Forskel på 10 procentpoint mellem grupperne
Steroidfri remission, uge 52	Kritisk	Alvorlige symptomer og bivirkninger	Andel patienter, der ikke er i steroidbehandling efter 52 uger og har en total Mayo score ≤ 2, ingen subscore > 1 og rektal blødning score = 0	Forskel på 10 procentpoint mellem grupperne
Alvorlige uønskede hændelser	Kritisk	Alvorlige symptomer og bivirkninger	Andel patienter der oplever en alvorlig uønsket hændelse	Forskel på 5 procentpoint
Mukosal heling, uge 8	Vigtig	Alvorlige symptomer og bivirkninger	Andel patienter med endoskopisk subscore ≤ 1	Forskel på 10 procentpoint mellem grupperne
Mukosal heling, uge 52	Vigtig	Alvorlige symptomer og bivirkninger	Andel patienter med endoskopisk subscore ≤ 1	Forskel på 10 procentpoint mellem grupperne
IBDQ	Vigtig	Helbredsrelateret livskvalitet	Andel patienter der opnår score ≥ 170	Forskel på 10 procentpoint mellem grupperne
			Ændring fra baseline	Forskel i ændring svarende til den validerede mindste klinisk relevante forskel (se nedenfor)

* For alle effektmål ønskes data med længst mulig opfølgningstid.

Fagudvalget ønsker at basere den samlede kliniske merværdi af tofacitinib på en tidshorisont på 52 uger, men vurderer også enkelte effektmål efter 8 uger, jf. tabel 1. Såfremt der ikke eksisterer data med disse tidshorisonter, ønsker fagudvalget data med en så lang opfølgningstid som muligt. Fagudvalget ønsker ligeledes data med en så lang opfølgningstid som muligt for effektmål omhandlende lægemidlets sikkerhed.

Kritiske effektmål

Klinisk remission, uge 8

Klinisk remission er defineret ved en total Mayo-score ≤ 2, ingen subscore > 1 og rektal blødning-score = 0. Mayo-score er det mest anvendte scoringssystem i kliniske studier til at vurdere sygdomsaktivitet i UC. Mayo-score indeholder en samlet vurdering af følgende fire subscores: afføringsmønster, rektal blødning, endoskopiske fund og en samlet vurdering af sygdomsaktiviteten foretaget af en kliniker. For hvert område er der fire svarmuligheder (0 til 3 point), og den samlede score går således fra 0 til 12 point, hvor en høj score indikerer værre sværhedsgrad af UC [6].

Fagudvalget finder, at klinisk remission ved uge 8 er et kritisk effektmål, da tidlig remission er afgørende for patienten. I en international undersøgelse med 46 klinikere, var størstedelen af de adspurgte (52,2 %) enige i, at den mindste klinisk relevante forskel for klinisk remission er 10 procentpoint ved sammenligning af to lægemidler [7]. Fagudvalget er enig i denne vurdering.

Steroidfri remission, uge 52
Steroidfri remission er defineret ved, at patienterne ikke er i steroidbehandling efter 52 uger og har en total Mayo-score ≤ 2, ingen subscore > 1 og rektal blødning-score = 0. Mayo-scoresystemet er beskrevet ovenfor.

Fagudvalget finder, at steroidfri remission efter 52 uger er et kritisk effektmål, da det anses som afgørende, at patienten ikke er i langvarig steroidbehandling og samtidig opretholder en langtidseffekt. Den forventede hændelsesrate ved behandling med vedolizumab er cirka 30 % [8], hvilket stemmer overens med fagudvalgets kliniske erfaring. På den baggrund vurderer fagudvalget, at hvis 10 procent flere opnår steroidfri remission ved behandling med tofacitinib, er det klinisk relevant.

Alvorlige uønskede hændelser
Fagudvalget finder, at andelen af patienter, som oplever en eller flere alvorlige uønskede hændelser, er særligt relevant for vurderingen, da tofacitinib er et nyt lægemiddel med en ny virkningsmekanisme. Fagudvalget vurderer, at en forskel på 5 procentpoint i andelen af patienter, der oplever alvorlige uønskede hændelser, er klinisk relevant.

Fagudvalget ønsker derudover en kvalitativ gennemgang af de forskellige typer af uønskede hændelser med henblik på at vurdere alvorlighed, hyppighed og håndterbarhed af hændelserne. Ansøger bedes derfor bidrage med en narrativ beskrivelse af bivirkningsprofilen for tofacitinib baseret på produktresuméet.

Vigtige effektmål
Mukosal heling, uge 8
Mukosal heling er defineret ved en endoskopisk subscore ≤ 1 (subscoren indgår i den samlede Mayo-score). Subscoren afspejler slimhindeudseendet ved en endoskopi, og scoren går fra 0-4, hvor en høj score indikerer værre sværhedsgrad af slimhindens udseende [6]. Mukosal heling er et vigtigt klinisk behandlingsmål, da det er prædiktor for behandlingseffekt og en prognostisk markør for langtidseffekt af behandlingen.

Fagudvalget finder, at mukosal heling ved uge 8 er et vigtigt effektmål, da tidlig mukosal heling er vigtig for patienten. Den forventede hændelsesrate ved behandling med vedolizumab eller infliximab er mellem 30-60 % [5], hvilket stemmer overens med fagudvalgets kliniske erfaring. På den baggrund vurderer fagudvalget, at hvis 10 procent flere opnår mukosal heling ved uge 8 ved behandling med tofacitinb, er det klinisk relevant.

Mukosal heling, uge 52
Mukosal heling er defineret ovenfor.

Fagudvalget finder, at mukosal heling ved uge 52 er et vigtigt effektmål, da langtidseffekten af behandlingen er betydningsfuld. Den forventede hændelsesrate ved behandling med vedolizumab eller infliximab er mellem 15-30 % [5], hvilket stemmer overens med fagudvalgets kliniske erfaring. På den baggrund vurderer fagudvalget, at hvis 10 procent flere opnår mukosal heling ved uge 52 ved behandling med tofacitinb, er det klinisk relevant.

IBDQ
IBDQ er et velvalideret, sygdomsspecifikt livskvalitetsinstrument, der vægter symptomer og problemer, der er særlige for patienter med inflammatoriske tarmsygdomme [6,9]. Spørgeskemaet består af 32 spørgsmål fordelt på fire dimensioner: afføringssymptomer, emotionel sundhed, systemiske symptomer og social funktion. Skalaen går fra 32 til 224, hvor en højere værdi indikerer bedre livskvalitet.

I litteraturen er det angivet, at patienter er i remission, når de har en absolut score på 170 [10]. Fagudvalget vurderer, at en forskel på 10 procentpoint i andelen af patienter, der opnår en samlet score på minimum 170, er klinisk relevant. Fagudvalget sætter den mindste klinisk relevante forskel relativt lavt, da fagudvalget vurderer, at man sjældent ser store ændringer i livskvalitetsskalaer i løbet af kliniske studier.

Det er ligeledes angivet i litteraturen, at en ændring på ≥ 16 point fra baseline er klinisk relevant og indikerer behandlingsrespons [10,11]. Fagudvalget ønsker derfor data også for gennemsnitlig ændring fra baseline og vurderer, at den mindste klinisk relevante forskel er en ændring på ≥ 16 point.

4 Litteratursøgning

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

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

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

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

Lægemiddel og komparator		**Indikation**
[tofacitinib, Xeljanz] *Termer for det generiske navn, handelsnavn og alternative stavemåder og eventuelle MeSH/Supplementary Concepts kombineres med OR. AND kan bruges, hvor flere termer skal forekomme samtidigt for at beskrive lægemidlet korrekt, fx ved coformuleringer.*	*Blokkene til venstre og højre kombineres med* **AND**	[ulcerative colitis] *Termer for indikationen, alternative stavemåder og eventuelle MeSH kombineres med OR. AND kan bruges, hvor flere termer skal forekomme samtidigt for at beskrive indikationen korrekt.*
Ovenstående og nedenstående blokke kombineres med **OR** (der forventes **IKKE** at være direkte sammenlignende studier, og derfor benyttes OR)		
[infliximab, Inflectra, Remicade, Remsima] [vedolizumab, Entyvio] *Udover termer for det generiske navn, handelsnavn, alternative stavemåder og eventuelle MeSH/Supplementary Concepts kombineres med OR. AND kan bruges, hvor flere termer skal forekomme samtidigt for at beskrive lægemidlet korrekt, fx ved coformuleringer*		

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

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

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

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

Vurderingen af klinisk merværdi baseres i udgangspunktet på data fra publicerede fuldtekstartikler og data fra EMAs EPAR. Data skal derudover stemme overens med protokollens beskrivelser.

5 Databehandling/analyse

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

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

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

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

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

Fagudvalget ønsker, at ansøger fastsætter det antagne niveau med udgangspunkt i tilgængelig litteratur. Ansøger bedes i den endelige ansøgning beskrive, hvordan det antagne niveau er fastsat.

Hvis der er mere end et sammenlignende studie, foretages en metaanalyse for de effektmål, hvor det er metodemæssigt forsvarligt. Hvis der ikke foreligger sammenlignende studier, kan data eventuelt syntetiseres indirekte (evt. i form af formelle netværksmetaanalyser eller ved brug af Buchers metode), hvis intervention og komparator er sammenlignet med samme alternative komparator i separate studier. Medicinrådet forbeholder sig retten til at foretage sensitivitets- og subgruppeanalyser på baggrund af studiernes validitet og relevans.

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

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

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

6 Andre overvejelser

Som angivet i afsnit 3.3 ønsker fagudvalget en opgørelse af bivirkningernes karakter ved behandling med tofacitinib. Fagudvalget finder dette særligt relevant, da tofacitinib er et nyt lægemiddel med en ny virkningsmekanisme ved UC, og da tofacitinibs administrationsvej (peroral) adskiller sig fra de biologiske lægemidler, der benyttes til behandling af UC i dag (s.c. og i.v.).

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8 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende inflammatoriske tarmsygdomme

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Charlotte Nielsen *Patient/patientrepræsentant*	Danske Patienter
Anders Pærregaard *Overlæge, dr.med.*	Inviteret af formanden

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