Medicinrådet

Baggrund for Medicinrådets anbefaling af ustekinumab til behandling af moderat til svær colitis ulcerosa

Versionsnr.: 1.0

Medicinrådet

Om Medicinrådet

Medicinrådet er et uafhængigt råd etableret af Danske Regioner.

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

Om Baggrunden for Medicinrådets anbefaling

Baggrund for Medicinrådets anbefaling er en sammenfatning af lægemidlets værdi for patienterne, omkostninger for samfundet og en gengivelse af de vurderinger, der er grundlag for Medicinrådets anbefaling.

Anbefalingen er Medicinrådets vurdering af, om omkostningerne vedrørende brug af lægemidlet er rimelige, når man sammenligner dem med lægemidlets værdi for patienterne.

Læs eventuelt mere i Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser – version 2 Håndbog for Medicinrådets proces og metode.

Godkendt af Medicinrådet den 2. april 2020
Dokumentnummer: 75470
Versionsnummer: 1.0

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

Indhold

1 Anbefaling vedrørende ustekinumab til moderat til svær colitis ulcerosa

Medicinrådet anbefaler
Ustekinumab til BMSL*-behandlingsnaive patienter med moderat til svær colitis ulcerosa.

Vi anbefaler ustekinumab til BMSL-behandlingsnaive patienter.

- Lægemidlet kan ikke kategoriseres, idet data ikke er gode nok til, at vi kan udtale os sikkert om lægemidlet. Vi vurderer dog, at lægemidlet for BMSL-behandlingsnaive patienter såvel med hensyn til effekt som bivirkninger kan ligestilles med de lægemidler, som man bruger i dag.

** Biologiske og målrettede syntetiske lægemidler*

Medicinrådet anbefaler ikke
Ustekinumab til BMSL*-behandlingserfarne patienter med moderat til svær colitis ulcerosa.

Vi anbefaler ikke ustekinumab til BMSL-behandlingserfarne patienter, fordi:

- det ikke kan kategoriseres. Det betyder, at data ikke er gode nok til, at vi kan udtale os sikkert om lægemidlet. Samtidig vurderer vi, datagrundlaget for effekten af lægemidlet hos BMSL-behandlingserfarne patienter er så usikkert, at vi ikke kan vurdere, hvorvidt lægemidlet er dårligere end de lægemidler, som man bruger i dag.

** Biologiske og målrettede syntetiske lægemidler*

2 Værdi for patienterne

Medicinrådet finder, at den samlede værdi af ustekinumab til BMSL-behandlingsnaive patienter med moderat til svær colitis ulcerosa sammenlignet med hhv. infliximab og vedolizumab **ikke kan kategoriseres**. Rådet vurderer dog, at ustekinumab samlet set har en sammenlignelig effekt og sikkerhedsprofil med infliximab og vedolizumab.

Medicinrådet finder, at den samlede værdi af ustekinumab til BMSL-behandlingserfarne patienter med moderat til svær colitis ulcerosa sammenlignet med vedolizumab **ikke kan kategoriseres**. Rådet finder, at datagrundlaget for vurderingen er forbundet med stor usikkerhed. Værdien af ustekinumab sammenlignet med infliximab kan ikke vurderes.

Ansøger har indsendt høringssvar den 25. februar 2020. Høringssvaret gav ikke anledning til ændringer i Medicinrådets kategorisering af den kliniske værdi af ustekinumab.

Læs mere i Medicinrådets vurdering af klinisk værdi og den bagvedliggende protokol (bilag 4 og bilag 6).

3 Omkostninger for sundhedsvæsenet

I officielle priser (apotekernes indkøbspriser) vil det over en periode på 18 måneder være dyrere at behandle en patient med ustekinumab end med infliximab, mens det vil være billigere at behandle med ustekinumab sammenlignet med vedolizumab. Lægemiddelfirmaet har dog givet en fortrolig rabat, og det er derfor ikke muligt at redegøre for de reelle omkostninger forbundet med brug af ustekinumab.

Læs mere i Medicinrådets sundhedsøkonomiske afrapportering (bilag 1) og i Amgros' forhandlingsnotat (bilag 2).

4 Alvorlighed

Medicinrådet har ikke fundet anledning til at anvende alvorlighedsprincippet i denne sag.

5 Anbefalingen betyder

Anbefalingen betyder, at regionerne kan bruge ustekinumab til BMSL-behandlingsnaive patienter med moderat til svær colitis ulcerosa, men det er ikke nødvendigvis førstevalg.

Anbefalingen betyder ligeledes, at regionerne i udgangspunktet ikke bør bruge ustekinumab til BMSL-behandlingserfarne patienter med moderat til svær colitis ulcerosa.

Medicinrådet er ved at udarbejde en behandlingsvejledning for moderat til svær colitis ulcerosa. Lægemidlet kommer til at stå på Medicinrådets lægemiddelrekommandation for moderat til svær colitis ulcerosa, når denne foreligger. Indtil da anbefaler Medicinrådet, at regionerne bruger det lægemiddel, der er forbundet med de laveste omkostninger.

En lægemiddelrekommandation er Medicinrådets anbefaling til regionerne om, hvilke lægemidler der er mest hensigtsmæssige til behandling af patienter. Der er i lægemiddelrekommandationen taget hensyn til både lægemidlets effekt og økonomi.

6 Sagsbehandlingstid

Medicinrådet har brugt 15 uger på sit arbejde med ustekinumab til moderat til svær colitis ulcerosa.

7 Kontaktinformation til Medicinrådet

Medicinrådets sekretariat
Dampfærgevej 27-29, 3. th.
2100 København Ø
+ 45 70 10 36 00
medicinraadet@medicinraadet.dk

8 Versionslog

Version	Dato	Ændring
1.0	2. april 2020	Godkendt af Medicinrådet.

9 Bilag

- Bilag 1 - Medicinrådets sundhedsøkonomiske afrapportering – ustekinumab (Stelara)
- Bilag 2 – Amgros' forhandlingsnotat – ustekinumab (Stelara)
- Bilag 3 - Høringssvar fra ansøger – ustekinumab (Stelara)
- Bilag 4 - Medicinrådets vurdering af klinisk merværdi for ustekinumab til behandling af moderat til svær colitis ulcerosa – vers. 1.0
- Bilag 5 – Ansøgers endelige ansøgning – ustekinumab (Stelara)
- Bilag 6 - Medicinrådets protokol for vurdering af klinisk merværdi for ustekinumab til behandling af moderat til svær colitis ulcerosa – vers. 1.0

Medicinrådet

Sundhedsøkonomisk afrapportering

Ustekinumab

Colitis Ulcerosa

Version 1.0

Indholdsfortegnelse

Om Medicinrådet

Medicinrådet er et uafhængigt råd, som udarbejder anbefalinger og vejledninger om lægemidler til de fem regioner. Medicinrådet vurderer, om nye lægemidler og nye indikationer kan anbefales som standardbehandling og udarbejder fælles regionale behandlingsvejledninger. Nye lægemidler vurderes i forhold til effekt, eksisterende behandling og pris. Det skal give lavere priser og lægemidler, der er til størst mulig gavn for patienterne. De fælles regionale behandlingsvejledninger er vurderinger af, hvilke lægemidler der er mest hensigtsmæssige til behandling af patienter inden for et terapiområde og dermed grundlag for ensartet høj kvalitet for patienterne på tværs af sygehuse og regioner.

Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 18. marts 2020

Opsummering

Baggrund

Lægemidlet Ustekinumab er indiceret til behandling af voksne patienter med moderat til svær aktiv colitis ulcerosa, som ikke har responderet tilstrækkeligt på, ikke længere responderer på eller er intolerante over for enten konventionel behandling eller et biologisk middel eller har medicinske kontraindikationer over for sådanne behandlinger. Medicinrådets sekretariats vurdering tager udgangspunkt i dokumentation indsendt af Janssen-Cilag.

Analyse

Den sundhedsøkonomiske analyse, indsendt af ansøger, estimerer de inkrementelle omkostninger pr. patient ved behandling med ustekinumab sammenlignet med infliximab og vedolizumab over en tidshorisont på 18 måneder. Analysen inkluderer dels patienter, som ikke tidligere har modtaget anden behandling end førstevalgs medicinsk behandling (biologiske og målrettede syntetiske lægemidler (BMSL)-behandlingsnaive patienter), dels patienter, som har modtaget behandling med et eller flere BMSL-lægemidler (BMSL-behandlingserfarne patienter).

Inkrementelle omkostninger og budgetkonsekvenser

Medicinrådets sekretariat har vurderet de gennemsnitlige inkrementelle omkostninger pr. patient ved brug af ustekinumab til BMSL-behandlingsnaive- og BMSL-behandlingserfarne patienter, sammenlignet med infliximab og vedolizumab. De inkrementelle omkostninger er først angivet i sygehusapotekernes indkøbspriser (SAIP) og derefter i apotekernes indkøbspris (AIP).

I det scenarie, som Medicinrådets sekretariat mener er mest sandsynligt i sammenligningen med infliximab, er de inkrementelle omkostninger for ustekinumab, angivet i SAIP, ca. [redacted] DKK over en tidshorisont på 18 måneder. Hvis analysen udføres med AIP, bliver de inkrementelle omkostninger ca. 40.000 DKK pr. patient.

I det scenarie, Medicinrådets sekretariat mener er mest sandsynligt i sammenligningen med vedolizumab, er de inkrementelle omkostninger for ustekinumab, angivet i SAIP, ca. [redacted] DKK over en tidshorisont på 18 måneder. Hvis analysen udføres med AIP, bliver de inkrementelle omkostninger ca. -4.000 DKK pr. patient.

Medicinrådets sekretariat vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af ustekinumab som standardbehandling vil være ca. [redacted] DKK i år 5 for BMSL-behandlingsnaive patienter. Hvis analysen udføres med AIP, bliver budgetkonsekvenserne ca. -0,5 mio. DKK i år 5.

For BMSL-behandlingserfarne patienter vil budgetkonsekvenserne for ustekinumab være ca. [redacted] DKK i år 5. Hvis analysen udføres med AIP, bliver budgetkonsekvenserne

ca. -2,7 mio. DKK i år 5.

Konklusion

Analysen viser, at de inkrementelle omkostninger næsten udelukkende er drevet af lægemiddelomkostninger. Usikkerheder i analysen blev undersøgt, og DRG-taksten til estimering af administrationsomkostningen for vedolizumab samt opjustering af dosis for lægemidlerne viste sig at være de parametre med størst indflydelse på den inkrementelle omkostning.

Dokumentoplysninger	
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Arbejdsgruppe	Emma Munk, Louise Greve Dal

Liste over forkortelser

AIP	Apotekernes indkøbspris
BMSL	Biologiske og målrettede syntetiske lægemidler
DRG	Diagnose Relaterede Grupper
IV	Intravenøs
RADS	Rådet for anvendelse af dyr sygehusmedicin
SAIP	Sygehusapotekernes indkøbspris

1. Baggrund for den økonomiske analyse

Janssen-Cilag (herefter omtalt som ansøger) er markedsføringstilladelsesindehaver af ustekinumab og har den 20. december 2019 indsendt en ansøgning til Medicinrådet om vurdering af ustekinumab som mulig standardbehandling på danske hospitaler. Medicinrådets sekretariat vurderer, på vegne af Medicinrådet, den økonomiske analyse, ansøger har sendt som en del af den samlede ansøgning til Medicinrådet. Denne rapport er Medicinrådets sekretariats vurdering af den fremsendte økonomiske analyse (herefter omtalt som analysen).

1.1 Patientpopulation

Colitis ulcerosa er en kronisk inflammatorisk tarmsygdom karakteriseret ved konfluerende inflammation i ende- og tyktarmens slimhilde (1). Antallet af patienter i Danmark blev i 2013 anslået til at være ca. 35.200 med en incidens på ca. 18,6:100.000 (1). Incidensen er i Danmark let stigende og blandt de højeste på verdensplan (1,2). Aktivitet i sygdommen klassificeres som mild, moderat eller svær.

1.1.1 Subpopulationer

Førstevalgsbehandling til patienter med colitis ulcerosa er medicinsk behandling med 5-aminosalicylsyre, suppleret med enten kortikosteroider eller immunsuppressiv behandling med azathioprin eller 6-mercatpurin. Ved manglende effekt, aktiv sygdom eller hvis sygdommen recidiverer trods immunsuppressiv behandling, kan behandling med BMSL iværksættes. Patienter, som ikke har modtaget anden behandling end førstevalgs medicinske behandlinger, betegnes BMSL-behandlingsnaive patienter. Patienter, som har modtaget behandling med et eller flere BMSL-lægemidler, betegnes BMSL-behandlingserfarne patienter.

1.1.2 Komparator

Medicinrådet har defineret infliximab og vedolizumab som komparator til ustekinumab for populationerne specificeret i afsnit 1.1.1, se Tabel 1.

Tabel 1: Definerede populationer og komparatorer.

Population	Komparator
Patienter med moderat til svær colitis ulcerosa, som enten er BMSL-behandlingsnaive eller BMSL-behandlingserfarne.	Infliximab Vedolizumab

1.2 Problemstilling

Formålet med analysen er at estimere de gennemsnitlige inkrementelle omkostninger pr. patient og de samlede budgetkonsekvenser for regionerne ved en eventuel anbefaling af ustekinumab som mulig standardbehandling på danske hospitaler indenfor indikationen. Medicinrådet vurderer den kliniske merværdi af ustekinumab og har specificeret følgende kliniske spørgsmål:

Klinisk spørgsmål 1*:*

Hvad er værdien af ustekinumab sammenlignet med henholdsvis infliximab og vedolizumab til behandling af voksne biologiske og målrettede syntetiske lægemiddel (BMSL)-behandlingsnaive patienter med moderat til svær aktiv colitis ulcerosa?

Klinisk spørgsmål 2:

Hvad er værdien af ustekinumab sammenlignet med henholdsvis infliximab og vedolizumab til behandling af voksne biologiske og målrettede syntetiske lægemiddel (BMSL)-behandlingserfarne patienter med moderat til svær aktiv colitis ulcerosa?

2. Vurdering af den økonomiske analyse

Ansøger har indsendt en økonomisk analyse, der estimerer de inkrementelle omkostninger pr. patient for ustekinumab sammenlignet med infliximab og vedolizumab. I nedenstående afsnit vil den økonomiske model, som ligger til grund for estimeringen af de inkrementelle omkostninger pr. patient, blive præsenteret.

2.1 Antagelser og forudsætninger for model

Den økonomiske model har til formål at estimere de inkrementelle omkostninger for ustekinumab sammenlignet med infliximab og vedolizumab, ved behandling af BMSL-behandlingsnaive- og BMSL-behandlingserfarne patienter med colitis ulcerosa.

For BMSL-behandlingsnaive patienter har ansøger indsendt en indirekte sammenligning mellem ustekinumab, infliximab og vedolizumab. Studierne brugt til sammenligningen er UNIFI-studiet for ustekinumab (3), ACT 1 og ACT 2 for infliximab (4) og GEMINI 1 for vedolizumab (5). Buchers metode er anvendt til sammenligningen og kan bruges, når lægemidlerne har en fælles komparator, som i dette tilfælde er placebo.

For BMSL-behandlingserfarne patienter er sammenligningen ligeledes baseret på en indirekte sammenligning, dog kun mellem ustekinumab og vedolizumab, da data på behandling med infliximab på BMSL-behandlingserfarne patienter ikke kunne identificeres.

2.1.1 Modelbeskrivelse

Ansøger har indsendt en simpel omkostningsmodel, hvilket betyder, at modellen kun estimerer omkostninger forbundet med behandling med ustekinumab, infliximab og vedolizumab.

Medicinrådets sekretariats vurdering

Sammenligningen for BMSL-behandlingserfarne patienter er baseret på en indirekte sammenligning mellem ustekinumab og vedolizumab, som er accepteret af fagudvalget vedrørende inflammatoriske tarmsygdomme.

I Medicinrådets sekretariats vurderingsrapport for ustekinumab fremgår det, at der ikke ses en signifikant effektmæssig forskel på lægemidlerne på nogle af de kritiske effektmål defineret i Medicinrådets protokol for ustekinumab. Da der ikke ses en effektmæssig forskel på lægemidlerne, accepterer Medicinrådets sekretariat ansøgers simple omkostningsanalyse.

Medicinrådets sekretariat accepterer ansøgers tilgang.

2.1.2 Analyseperspektiv

Ansøgers omkostningsanalyse har et begrænset samfundsperspektiv og en tidshorisont på 18 måneder. Ansøger har baseret denne tidshorisont på et baggrundsnotat fra rådet for anvendelse af dyr sygehusmedicin (RADS) vedrørende behandling af kronisk inflammatoriske tarmsygdomme. Omkostninger, der ligger efter det første år, er diskonteret med en rate på 4 %.

Medicinrådets sekretariats vurdering

I Medicinrådets metodevejledning for den sundhedsøkonomiske analyse står, at tidshorisonten skal være så lang, at alle relevante forskelle i omkostninger inkluderes. Medicinrådets sekretariat vurderer, at en tidshorisont på 18 måneder er tilstrækkelig til at inkludere alle relevante omkostninger forbundet med alternativerne, og ser derfor ingen grund til at ændre på tidshorisonten.

Medicinrådets sekretariat accepterer ansøgers tilgang.

2.2 Omkostninger

I det følgende præsenteres ansøgers antagelser for omkostningerne i den økonomiske analyse af ustekinumab sammenlignet med infliximab og vedolizumab. De inkluderede omkostninger i ansøgers analyse er lægemiddelomkostninger, hospitalsomkostninger og patientomkostninger.

Ansøger har ikke inkluderet bivirkningsrelaterede omkostninger med det argument, at bivirkningsfrekvenserne i UNIFI-studiet (3), ACT 1 og ACT 2-studierne (4) samt GEMINI-studiet (5) er tilsvarende bivirkningerne for placebo.

Estimeringen af lægemiddelomkostninger i ansøgers ansøgning til Medicinrådet bygger altid på AIP, hvilket i nærværende analyse udskiftes med SAIP.

2.2.1 Lægemiddelomkostninger

De anvendte doser er hentet i de respektive lægemidlers produktresuméer. Behandling med ustekinumab er inddelt i en induktionsfase og en efterfølgende vedligeholdelsesfase. I induktionsfasen administreres en enkelt dosis ustekinumab intravenøst (IV) baseret på legemsvægt med 6 mg/kg. På baggrund af produktresuméet for ustekinumab er følgende doseringer specificeret: ≤ 55 kg gives 260 mg, 55-85 kg gives 390 mg og ≥ 85 kg gives 520 mg (6). I hovedanalysen er en gennemsnitlig legemsvægt på 75 kg antaget og en IV-dosering af ustekinumab på 390 mg.

Den efterfølgende vedligeholdelsesbehandling startes ved uge 8, hvor der gives 90 mg ustekinumab subkutant. Efter uge 8 gives 90 mg hver 12. uge.

Hvis responset mistes ved dosering hver 12. uge, kan doseringsfrekvensen øges til hver 8. uge (6).

Infliximab doseres IV med 5 mg/kg ved uge 0, uge 2 og uge 6 og herefter hver 8. uge. Hvis responset mistes, kan doseringen øges til 10 mg hver 8. uge (7).

Vedolizumab gives IV med 300 mg ved uge 0, 2 og uge 6. Herefter hver 8 uge. Hvis responset mistes kan doseringsfrekvensen øges til 300 mg hver 4. uge (8).

Information om lægemidlerne er angivet i Tabel 2.

Tabel 2: Anvendte lægemiddelpriser, SAIP, februar 2020.

Lægemiddel	Styrke	Mg/dosis	Pakningsstørrelse	Pris [DKK]	Kilde
Ustekinumab	130 mg	390 mg	1 stk.	[redacted]	Amgros
Ustekinumab	90 mg	90 mg	1 stk.	[redacted]	Amgros
Infliximab	100 mg	5 mg	1 stk.	[redacted]	Amgros
Vedolizumab	300 mg	300 mg	1 stk.	[redacted]	Amgros

Medicinrådets sekretariats vurdering

Medicinrådets sekretariat accepterer ansøgers antagelser for lægemiddelomkostninger.

2.2.2 Hospitalsomkostninger

Ansøger har inkluderet hospitalsomkostninger til lægemiddeladministration, da ustekinumab administreres IV på hospitalet i induktionsfasen og subkutant på hospitalet i vedligeholdelsesfasen, samt alle IV infliximab- og vedolizumab doser administreres på hospitalet.

Ansøger har brugt DRG2019-taksten med koden 06MA98 på 2.446 DKK til at estimere hospitalsomkostningen pr. IV administration af de 3 lægemidler.

Til at estimere hospitalsomkostningen ved subkutan administration af ustekinumab, har ansøger benyttet Amgros' udvidede sammenligningsgrundlag for leddegigt (9) og taget udgangspunkt i administrationsomkostningen for golimumab, som også administreres subkutant (9). De estimerede omkostninger pr. IV administration, samt subkutan administration af ustekinumab, er præsenteret i Tabel 3.

Tabel 3: Hospitalsomkostning pr. lægemiddeladministration.

	Ustekinumab	Infliximab	Vedolizumab	Kilde
IV administration, DKK	2.446	2.446	2.446	Interaktiv DRG-takster 2019
Subkutan administration, DKK	346,39	-	-	Udvidede sammenlignings-grundlag (9)

Medicinrådets sekretariats vurdering

Medicinrådets sekretariat ændrer DRG2019-taksterne til DRG2020-takster, da disse angiver det nyeste estimat af DRG-taksterne. Medicinrådets sekretariat ændrer ikke på ansøgers tilgang til at estimere hospitalsomkostningerne for subkutan administration af ustekinumab, da sekretariatet anser estimatet for på nuværende tidspunkt at være det bedst mulige.

Medicinrådets sekretariat accepterer ansøgers tilgang. Dog vælger Medicinrådets sekretariat at ændre DRG2019-takster til DRG2020-takster.

2.2.3 Patientomkostninger

Ansøger har benyttet Amgros' udvidede sammenligningsgrundlag for leddegigt til at estimere patientomkostninger relateret til behandling med ustekinumab, infliximab og vedolizumab (9). Da ustekinumab og vedolizumab ikke er inkluderet i det udvidede sammenligningsgrundlag, har ansøger antaget, at patientomkostningerne for vedolizumab og IV-behandlingen med ustekinumab er tilsvarende dem for infliximab. Ansøgers begrundelse er, at administrationsformen og administrationsfrekvensen over analysens tidshorisont for lægemidlerne er ens.

I det udvidede sammenligningsgrundlag er angivet en patientomkostning på 5.275 DKK og en transportomkostning på 1.680 DKK ved behandling med infliximab (9). Ansøger har divideret disse omkostninger med antal administrationer i løbet af 78 uger, som er estimeret til 11 og estimeret omkostningerne præsenteret i Tabel 4.

For subkutan behandling med ustekinumab har ansøger antaget en times behandlingstid og anvendt Medicinrådets sekretariats værdisætning af enhedsomkostninger (10) til estimering af den relaterede patientomkostning.

Transportomkostningen ved behandling med ustekinumab antages at være tilsvarende den for infliximab og vedolizumab.

De estimerede patient- og transportomkostninger for ustekinumab, infliximab og vedolizumab kan ses i Tabel 4.

Tabel 4: Ansøgers estimat af patientomkostninger og transportomkostninger pr. lægemiddeladministration, DKK.

	Ustekinumab	Infliximab	Vedolizumab
Omkostning, IV	479,55	479,55	479,55
Omkostning, subkutan	180	-	-
Transport	152,73	152,73	152,73
I alt	**812,28**	**632,28**	**632,28**

Medicinrådets sekretariats vurdering

I produktresuméet for infliximab fremgår det, at infliximab skal administreres over to timer, hvorefter patienten skal observeres i en til to timer. I produktresuméet for vedolizumab fremgår det, at vedolizumab skal administreres over 30 minutter. I produktresuméet for ustekinumab fremgår det, at ustekinumab skal gives IV over en time.
Medicinrådets sekretariat anvender disse oplysninger til at estimere patienttid i forbindelse med administration af lægemidlerne i sin hovedanalyse. Medicinrådets sekretariat anvender Medicinrådets sekretariats nyeste version af værdisætning af enhedsomkostninger til estimeringen af patienttid (10).

Medicinrådets sekretariat ændrer på estimeringen af patientomkostninger til lægemiddeladministration i sin hovedanalyse.

2.3 Følsomhedsanalyser

Formålet med følsomhedsanalyserne er at belyse usikkerhederne i analysen.
Ansøger har udarbejdet en række følsomhedsanalyser, hvor effekten af variation i forskellige parametre undersøges. Følgende følsomhedsanalyser er udført:

- Anvendelse af DRG2019-taksten med koden 27MP26 til estimering af administrationsomkostninger for vedolizumab
- Estimering af lægemiddelomkostninger ved anvendelse af en legemsvægt under 55 kg og over 85 kg
- Inkludering af spild
- Opjustering af lægemiddeldosis.

Medicinrådets sekretariats vurdering

Hvis DRG-taksten med koden 27MP26 anvendes i stedet for DRG-taksten anvendt i ansøgers hovedanalyse, øges administrationsomkostningerne for vedolizumab. Medicinrådets sekretariat vælger at præsentere denne analyse, da det forventes at påvirke den inkrementelle omkostning for ustekinumab sammenlignet med vedolizumab betydeligt.

Da doseringen af ustekinumab er vægtbaseret vælger Medicinrådets sekretariat at præsentere ansøgers følsomhedsanalyse, der undersøger, hvad den inkrementelle omkostning for ustekinumab bliver for en gennemsnitlig patient med en legemsvægt under 55 kg og over 85 kg. Følsomhedsanalysen bliver præsenteret, da Medicinrådets sekretariat vurderer, at lægemiddelomkostningerne har betydning for resultatet.

Medicinrådets sekretariat vælger desuden at udarbejde en følsomhedsanalyse, hvor den subkutane vedligeholdelsesbehandling med ustekinumab kan foregå i hjemmet, da ustekinumab inden for andre terapiområder har indikation til hjemmebehandling.

Medicinrådets sekretariat vælger ikke at præsentere ansøgers følsomhedsanalyse som inkluderer spild, da det forventes at have minimal betydning for resultatet.

Medicinrådets sekretariat vælger at præsentere ansøgers følsomhedsanalyser med undtagelse af følsomhedsanalysen, der inkluderer spild.

2.4 Opsummering af basisantagelser

I Tabel 5 opsummeres basisantagelserne for ansøgers hovedanalyse sammenlignet med de ændringer, som Medicinrådets sekretariatet laver i sin hovedanalyse.

Tabel 5: Basisantagelser i ansøgers hovedanalyse og Medicinrådets sekretariats hovedanalyse.

Basisantagelser	Ansøger	Medicinrådets sekretariat
Tidshorisont	78 uger	78 uger
Diskonteringsrate	4 %	4 %
Inkluderede omkostninger	Lægemiddel Hospital Patient Transport	Lægemiddel Hospital Patient Transport
Dosering		
Ustekinumab	Vægtbaseret	Vægtbaseret
Infliximab	Vægtbaseret	Vægtbaseret
Vedolizumab	300 mg	300 mg
Inkludering af spild	nej	nej

3. Resultater

3.1 Resultatet af ansøgers hovedanalyse

I ansøgers hovedanalyse bliver den inkrementelle omkostning pr. patient for ustekinumab ca. [redacted] DKK sammenlignet med infliximab over en tidshorisont på 18 måneder.

I sammenligningen med vedolizumab bliver den inkrementelle omkostning pr. patient for ustekinumab ca. [redacted] DKK over en tidshorisont på 18 måneder.

Resultaterne fra ansøgers hovedanalyse er for sammenligningen med infliximab præsenteret i Tabel 6 og i Tabel 7 for sammenligningen med vedolizumab.

Tabel 6: Resultatet af ansøgers hovedanalyse for ustekinumab sammenlignet med infliximab over en tidshorisont på 18 måneder, DKK, diskonterede tal.

	Ustekinumab	Infliximab	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	4.510	26.763	-22.252
Patientomkostninger	2.615	6.918	-4.302
Totale omkostninger	[redacted]	[redacted]	[redacted]

Tabel 7: Resultatet af ansøgers hovedanalyse for ustekinumab sammenlignet med vedolizumab over en tidshorisont på 18 måneder, DKK, diskonterede tal.

	Ustekinumab	Vedolizumab	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	4.510	26.763	-22.252
Patientomkostninger	2.615	6.918	-4.302
Totale omkostninger	[redacted]	[redacted]	[redacted]

3.1.1 Resultatet af ansøgers følsomhedsanalyser

Vedolizumab er ligesom ustekinumab et monoklonalt antistof. Vælges diagnosen "ulcerøs colitis UNS" samt "behandling med vedolizumab" som procedure i det interaktive DRG-system, angives DRG-taksten "antistofbehandling" med koden 27MP26 (11). Ansøger har udarbejdet en følsomhedsanalyse, hvor denne DRG2019-takst anvendes til at estimere de IV administrationsomkostninger for vedolizumab. Taksten, som er anvendt i hovedanalysen, og taksten, som er anvendt i følsomhedsanalysen, er præsenteret i Tabel 8.

Tabel 8: DRG2019-taksten anvendt i hovedanalysen sammenlignet med DRG2019-taksten anvendt i følsomhedsanalysen.

Analyse	Omkostning [DKK]	Kode
Hovedanalyse	**2.446**	**06MA98**
Følsomhed	17.228	27MP26

Ansøger har udarbejdet en følsomhedsanalyse, der undersøger, hvad den inkrementelle omkostning for ustekinumab bliver, hvis den gennemsnitlige patient har en vægt under 55 kg eller over 85 kg. Ved en legemsvægt på under 55 kg gives en ustekinumabdosis på 260 mg, og ved en legemsvægt på over 85 kg gives en ustekinumabdosis på 520 mg (6).

Ansøger har udarbejdet en følsomhedsanalyse, der undersøger påvirkningen af den inkrementelle omkostning for ustekinumab, hvis dosis opjusteres. Hvis patienter mister respons på vedligeholdelsesbehandling med ustekinumab hver 12. uge, kan dosis opjusteres til hver 8. uge. Tilsvarende gør sig gældende for infliximab og vedolizumab, hvor patienter kan opjusteres til 300 mg vedolizumab hver 4. uge og 10 mg infliximab hver 8. uge. Ansøger har i følsomhedsanalysen antaget, at mellem 25 % og 35 % af patienterne bliver opjusteret.

Resultaterne af ansøgers følsomhedsanalyser er præsenteret i Tabel 9.

Tabel 9: Resultatet af ansøgers følsomhedsanalyser sammenlignet med hovedanalysen. Tallene i tabellen er inkrementelle omkostninger for ustekinumab sammenlignet med hhv. Infliximab og vedolizumab over 18 måneder, DKK.

Analyse	Infliximab	vedolizumab
Hovedanalyse	[redacted]	[redacted]
Administrationsomkostning for vedolizumab	[redacted]	[redacted]
Under 55 kg	[redacted]	[redacted]
Over 85 kg	[redacted]	[redacted]
Opjustering af dosis hos 30 %	[redacted]	[redacted]

3.2 Resultatet af Medicinrådets sekretariats hovedanalyse

Medicinrådets sekretariats hovedanalyse bygger på samme antagelser som ansøgers hovedanalyse med følgende justeringer:

- Anvendelse af DRG2020-takst i stedet for DRG2019-takst til estimering af hospitalsomkostninger
- Anvendelse af information fra de respektive produktresuméer om patienters tidsforbrug ved administration frem for Amgros' udvidede sammenligningsgrundlag for leddegigt.

I Medicinrådets sekretariats hovedanalyse bliver den inkrementelle omkostning pr. patient ca. [redacted] DKK sammenlignet med infliximab over en tidshorisont på 18 måneder. Udføres analysen med AIP bliver den inkrementelle omkostning pr. patient 40.000 DKK.

I sammenligningen med vedolizumab bliver den inkrementelle omkostning pr. patient ca. [redacted] DKK over en tidshorisont på 18 måneder.
Udføres den med AIP bliver den inkrementelle omkostning pr. patient ca. -4.000 DKK.

Resultaterne fra Medicinrådets sekretariats hovedanalyse præsenteres i Tabel 10 og Tabel 11.

Tabel 10: Resultatet af Medicinrådets sekretariats hovedanalyse for ustekinumab ved sammenligning med infliximab, over en tidshorisont på 18 måneder, DKK, diskonterede tal.

	Ustekinumab	Infliximab	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	4.407	25.636	-21.228
Patientomkostninger	2.615	6.918	-4.302
Totale omkostninger	[redacted]	[redacted]	[redacted]

Tabel 11: Resultatet af Medicinrådets sekretariats hovedanalyse for ustekinumab ved sammenligning med vedolizumab, over en tidshorisont på 18 måneder, DKK, diskonterede tal.

	Ustekinumab	Vedolizumab	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	4.407	25.636	-21.228
Patientomkostninger	2.615	6.918	-4.302
Totale omkostninger	[redacted]	[redacted]	[redacted]

3.2.1 Resultatet af Medicinrådets sekretariats følsomhedsanalyser

Ustekinumab som subkutan vedligeholdelsesbehandling kan i fremtiden få indikation til hjemmebehandling. Derfor vælger Medicinrådets sekretariat at udarbejde en følsomhedsanalyse, der undersøger påvirkningen af den inkrementelle omkostning for ustekinumab, hvis de subkutane vedligeholdelsesbehandlinger foregår i hjemmet fremfor på hospitalet. Resultatet af følsomhedsanalysen fremgår i Tabel 12.

Tabel 12: Resultatet af Medicinrådets sekretariats følsomhedsanalyse. Resultaterne er inkrementelle omkostninger ved behandling med ustekinumab sammenlignet med de to komparatorer over 18 måneder, DKK.

	Infliximab	Vedolizumab
Hovedanalyse	[redacted]	[redacted]
Subkutan hjemmebehandling	[redacted]	[redacted]

4. Budgetkonsekvenser

Budgetkonsekvenserne pr. år er baseret på to mulige scenarier:

- Ustekinumab bliver anbefalet som mulig standardbehandling af Medicinrådet til indikationen, som denne analyse omhandler.
- Ustekinumab bliver ikke anbefalet som mulig standardbehandling.

Budgetkonsekvenserne bliver differencen mellem budgetkonsekvenserne i de to scenarier, angivet i SAIP. Budgetkonsekvensen i år 5 angivet i AIP vil også blive præsenteret.

4.1 Ansøgers budgetkonsekvensanalyse

4.1.1 Ansøgers estimat af patientantal og markedsandel

Ansøger har estimeret budgetkonsekvenserne ved anvendelse af ustekinumab til BMSL-behandlingsnaive patienter og budgetkonsekvenserne ved at anvende ustekinumab til BMSL-behandlingserfarne patienter.

Til at estimere patientantallet, som behandles med ustekinumab, infliximab eller vedolizumab, har ansøger brugt data fra den danske database for biologisk behandling af inflammatoriske tarmsygdomme (BIOIBD) (12). Ansøger har i databasen fundet, hvor mange BMSL-behandlingsnaive patienter som årligt opstarter behandling med biologiske lægemidler, og hvor mange BMSL-behandlingserfarne patienter som årligt skifter behandling til biologiske lægemidler.

I perioden fra 01. oktober 2017 til 30. september 2018 blev 223 BMSL-behandlingsnaive patienter og 148 BMSL-behandlingserfarne patienter behandlet med biologiske lægemidler. 88 % af de 223 BMSL-behandlingsnaive patienter blev behandlet med infliximab i perioden (196 patienter), mens 8 % blev behandlet med vedolizumab (18 patienter).

Antallet af BMSL-behandlingserfarne patienter blev estimeret ved at trække incidensen af BMSL-behandlingsnaive patienter, som enten modtager infliximab (196) eller vedolizumab (18), fra det totale antal patienter på behandling med infliximab eller vedolizumab i slutningen af ovenstående periode.

I slutningen af perioden var 187 BMSL-behandlingsnaive patienter på behandling med infliximab, ud af en incidens på 196 patienter. Ansøger har derfor antaget, at 0 BMSL-behandlingserfarne patienter skifter til biologisk behandling med infliximab, og estimeret et patientantal for BMSL-behandlingserfarne patienter, som modtager infliximab på 0.

I slutningen af perioden var 116 BMSL-behandlingsnaive patienter på behandling med vedolizumab, ud af en incidens på 18 patienter. Ansøger har derfor antaget, at 98 BMSL-behandlingserfarne patienter skifter til biologisk behandling med vedolizumab, og estimeret et patientantal for BMSL-behandlingserfarne patienter, som modtager vedolizumab på 98.

Hvert år vil nye patienter opstarte behandling med lægemidlerne og blive inkluderet i de efterfølgende år. Ansøger har antaget, at 100 % behandles i år 1, mens 15 % stadig behandles i år 5 grundet behandlingsfrafald (12).

Ansøger antager, at ustekinumab ved en anbefaling vil få 100 % af vedolizumabs markedsandel, både for BMSL behandlingsnaive- og BMSL-behandlingserfarne patienter, hvorimod ustekinumab vil få 0 % af infliximabs markedsandel. Ansøger har opdelt det estimerede patientantal for BMSL-behandlingsnaive patienter og BMSL-behandlingserfarne patienter.

Tabel 13 viser ansøgers estimat af antal BMSL-behandlingsnaive patienter årligt ved en anbefaling og uden en anbefaling.

Tabel 14 viser ansøgers estimat af antal BMSL-behandlingserfarne patienter ved en anbefaling og uden anbefaling.

Tabel 13: Ansøgers estimat af antal BMSL behandlingsnaive patienter pr. år, i det scenarie at ustekinumab anbefales og ikke anbefales som standardbehandling.

Anbefales					
	År 1	År 2	År 3	År 4	År 5
Ustekinumab	18	29	36	41	43
Infliximab	196	318	394	441	471
Vedolizumab	0	0	0	0	0
Anbefales ikke					
	År 1	År 2	År 3	År 4	År 5
Ustekinumab	0	0	0	0	0
Infliximab	196	318	394	441	471
Vedolizumab	18	29	36	41	43

Tabel 14: Ansøgers estimat af antal BMSL behandlingserfarne patienter pr. år, i det scenarie at ustekinumab anbefales og ikke anbefales som standardbehandling.

Anbefales					
	År 1	År 2	År 3	År 4	År 5
Ustekinumab	98	159	197	221	235
Infliximab	0	0	0	0	0
Vedolizumab	0	0	0	0	0
Anbefales ikke					
	År 1	År 2	År 3	År 4	År 5
Ustekinumab	0	0	0	0	0
Infliximab	0	0	0	0	0
Vedolizumab	98	159	197	221	235

4.1.2 Ansøgers estimat af budgetkonsekvenser

Ansøger har inkluderet de samme omkostninger i budgetkonsekvensanalysen, som der er inkluderet i omkostningsanalysen, med undtagelse af patientomkostninger og ikke diskonterede omkostninger. Ansøger har estimeret budgetkonsekvenserne for BMSL-behandlingsnaive patienter og BMSL-behandlingserfarne patienter.

Med de ovenstående antagelser om patientantal og markedsandel estimerer ansøger, at anvendelse af ustekinumab til BMSL-behandlingsnaive patienter vil resultere i budgetkonsekvenser på ca. [redacted]. DKK i år 5.

Ved anvendelse af ustekinumab til BMSL-behandlingserfarne patienter bliver budgetkonsekvenserne ca. [redacted]. DKK i år 5. Ansøgers estimat af budgetkonsekvenserne fremgår af Tabel 15 og Tabel 16.

Tabel 15: Ansøgers hovedanalyse for totale budgetkonsekvenser ved anvendelse af ustekinumab til behandling af BMSL-behandlingsnaive 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 16: Ansøgers hovedanalyse for totale budgetkonsekvenser ved anvendelse af ustekinumab til BMSL-behandlingserfarne 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]

Medicinrådets sekretariats vurdering

Ifølge Medicinrådets sekretariats vurderingsrapport for ustekinumab findes der ikke nogen præcis opgørelse over, hvor mange patienter med moderat til svær colitis ulcerosa, som er i behandling med et BMSL. Det vurderes, at ca. 300 patienter er BMSL-behandlingsnaive, mens ca. 200 er BMSL-behandlingserfarne. Dog er det er uvist, hvordan fordelingen mellem infliximab og vedolizumab er i de to patientgrupper. Derfor vælger Medicinrådets sekretariat at acceptere ansøgers estimat af patientantal og markedsandel for hver af lægemidlerne, i mangel på mindre usikre estimater.

Medicinrådets sekretariat accepterer ansøgers fremgangsmåde i budgetkonsekvensanalysen.

4.2 Medicinrådets sekretariats budgetkonsekvensanalyse

Medicinrådets sekretariat har korrigeret følgende estimater i sin budgetkonsekvensanalyse i forhold til ansøgers budgetkonsekvensanalyse:

- Anvendt DRG2020-takster i stedet for DRG2019-takster.

Medicinrådets sekretariat estimerer, at anvendelse af ustekinumab til BMSL-behandlingsnaive patienter vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Ved

anvendelse af ustekinumab til BMSL-behandlingserfarne patienter vil budgetkonsekvenserne være ca. [redacted]. DKK i år 5.

Hvis analysen udføres med AIP, bliver budgetkonsekvenserne henholdsvis ca. -0,5 mio. DKK i år 5 og -2,7 mio. DKK i år 5.

Resultatet er præsenteret i Tabel 17 og Tabel 18.

Tabel 17: Medicinrådets sekretariats analyse af totale budgetkonsekvenser for anvendelse af ustekinumab til BMSL-behandlingsnaive 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 18: Medicinrådets sekretariats analyse af totale budgetkonsekvenser for anvendelse af ustekinumab til BMSL-behandlingserfarne 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

Analysen af omkostning pr. patient for ustekinumab viste, at behandling af BMSL-behandlingsnaive og -behandlingserfarne patienter med ustekinumab er forbundet med en meromkostning sammenlignet med infliximab. Sammenlignet med vedolizumab er ustekinumab forbundet med en besparelse. De omkostninger, som har størst betydning for resultatet, er lægemiddelomkostningerne, da de inkrementelle omkostninger i høj grad er drevet af lægemiddelomkostningerne.

5.1 Usikkerheder

Usikkerheder blev undersøgt i analysen. Da de inkrementelle omkostninger i høj grad afhænger af lægemiddelomkostningerne, blev parametre, som kan påvirke lægemiddelomkostningerne, undersøgt. Påvirkningen af den inkrementelle omkostning ved en dosering af ustekinumab til patienter med lavere eller højere legemsvægt end antaget i hovedanalysen blev undersøgt og viste sig ikke at have stor betydning for resultatet.

Opjustering af dosis for lægemidlerne viste sig at påvirke den inkrementelle omkostning med ca. [redacted] DKK i sammenligningen med infliximab og ca. [redacted] DKK i sammenligningen med vedolizumab over en tidshorisont på 18 måneder.

DRG-taksten brugt til estimering af administrationsomkostningen for vedolizumab har betydning for resultatet, men resulterer blot i en større besparelse forbundet med ustekinumab. Resultatet er heller ikke følsomt overfor, om ustekinumab får indikation til subkutan hjemmebehandling.

6. Referencer

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Forhandlingsnotat

Dato for behandling i Medicinrådet	18. marts 2020
Leverandør	Janssen-Cilag
Lægemiddel	Ustekinumab (Stelara)
EMA-indikation	Behandling af moderat til svær colitis ulcerosa

Forhandlingsresultat

Amgros har opnået følgende pris på ustekinumab (Stelara):

Lægemiddel	Styrke/dosis	Pakningsstørrelse	AIP	SAIP	Rabatprocent ift. AIP
033918 - Stelara	45 mg/0,5 ml	1 stk.	22.677,47	[redacted]	[redacted]
093827 - Stelara	45 mg	1 stk. (0,5 ml)	22.677,47	[redacted]	[redacted]
093838 - Stelara	90 mg	1 eng. spr. á 1 ml	22.677,47	[redacted]	[redacted]
553118 - Stelara	130 mg	1 stk.	25.094,36	[redacted]	[redacted]

Aftalen er en del af det store biologiske udbud. Aftalen startede 1. april 2019 og løber til og med 30. juni 2020 med mulighed for forlængelse.

Vurdering af forhandlingsresultatet

Det er Amgros' vurdering, at vi på nuværende tidspunkt **har** opnået den bedst mulige pris. Denne vurdering baserer vi på følgende punkter:

Bionaive patienter:

Bioerfarne patienter:

Konklusion

Relation til markedet

Ustekinumab (Stelara) er allerede godkendt til behandling af psoriasis, hvor de i dag omsætter for . Der er stor konkurrence inden for behandling af psoriasis,

25-02-2020

Høringssvar for Stelara® (ustekinumab)

I forbindelse med modtagelsen af vurderingsrapporten for Stelara® (ustekinumab) vil Janssen gerne sige tak for et godt forløb, hvor sekretariatet har været yderst behjælpelige hele vejen igennem processen.

I henhold til Medicinrådets vurderingen af ustekinumab accepterer vi, at den samlede værdi af ustekinumab til BMSL-behandlingsnaive patienter med moderat til svær colitis ulcerosa sammenlignet med hhv. infliximab og vedolizumab ikke kan kategoriseres.

Endvidere accepterer vi, at den samlede værdi af ustekinumab til BMSL-behandlingserfarne patienter med moderat til svær colitis ulcerosa sammenlignet med vedolizumab ikke kan kategoriseres samt at værdien af ustekinumab sammenlignet med infliximab ikke kan vurderes.

Janssen har ikke yderligere bemærkninger til vurderingen af ustekinumab.

Med venlig hilsen,
Janssen-Cilag A/S

Nikolaj Bødker
Country HEMAR manager
Immunology & Neuroscience

Medicinrådet

Medicinrådets vurdering af ustekinumab til behandling af moderat til svær colitis ulcerosa

Versionsnr.: 1.0

Medicinrådet

Om Medicinrådet

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

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

Nye lægemidler og indikationsudvidelser 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

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

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

Lægemidlet vurderes efter Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser – version 2. Se Medicinrådets metodehåndbog for yderligere information.

Dokumentoplysninger	
Godkendelsesdato	19. februar 2020
Ikrafttrædelsesdato	19. februar 2020
Dokumentnummer	72711
Versionsnummer	1.0

Medicinrådet, Dampfærgevej 27-29, 3. th., 2100 København Ø
www.medicinraadet.dk
Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 19. februar 2020

Indhold

1 Lægemiddelinformationer

Lægemidlets oplysninger	
Handelsnavn	Stelara
Generisk navn	Ustekinumab
Firma	Janssen-Cilag
ATC-kode	L04AC05
Virkningsmekanisme	Ustekinumab er et humant monoklonalt antistof, som binder sig til cytokinerne IL-12 og IL-23. Ustekinumab forhindrer derved, at IL-12 og IL-23 bidrager til immunaktivering.
Administration/dosis	Induktion: Enkelt i.v. dosis baseret på kropsvægt ~ 6 mg/kg infusion uge 0: 260 mg [≤ 55 kg]; 390 mg [55 kg - 85 kg]; 520 mg [> 85 kg]. Vedligeholdelsesbehandling: Subkutan injektion á 90 mg i uge 8, herefter hver 12. uge.
EMA-indikation	Behandling af voksne patienter med moderat til svær aktiv colitis ulcerosa, som ikke har responderet tilstrækkeligt på, ikke længere responderer på eller er intolerante over for enten konventionel behandling eller et biologisk middel eller har medicinske kontraindikationer over for sådanne behandlinger.
Accelerated assessment	Nej
Orphan drug	Nej
Conditional approval	Nej
Øvrige indikationer	Moderat til svær plaque psoriasis, psoriasis artrit og moderat til svær aktiv Crohns sygdom.

2 Medicinrådets konklusion

Medicinrådet finder, at den samlede værdi af ustekinumab til BMSL-behandlingsnaive patienter med moderat til svær colitis ulcerosa sammenlignet med hhv. infliximab og vedolizumab **ikke kan kategoriseres**. Rådet vurderer dog, at ustekinumab samlet set har en sammenlignelig effekt og sikkerhedsprofil med infliximab og vedolizumab.

Medicinrådet finder, at den samlede værdi af ustekinumab til BMSL-behandlingserfarne patienter med moderat til svær colitis ulcerosa sammenlignet med vedolizumab **ikke kan kategoriseres**. Rådet finder, at datagrundlaget for vurderingen er forbundet med stor usikkerhed. Værdien af ustekinumab sammenlignet med infliximab kan ikke vurderes.

Medicinrådet kategoriserer lægemidlers værdi i en af følgende kategorier:

• **Stor merværdi:** Der er påvist en stor forbedring i effektforhold i forhold til gældende standardbehandling, eksempelvis markant forbedret overlevelse, markant reduktion i forekomsten af alvorlige symptomer og/eller alvorlige bivirkninger.

• **Moderat merværdi:** Der er påvist en moderat forbedring i forhold til gældende standardbehandling, eksempelvis moderat forbedret overlevelse, moderat reduktion i forekomsten af symptomer og/eller bivirkninger.

• **Lille merværdi:** Der er påvist en lille forbedring i forhold til gældende standardbehandling, eksempelvis en dokumenteret forbedret overlevelse, en reduktion i forekomsten af symptomer og/eller bivirkninger.

• **Merværdi af ukendt størrelse:** Der er påvist en forbedring i forhold til gældende standardbehandling, men størrelsen af forbedring kan ikke bestemmes. Lægemidlets merværdi er som minimum lille, men kunne også være moderat eller stor.

• **Ingen dokumenteret merværdi:** Der er ikke påvist en merværdi i forhold til gældende standardbehandling. Omvendt tyder den tilgængelige evidens heller ikke på, at der er en negativ værdi.

• **Negativ værdi:** Der er påvist en negativ værdi i forhold til gældende standardbehandling.

• **Samlet værdi kan ikke kategoriseres:** På grund af usikkerheder omkring effektforhold, er det ikke muligt at kategorisere lægemidlets samlede værdi.

3 Forkortelser

ARR:	Absolut risikoreduktion
BMSL:	Biologiske og målrettede syntetiske lægemidler
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*)
IL:	Interleukin
ITT:	*Intention-to-treat*
i.v.:	Intravenøs
HR:	*Hazard ratio*
MKRF:	Mindste klinisk relevante forskel
NCT	*National Clinical Trial*
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:	Standardafvigelse
SMD:	*Standardized Mean Difference*

4 Formål

Formålet med Medicinrådets vurdering af ustekinumab til behandling af patienter med colitis ulcerosa er at vurdere den værdi, lægemidlet har i forhold til et eller flere lægemidler til samme patientgruppe.

Vurderingen af ustekinumab vil tage udgangspunkt i de to kliniske spørgsmål:

1) *Hvad er værdien af ustekinumab sammenlignet med hhv. infliximab og vedolizumab til behandling af voksne BMSL (biologiske og målrettede syntetiske lægemiddel)-behandlingsnaive patienter med moderat til svær aktiv colitis ulcerosa?*
2) *Hvad er værdien af ustekinumab sammenlignet med hhv. infliximab og vedolizumab til behandling af voksne BMSL (biologiske og/eller målrettede syntetiske lægemiddel)-behandlingserfarne patienter med moderat til svær aktiv colitis ulcerosa?*

Vurderingen af de to kliniske spørgsmål kan findes i afsnit 9.1 og 9.2 på hhv. side 10 og 23 i denne rapport.

Med udgangspunkt i vurderingen og en omkostningsanalyse beslutter Medicinrådet, om ustekinumab kan anbefales som mulig standardbehandling[1].

5 Baggrund

Colitis ulcerosa

Colitis ulcerosa er en kronisk, inflammatorisk tarmsygdom, karakteriseret ved konfluerende inflammation i ende- og tyktarmens slimhinde [1]. Inflammationen fører til sårdannelse i slimhinden, og inflammationen involverer altid endetarmen og oftest den nedre del af tyktarmen men kan involvere hele tyktarmen. De mest almindelige symptomer ved colitis ulcerosa er blodig og pusholdig diarré, mavesmerter (ofte i relation til afføring) og almen sygdomsfornemmelse [2,3]. Colitis ulcerosa kan også medføre symptomer i organer udenfor tarmen, i særdeleshed fra led, lever, øjne og hud (såkaldte ekstraintestinale manifestationer) og kan ledsages af komplikationer som knogleskørhed, nyresten og anæmi [4].

Colitis ulcerosa er en livsvarig sygdom med skiftende perioder af sygdomsaktivitet og remission (periode, hvor sygdommen er i ro) [3]. Sygdommen betegnes som værende i remission ved ophør af symptomer og heling af slimhinden, påvist ved endoskopi [2].

Colitis ulcerosa debuterer hyppigst omkring 20-35-årsalderen men kan debutere i tidlig barnealder og hos ældre. Antallet af patienter med colitis ulcerosa i Danmark (prævalensen) blev i 2013 anslået til 35.200, og antallet af nye patienter (incidensen) var ca. 18,6 pr. 100.000 [1]. Incidensen i Danmark er let stigende og blandt de højeste i verden [1,5].

En eventuel aktivitet i sygdommen kan klassificeres som mild, moderat eller svær. I beskrivelsen af sygdommen er udbredelsen også af betydning [2,3]. Der anvendes forskellige skalaer til at beskrive sygdomsaktiviteten i forbindelse med klinisk kontrollerede undersøgelser. Mayo-score (baseret på symptomer og endoskopi) anvendes hyppigt til voksne [2,3].

[1] Ved dansk standardbehandling forstås de(t) generelt anerkendte kliniske alternativ(er), som anvendes i klinisk praksis i Danmark.

Nuværende behandling

Der findes ikke lægemidler, som helbreder patienterne. Førstevalgs medicinsk behandling ved colitis ulcerosa er 5-aminosalicylsyre, der anvendes både ved aktiv sygdom og som recidivprofylakse. Ved manglende effekt suppleres oftest med kortikosteroider og som vedligeholdelsesterapi med immunsuppressiv behandling (azathioprin eller 6-mercaptopurin). Ved manglende effekt af denne behandling, ved aktiv sygdom eller hvis sygdommen recidiverer trods immunsuppressiv behandling, og hvis kirurgi ikke er at foretrække, kan behandling med biologiske og målrettede syntetiske lægemidler (BMSL) iværksættes efter Dansk Selskab for Gastroenterologi og Hepatologis (DSGH) retningslinjer [6].

Målet med behandlingen af colitis ulcerosa er at behandle den akutte sygdom, dvs. inducere klinisk remission og dernæst at fastholde remissionen uden brug af kortikosteroider for dermed at forbedre patientens livskvalitet.

Hvis sygdommen er i langvarig remission, kan man forsøge at ophøre behandling med et BMSL, følge tilstanden og revurdere behov for at genoptage behandlingen [6]. Hos cirka en tredjedel af patienterne aftager effekten af behandlingen (sekundært tab af respons), og her kan dosis øges, eller intervallerne mellem behandling afkortes. Ved ophør af behandlingseffekt kan patienterne i 25-35 % af tilfældene opnå en effekt ved at skifte behandling til et andet BMSL. Ved manglende respons må behandlingen med et BMSL ophøre, og kirurgi kan anbefales [6].

Rådet for Anvendelse af Dyr Sygehusmedicin (RADS) har i 2016 ligestillet de tre lægemidler golimumab, infliximab og vedolizumab til behandling af moderat til svær aktiv colitis ulcerosa, mens adalimumab kan overvejes [7]. Sidenhen har Medicinrådet anbefalet endnu et lægemiddel, tofacitinib, som mulig standardbehandling af bio-erfarne patienter, dvs. det kan anvendes, efter at et eller flere af de ovenstående ligestillede præparater har været afprøvet.

Der findes ingen præcise opgørelser over andelen af danske patienter med moderat til svær aktiv colitis ulcerosa, som er i behandling med et BMSL. På baggrund af data fra Region Nordjylland skønnes det på landsplan, at der er ca. 1.600 patienter i behandling, og at ca. 500 patienter pr. år starter ny behandling med et af de lægemidler, som indgår i behandlingsvejledningen. Det skønnes, at 300 af disse patienter er BMSL-behandlingsnaive, mens 200 er BMSL-behandlingserfarne.

Anvendelse af det nye lægemiddel

Ustekinumab er et fuldt humant monoklonalt antistof, der specifikt binder sig til den delte p40-proteinunderenhed af interleukin (IL)-12 og IL-23, som er associerede med immunmedierede sygdomme. Ustekinumab hæmmer derved bioaktiviteten af IL-12 og IL-23 ved at forhindre, at p40 binder sig til receptorproteinet, der er udtrykt på overfladen af immunceller. Herved hæmmes det immunologiske respons, som skal medføre, at den inflammatoriske tilstand mindskes.
Ustekinumab gives som induktion de første 8 uger og efterfølgende som vedligeholdelsesbehandling under vejledning og supervision af læger med erfaring i diagnosticering og behandling af colitis ulcerosa:

- Induktion: ~ 6 mg/kg intravenøs (i.v.) infusion uge 0: 260 mg [≤ 55 kg]; 390 mg [55 kg - 85 kg]; 520 mg [> 85 kg].
- Vedligeholdelsesbehandling: subkutan (s.c.) injektion 90 mg uge 8, herefter hver 12. uge [8].

6 Metode

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

Den endelige ansøgning fra Janssen blev modtaget den 20. december 2019. Ansøger har anvendt og fulgt den præspecificerede metode, jf. protokol, som blev godkendt af Medicinrådet den 5. november 2019.

Ansøger har indsendt indirekte sammenligninger af ustekinumab og hhv. infliximab og vedolizumab til at besvare klinisk spørgsmål 1. Ansøger har anvendt Buchers metode [9]. For effektmålene alvorlige uønskede hændelser og livskvalitet har ansøger ikke kunnet identificere stratificerede data for BMSL-behandlingsnaive og -behandlingserfarne patienter. Ansøger har derfor udført én samlet analyse på populationerne for disse effektmål. Ansøger har ligeledes ikke kunnet identificere data for infliximab i en BMSL-behandlingserfaren population og har derfor kun indsendt en indirekte sammenligning af ustekinumab og vedolizumab til at besvare klinisk spørgsmål 2. Fagudvalget har accepteret denne fremgangsmåde, da den er baseret på det bedst mulige datagrundlag, som foreligger.

Fra evidens til kategori. Medicinrådet vurderer værdien 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 vægter de kritiske højest, de vigtige næsthøjest og de mindre vigtige indgår ikke.

Både den relative og absolutte effekt indgår i kategoriseringen af et lægemiddel. Dette foregår i en trinvis proces. Fagudvalget kategoriserer først den relative foreløbige kategori på baggrund af væsentlighedskriterierne og den absolutte foreløbige kategori på baggrund af de præspecificerede mindste klinisk relevante forskelle. Her er der tale om en ren kvantitativ proces. Herefter fastlægger fagudvalget den aggregerede kategori for hvert effektmål ved at sammenholde de foreløbige kategorier. Her kan fagudvalget inddrage deres kliniske indsigt. Når den samlede kategori for lægemidlets værdi skal fastlægges, sammenvejer fagudvalget alle effektmål. Effektmålenes kategorier kombineres med effektmålenes vægt, og eventuelle kliniske overvejelser inddrages. Den samlede kategorisering af lægemidlets værdi er således delvis en kvantitativ og delvis en kvalitativ proces, hvor der foretages en klinisk vurdering af det foreliggende datagrundlag. Vurdering af evidensens kvalitet foretages med udgangspunkt i GRADE og udtrykker tiltroen til evidensgrundlaget for de enkelte effektstørrelser og den endelige kategori for klinisk værdi. 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 beskrevet i protokollen, og 6 artikler omhandlende 4 kliniske studier blev inkluderet. Til besvarelse af klinisk spørgsmål 1 er alle 6 artikler anvendt. 4 af de 6 artikler er anvendt til at besvare klinisk spørgsmål 2. De 6 artikler er beskrevet i tabel 1.

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

Reference	Klinisk forsøg	*National Clinical trial* (NCT) identifikationsnummer	Relevant for klinisk spørgsmål
Ustekinumab			
Ustekinumab as Induction and Maintenance Therapy for Ulcerative Colitis. **Sands et al. 2019. NEJM** [10].	UNIFI	NCT02407236	Klinisk spørgsmål 1 og 2
Infliximab			
Infliximab for induction and maintenance therapy for ulcerative colitis. **Rutgeerts et al. 2005. NEJM** [11].	ACT 1 & ACT 2	NCT00036439 NCT00096655	Klinisk spørgsmål 1
The effects of infliximab therapy on health-related quality of life in ulcerative colitis patients. **Feagan et al. 2007 Am J Gastroenterol** [12]**.**	ACT 1 & ACT 2	NCT00036439 NCT00096655	Klinisk spørgsmål 1
Vedolizumab			
Vedolizumab as induction and maintenance therapy for ulcerative colitis**. Feagan BG et al. 2013. NEJM** [13]**.**	GEMINI 1	NCT00783718	Klinisk spørgsmål 1 og 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** [14]**.**	GEMINI 1	NCT00783718	Klinisk spørgsmål 1 og 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** [15]**.**	GEMINI 1	NCT00783718	Klinisk spørgsmål 1 og 2

Ovenstående studier samt *European Public Assessment Report* (EPAR) for ustekinumab [16] og vedolizumab [17] og produktresuméer for ustekinumab [8], infliximab [18] og vedolizumab [19] udgør datagrundlaget for de analyser, som benyttes til besvarelse af de kliniske spørgsmål. Under hvert effektmål fremgår det, hvilke publikationer data er ekstraheret fra.

8 Databehandling

De statistiske analyser er udført af ansøger og valideret af Medicinrådets sekretariat. Til udarbejdelsen af de indirekte sammenligninger har ansøger anvendt Buchers metode, der kan anvendes til at foretage en justeret indirekte sammenligning af lægemidler med en fælles komparator [9]. Medicinrådet har suppleret med beregninger af konfidensintervaller på frekvensen af alvorlige uønskede hændelser samt på andelen af patienter, der opnår hhv. klinisk remission ved uge 8, systemisk steroidfri remission ved uge 52 og mukosal heling ved uge 52. Beregningerne er baserede på frekvenserne opgjort i de kliniske studier for ustekinumab, infliximab og vedolizumab. Derudover har Medicinrådet ikke suppleret med yderligere beregninger.

Fagudvalget vurderer, at det indleverede datagrundlag er tilstrækkeligt til at vurdere den kliniske merværdi af ustekinumab. Fagudvalget har dog bemærkninger til datagrundlaget, og disse bemærkninger er anført som en del af vurderingen af de effektmål, hvor data er anvendt (se afsnit 9.1.2 og 2.2.2).

9 Lægemidlets værdi

9.1 Konklusion på klinisk spørgsmål 1

Hvad er værdien af ustekinumab sammenlignet med hhv. infliximab og vedolizumab til behandling af voksne BMSL (biologiske og målrettede syntetiske lægemiddel)-behandlingsnaive patienter med moderat til svær aktiv colitis ulcerosa?

Fagudvalget finder, at den samlede værdi af ustekinumab sammenlignet med hhv. infliximab og vedolizumab ikke kan kategoriseres. Fagudvalget vurderer dog, at ustekinumab samlet set har en sammenlignelig effekt og sikkerhedsprofil med infliximab og vedolizumab.

I tabel 2 fremgår den samlede kategori for lægemidlet og kvaliteten af den samlede evidens. Derudover fremgår både absolutte og relative effektforskelle samt foreløbige og aggregerede værdier.

Tabel 2: Kategorier og resultater for vurdering af ustekinumab sammenlignet med hhv. infliximab (INF) og vedolizumab (VED) (BMSL-behandlingsnaive patienter)

Effektmål	Måleenhed (MKRF)	Vigtighed	Absolutte forskelle mellem ustekinumab og komparatorer		Relative forskelle (RR) mellem ustekinumab og komparatorer		Aggregeret værdi pr. effektmål
			Forskel (95 % CI)	Foreløbig værdi	Forskel (95 % CI)	Foreløbig værdi	
Klinisk remission, efter induktionsbehandling, uge 8	Andel patienter med total Mayo-score ≤ 2, ingen subscore > 1 og rektal blødning score = 0 (10 procentpoint)	Kritisk	INF: -17,3 procentpoint [-29,31; 15,01] VED: -10,2 procentpoint [-18,7; 14,99]	INF: Kan ikke kategoriseres¤ VED: Kan ikke kategoriseres¤	INF: 0,52 [0,19; 1,41] VED: 0,56 [0,19; 1,64]	INF: Kan ikke kategoriseres¤ VED: Kan ikke kategoriseres¤	INF: Kan ikke kategoriseres¤ VED: Kan ikke kategoriseres¤
Systemisk steroidfri remission, efter vedligeholdelsesbehandling, uge 52	Andel patienter, der ikke er i systemisk steroidbehandling efter 52 uger og har en total Mayo-score ≤ 2, ingen subscore > 1 og rektal blødningscore = 0 (10 procentpoint)	Kritisk	INF: -11,99 procentpoint [-20,09; 7,78] VED: -7,1 procentpoint [-23,5; 30,8]	INF: Kan ikke kategoriseres¤ VED: Kan ikke kategoriseres¤	INF: 0,53 [0,22; 1,30] VED: 0,80 [0,35; 1,86]	INF: Kan ikke kategoriseres¤ VED: Kan ikke kategoriseres¤	INF: Kan ikke kategoriseres¤ VED: Kan ikke kategoriseres¤
Mukosal heling, vedligeholdelsesbehandling, uge 52	Andel patienter med endoskopisk subscore ≤ 1 (10 procentpoint)	Vigtig	INF: -16 procentpoint [-28,4; 5,3] VED: -19,2% [-36,3; 10,4]	INF: Kan ikke kategoriseres¤ VED: Kan ikke kategoriseres¤	INF: 0,65 [0,38; 1,12] VED: 0,68 [0,39; 1,17]	INF: Kan ikke kategoriseres¤ VED: Kan ikke kategoriseres¤	INF: Kan ikke kategoriseres¤ VED: Kan ikke kategoriseres¤
Bivirkninger[#]	Andel patienter, der oplever en alvorlig uønsket hændelse (5 procentpoint)	Kritisk	UST: 7.6%; PBO: 9,7 %[§] INF_{ACT1}: 21,5 %; PBO_{ACT1}: 25,6 % INF_{ACT2}: 10,7 %; PBO_{ACT2}: 19,5 % VED: 8,2 %; PBO: 15,9 %[§]	INF: Kan ikke kategoriseres¤ VED: Kan ikke kategoriseres¤	INF: Beregning ikke mulig VED: Beregning ikke mulig	INF: Kan ikke kategoriseres¤ VED: Kan ikke kategoriseres¤	INF: Kan ikke kategoriseres¤ VED: Kan ikke kategoriseres¤

	Kvalitativ gennemgang af bivirkningsprofil. Se afsnit 9.1.2		INF: Beregning ikke relevant VED: Beregning ikke relevant	INF: Kan ikke kategoriseres¤ VED: Kan ikke kategoriseres¤	INF: Beregning ikke relevant VED: Beregning ikke relevant	INF: Kan ikke kategoriseres¤ VED: Kan ikke kategoriseres¤	
Livskvalitet	Andel patienter, der opnår score ≥ 170 på Inflammatory Bowel Disease Questionnaire (IBDQ) (10 procentpoint)	Vigtig	INF: Data ikke opgjort VED: Data ikke opgjort	INF: Kan ikke kategoriseres¤ VED: Kan ikke kategoriseres¤	INF: Data ikke opgjort VED: Data ikke opgjort	INF: Kan ikke kategoriseres¤ VED: Kan ikke kategoriseres¤	INF: Kan ikke kategoriseres¤ VED: Kan ikke kategoriseres¤
	Forskel i ændring fra baseline på IBDQ (16 point)		INF: Beregning ikke mulig VED: Beregning ikke mulig	INF: Kan ikke kategoriseres¤ VED: Kan ikke kategoriseres¤	INF: Beregning ikke mulig VED: Beregning ikke mulig	INF: Kan ikke kategoriseres¤ VED: Kan ikke kategoriseres¤	INF: Kan ikke kategoriseres¤ VED: Kan ikke kategoriseres¤
Samlet kategori for lægemidlets værdi		Kan ikke kategoriseres					
Kvalitet af den samlede evidens		Meget lav					

INF: Infliximab; MKRF: Mindste klinisk relevante forskel; PBO: Placebo; RR: Relativ risiko. UST: Ustekinumab; VED: Vedolizumab.

¤ På baggrund af den tilgængelige evidens er det ikke muligt at foretage en kategorisering baseret på resultaterne.

Naiv sammenligning. Estimaterne stammer fra UNIFI [10], GEMINI-1[13] og ACT1- og 2-studierne[11].

§ Andelen er opgjort i en population bestående af både bionaive og -erfarne patienter.

* Gennemsnitlig forskel i ændring fra baseline IBDQ-score for ustekinumab sammenlignet med placebo i en population bestående af både bio-naive og bio-erfarne patienter [16].

** Gennemsnitlig forskel i ændring fra baseline IBDQ-score for vedolizumab sammenlignet med placebo i en population bestående af bio-naive patienter [15].

*** Gennemsnitlig forskel i ændring fra baseline IBDQ-score for vedolizumab sammenlignet med placebo i en population bestående af både bio-naive og bio-erfarne patienter [15].

9.1.1 Gennemgang af studier

Ansøger identificerede et studie af vedolizumab, to studier af infliximab og et studie af ustekinumab. Studiernes design og karakteristika for populationer er beskrevet nedenfor.

Studiedesign

UNIFI (ustekinumab) [10]
UNIFI-studiet består af et 8 ugers induktionsstudie med 961 patienter og et 44 ugers vedligeholdelsesstudie med patienter med 523 patienter. Begge er randomiserede, kontrollerede dobbeltblindede studier med patienter, der ikke har responderet tilstrækkeligt på eller har haft uacceptable bivirkninger ved behandling med tumor nekrosis faktor antagonister, vedolizumab eller konventionel behandling. I induktionsstudiet blev patienterne randomiseret 1:1:1 til at modtage hhv. placebo i.v. (n = 319), ustekinumab 130 mg i.v. (n = 320) eller ustekinumab 6mg/kg (n = 322). Patienter, som ved uge 8 havde klinisk respons på i.v. ustekinumab, indgik i vedligeholdelsesstudiet og blev rerandomiseret 1:1:1 til at modtage subkutan (s.c.) placebo, 90 mg ustekinumab s.c. hver 12. uge eller 90 mg ustekinumab s.c. hver 8. uge. Patienter, som ikke havde respons på placebo, modtog induktionsdosis på 6 mg/kg ustekinumab. Ved respons i uge 16 indgik disse patienter i vedligeholdelsesstudiet på samme måde som de patienter, som responderede i den randomiserede del. Patienter, som ikke opnåede respons på i.v. ustekinumab i induktionsstudiet, modtog blindet behandling med 90 mg ustekinumab s.c. og blev reevalueret i uge 16. Ved respons indgik patienterne i vedligeholdelsesstudiet og modtag 90 mg ustekinumab s.c. hver 8. uge. Patienterne blev ikke randomiseret. Patienter med respons på i.v. placebo fortsatte med s.c. placebo i vedligeholdelsesstudiet. Effektanalyser er baseret på intention-to-treat (ITT)-populationen. Sikkerhedsanalyser er baseret på alle randomiserede patienter, der modtog mindst én studiedosis. Data for induktionsstudiet er analyseret i henhold til den givne substans, patienterne modtog, hvorimod data for vedligeholdelsesstudiet er analyseret i forhold til patienternes tilordning til studiearmene. I induktionsperioden var studiets primære endepunkter klinisk remission ved uge 8. I vedligeholdelsesperioden var studiets primære endepunkt klinisk remission ved uge 44, mens relevante sekundære endepunkter var systemisk steroidfri remission ved uge 44, mukosal heling, livskvalitet målt ved IBDQ og sikkerhed.

GEMINI 1 (vedolizumab) [13–15]
GEMINI 1 består af to integrerede randomiserede, kontrollerede, dobbeltblindede 6- og 52-ugers studier, der undersøger induktionsbehandling og vedligeholdelsesbehandling med vedolizumab. Induktionsbehandling blev undersøgt i den randomiserede kohorte 1 (n= 225) samt i en open label kohorte (kohorte 2; n=521). I induktionsstudiets kohorte 1 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. Patienter, der ved afslutningen af induktionsdelen havde klinisk respons blev inkluderet i vedligeholdelsesdelen og blev rerandomiseret 1:1:1 til vedolizumab hver 8. uge, vedolizumab hver 4. uge eller placebo. Effektanalyser er baseret på ITT-populationen. Sikkerhedsanalyser er baseret på alle randomiserede patienter, der modtog mindst én studiedosis (n = 895)[2]. I induktionsdelen er studiets primære effektmål klinisk respons ved uge 6, og studiets sekundære effektmål af relevans for vurderingen af ustekinumab er klinisk remission ved uge 6. I vedligeholdelsesdelen er studiets primære endepunkt klinisk remission ved uge 52, og studiets sekundære relevante endepunkter er mukosal heling ved uge 52, steroidfri remission ved uge 52, livskvalitet målt ved IBDQ og sikkerhed.

ACT 1 og ACT 2 (infliximab) [11,12]

[2] Heraf indgår 521 patienter, der fik open-label vedolizumab.

ACT 1 og ACT2 er randomiserede, kontrollerede, dobbeltblindede studier. Studierne undersøger induktions- og vedligeholdelsesbehandling med infliximab hos patienter, 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 relevante effektmål 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 tabel 3 fremgår baselinekarakteristika for patienter i de inkluderede studier. Baselinekarakteristika er ikke fordelt på bionaive og -erfarne patienter, men for den samlede population, hvad angår ustekinumab og vedolizumab. For infliximab er der kun data på bionaive patienter.

Tabel 3. Baselinekarakteristika for populationerne i de aktive studiearme

	UNIFI			GEMINI 1		ACT 1		ACT 2	
	Placebo (N = 319)	Ustekinumab 130 mg (N = 320)	Ustekinumab 6 mg/kg (N = 322)	1 Placebo (N = 149)	Vedolizumab (N = 225)	Placebo (N = 121)	Infliximab 5 mg (N = 121)	Placebo (N = 123)	Infliximab 5 mg (N = 121)
Mænd (%)	61,8	59,4	60,6	61,7	58,0	59,5	64,5	57,7	62,8
Alder, år (gns. ± SD)	41,2 (13,5)	42,2 (13,9)	41,7 (13,7)	41,2 (12,5)	40,1 (13,2)	41,4 (13,7)	42,4 (14,3)	39,3 (13,5)	40,5 (13,1)
Sygdomsvarighed, år, median (range) (gns. ± SD)	8,0 (7,2)	8,1 (7,2)	8,2 (7,8)	7,1 (7,2)	6,8 (6,2)	6,2 (5,9)	5,9 (5,4)	6,5 (6,7)	6,7 (5,3)
Sværhedsgrad, Mayo-score (gns. ± SD)*	8,9 (1,6)	8,9 (1,6)	8,9 (1,5)	8,6 (1,7)	8,6 (1,8)	8,4 (1,8)	8,5 (1,7)	8,5 (1,5)	8,3 (1,5)
Tidligere behandling med TNF-alfa hæmmer (%)	47,3**	45,3**	45,7**	49,0	48,0	0	0	0	0
Samtidig behandling (%) - Steroid - Immunsuppressiva[#]	 49,2 27,9	 54,1 29,1	 52,2 27,6	 38,9 12,1	 36,7 18,9	 65,3 43,8	 57,9 54,5	 48,8 43,9	 49,6 43,0

SD = Standardafvigelse (Standard Deviation).
* Total Mayo-score går fra 0-12, hvor en højere score indikerer svær colitis ulcerosa.
** Procent opgjort for patienter, som ikke har modtaget biologisk behandling.
[#] Inkluderer azathioprin og mercaptopurin. I studierne for ustekinumab omfatter behandling med immunsuppressiva også methotrexat.

Overordnet vurderer fagudvalget, at der ikke er betydelige forskelle i baselinekarakteristika i studierne mellem de indbyrdes placebo- og interventionsarme og imellem de fire studier.

Fagudvalget bemærker, at der en forskel i andelen af patienter, der sideløbende fik steroidbehandling, på tværs af de inkluderede studier. Desuden ses der en forskel mellem UNIFI-studiet og hhv. GEMINI-studiet og ACT1- og ACT2-studierne i andelen af patienter, som modtog samtidig immunsuppressiv behandling. Denne forskel i andelen af patienter, som har modtaget samtidig behandling, kan indikere, at de inkluderede patientpopulationer har varierende behandlingsresistens. Fagudvalget vægter dog, at sværhedsgraden (målt

ved Mayo-score) ikke varierer betydeligt mellem studiepopulationerne og finder på denne baggrund, at populationerne er sammenlignelige.

Fagudvalget finder, at der derudover ikke er betydende forskelle i baselinekarakteristika mellem studierne. Fagudvalget vurderer, at patientkarakteristika i studierne ikke afviger væsentligt fra den danske patientpopulation.

Studierne for infliximab inkluderer ikke BMSL-behandlingserfarne patienter, og infliximab indgår derfor kun som komparator i klinisk spørgsmål 1 omhandlende BMSL-behandlingsnaive patienter. Forskellen i TNF-behandlingserfarne patienter mellem UNIFI og ACT1/2 er derfor ikke relevant for klinisk spørgsmål 2.

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 ustekinumab 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, efter induktionsbehandling, uge 8 (kritisk)

Klinisk remission er i Medicinrådet protokol defineret ved en total Mayo-score ≤ 2, ingen subscore > 1 og blod i afføringen-score = 0. Mayo-score indeholder en samlet vurdering af følgende fire subscores: afføringshyppighed, blod i afføringen, endoskopiske fund og en samlet vurdering af sygdomsaktiviteten (global assessment) 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 højere score indikerer sværere sygdomsaktivitet [20,21].

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

Ansøger har udarbejdet en metaanalyse for studierne ACT1 og ACT2 med infliximab. Resultaterne for metaanalysen af ACT1- og 2- samt GEMINI-1-studiet for vedolizumab er anvendt i en indirekte sammenligning ved brug af Buchers metode mellem ustekinumab og hhv. infliximab og vedolizumab.

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

- Ingen af de inkluderede studier for ustekinumab, infliximab og vedolizumab [10,11,13] definerer klinisk remission som efterspurgt i protokollen. Klinisk remission er i alle inkluderede studier defineret som en total Mayo-score ≤ 2 og ingen subscore > 1, hvorved patienterne i studierne kan have en højere sygdomsaktivitet end præspecificeret af fagudvalget [22]. Fagudvalget bemærker denne forskel i definitionen, men vurderer, at effektmålene kan anvendes i sammenligningen mellem lægemidlerne, idet studierne opgør effektmålet på samme måde.
- Effektmålet er i GEMINI 1-studiet opgjort efter 6 uger og ikke efter 8 uger som efterspurgt i protokollen. Den kortere opfølgningstid kan medføre, at andelen af patienter, som oplever klinisk remission ved behandling med vedolizumab, er lavere end ved behandling med ustekinumab.
- I studierne af infliximab og vedolizumab er den endoskopiske vurdering foretaget lokalt, mens vurderingen i studierne af ustekinumab er foretaget centralt. Der er i EPAR'en for ustekinumab

beskrevet, at der er udført sensitivitetsanalyser, hvori data er baseret på lokale endoskopiske vurderinger. Der fremgår dog ingen resultater for disse analyser i EPAR'en. Fagudvalget bemærker, at forskellen på vurderingsmetoderne kan have en betydning for de data, der indgår i vurderingen af effektmålet, men indtil videre er en eventuel betydning uafklaret [22].

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

Ustekinumab sammenlignet med infliximab

I tabel 4 er angivet, hvor mange patienter, samt den procentvise andel, som opnåede klinisk remission, efter induktionsbehandling, uge 8 i UNIFI-studiet, ACT1- og ACT2-studiet.

Tabel 4.

Intervention	ACT1 - infliximab		ACT2 - infliximab		UNIFI - ustekinumab	
	n/N	Procent [95 % KI]	n/N	Procent [95 % KI]	n/N	Procent [95 % KI]
Placebo	18/121	14,9 % [9,1; 22,5]	7/123	5,7 % [2,3; 11,4]	15/158	9,5 % [5,4; 15.2]
Lægemiddel	47/121	38,8 % [30,1; 48,1]	41/121	33,9 % [25,5; 43,0]	29/156	18,6 % [12,8; 25,6]

KI: Konfidensinterval; n: antal patienter som opnår hændelse; N: Totale antal patienter.

Den relative forskel, der er beregnet som en relativ risiko (RR), er: 0,52 [0,19; 1,41], hvilket er til fordel for infliximab. Der ses dog ingen statistisk signifikant forskel mellem lægemidlerne, og der er stor usikkerhed omkring effektestimatet, hvilket er afspejlet i det brede konfidensinterval. Værdien af ustekinumab sammenlignet med infliximab indplaceres derfor foreløbigt i kategorien **kan ikke kategoriseres**.

Den absolutte forskel i andelen af bio-naive patienter, der opnår klinisk remission ved uge 8 er -17,3 procentpoint [-29,31; 15,01]. Pga. det brede konfidensinterval kan værdien af ustekinumab sammenlignet med infliximab foreløbigt **ikke kategoriseres**.

På aggregeret niveau kan værdien af ustekinumab **ikke kategoriseres** vedr. klinisk remission ved uge 8 sammenlignet med infliximab (lav evidenskvalitet).

Ustekinumab sammenlignet med vedolizumab

I tabel 5 er angivet, hvor mange patienter, samt den procentvise andel, som opnåede klinisk remission, efter induktionsbehandling uge 8 i UNIFI-studiet og GEMINI-1-studiet.

Tabel 5.

	GEMINI-1 - vedolizumab		UNIFI - ustekinumab	
	n/N	Procent [95 % KI]	n/N	Procent [95 % KI]
Placebo	5/76	6,6 % [2,2; 14,7]	15/158	9,5 % [5,4; 15.2]
Lægemiddel	30/130	23,1% [16,1; 31,3]	29/156	18,6 % [12,8; 25,6]

KI: Konfidensinterval; n: antal patienter som opnår hændelse; N: Totale antal patienter.

Den relative forskel (målt som RR) mellem ustekinumab og vedolizumab er på 0,56 [0,19; 1,64], hvilket er til fordel for vedolizumab. Der ses dog ingen statistisk signifikant forskel mellem lægemidlerne, og der er stor usikkerhed omkring effektestimatet, hvilket er afspejlet i det brede konfidensinterval. Værdien af ustekinumab sammenlignet med vedolizumab kan derfor foreløbigt **ikke kategoriseres**.

Den absolutte forskel i andelen af BMSL-behandlingsnaive patienter, der opnår klinisk remission ved uge 8, er -10,2 procentpoint [-18,7; 14,99]. Pga. det brede konfidensinterval kan værdien af ustekinumab sammenlignet med vedolizumab foreløbigt **ikke kategoriseres**.

På aggregeret niveau kan værdien af ustekinumab **ikke kategoriseres** vedr. klinisk remission ved uge 8 sammenlignet med vedolizumab (meget lav evidenskvalitet).

Systemisk steroidfri remission, efter vedligeholdelsesbehandling, uge 52 (kritisk)

Systemisk steroidfri remission er defineret ved, at patienterne ikke er i systemisk kortikosteroidbehandling og har en total Mayo-score ≤ 2, ingen subscore > 1 og blødning fra endetarmen-score = 0 i uge 52.

Langvarig behandling med systemiske kortikosteroider kan være forbundet med væsentlige bivirkninger. Fagudvalget har vurderet, at en forskel på 10 procentpoint i andelen af patienter, der oplever systemisk steroidfri remission ved uge 52, er klinisk relevant.

Ansøger har anvendt data fra ACT1-studiet med infliximab samt data fra GEMINI-1-studiet med vedolizumab i en indirekte sammenligning ved brug af Buchers metode mellem ustekinumab og hhv. infliximab og vedolizumab. Data for ACT2-studiet er ikke medtaget i analysen, da der er stor forskel i opfølgningstiden.

Fagudvalget har et forbehold for analyserne af dette effektmål:

- Som ved effektmålet "Klinisk remission, efter induktionsbehandling, uge 8", er der i forskel i måden, hvorpå den endoskopiske vurdering er foretaget i de inkluderede studier. Fagudvalget bemærker, at det er opgjort forskelligt, men vurderer, at effektmålet kan anvendes i vurderingen.

Ustekinumab sammenlignet med infliximab

I tabel 6 er angivet, hvor mange patienter, samt den procentvise andel, som opnåede systemisk steroidfri remission, efter vedligeholdelsesbehandling, uge 52 i UNIFI-studiet og ACT1-studiet.

Tabel 6.

	ACT1 - infliximab		UNIFI - ustekinumab	
	n/N	Procent [95 % KI]	n/N	Procent [95 % KI]
Placebo	7/79	8,9 % [3,6; 17,4]	27/87	31,0 % [21,5; 41,9]
Lægemiddel	18/70	25,7 % [16,0; 37,6]	49/102	48,0 % [38,0; 58,2]

KI: Konfidensinterval; n: antal patienter som opnår hændelse; N: Totale antal patienter.

Den relative forskel (målt ved RR) mellem ustekinumab og infliximab er 0,53 [0,22; 1,30]. Det relative effektestimat er til fordel for infliximab, men der ses ingen statistisk signifikant forskel mellem lægemidlerne. Pga. det brede konfidensinterval kan værdien af ustekinumab sammenlignet med infliximab foreløbigt **ikke kategoriseres**.

Den absolutte forskel i andelen af BMSL-behandlingsnaive patienter, der opnår systemisk steroidfri remission, efter vedligeholdelsesbehandling ved uge 52, er -11,99 procentpoint [-20,09; 7,78]. Pga. det brede konfidensinterval kan værdien af ustekinumab sammenlignet med infliximab foreløbigt **ikke kategoriseres**.

På aggregeret niveau kan værdien af ustekinumab **ikke kategoriseres** vedr. systemisk steroidfri remission, efter vedligeholdelsesbehandling ved uge 52 sammenlignet med infliximab (meget lav evidenskvalitet).

Ustekinumab sammenlignet med vedolizumab

I tabel 7 er angivet hvor mange patienter, samt den procentvise andel, som opnåede systemisk steroidfri remission, efter vedligeholdelsesbehandling, uge 52 i UNIFI-studiet og GEMINI-1-studiet.

Tabel 7.

	GEMINI-1 - vedolizumab		UNIFI - ustekinumab	
	n/N	Procent [95 % KI]	n/N	Procent [95 % KI]
Placebo	8/43	18,6 % [8,4; 33,4]	27/87	31,0 % [21,5; 41,9]
Lægemiddel	14/39	35,9 % [21,2; 52,8]	49/102	48,0 % [38,0; 58,2]

KI: Konfidensinterval; n: antal patienter som opnår hændelse; N: Totale antal patienter.

Den relative forskel (målt ved RR) mellem ustekinumab og vedolizumab er 0,80 [0,35; 1,86] til fordel for vedolizumab, men der ses ingen signifikant forskel mellem lægemidlerne. Pga. det brede konfidensinterval kan værdien af ustekinumab sammenlignet med vedolizumab foreløbigt **ikke kategoriseres**.

Den absolutte forskel i andelen af BMSL-behandlingsnaive patienter, der opnår systemisk steroidfri remission, efter vedligeholdelsesbehandling ved uge 52, er på -7,1 procentpoint [-23,5; 30,8]. Pga. det brede konfidensinterval kan værdien af ustekinumab sammenlignet med vedolizumab foreløbigt **ikke kategoriseres**.

På aggregeret niveau kan værdien af ustekinumab **ikke kategoriseres** vedr. systemisk steroidfri remission, efter vedligeholdelsesbehandling ved uge 52 sammenlignet med vedolizumab (meget lav evidenskvalitet).

Mukosal heling, vedligeholdelsesbehandling, uge 52 (vigtig)

Mukosal heling er defineret ved en endoskopisk subscore ≤ 1 (subscoren indgår i den samlede Mayo-score). Subscoren afspejler inflammationens sværhedsgrad i slimhinden, og scoren går fra 0-3, hvor en højere score indikerer mere udtalt inflammation i slimhinden [21].

Fagudvalget finder, at mukosal heling i uge 52 er et vigtigt effektmål, da langtidseffekten af behandlingen er betydningsfuld. Fagudvalget vurderer, at hvis 10 procent flere opnår mukosal heling i uge 52 ved behandling med ét eller flere lægemidler i indbyrdes sammenligning, er det klinisk relevant.

Ansøger har anvendt data fra ACT1-studiet med infliximab samt data fra GEMINI-1-studiet med vedolizumab i en indirekte sammenligning ved brug af Buchers metode mellem ustekinumab og hhv. infliximab og vedolizumab. Data for ACT2-studiet er ikke medtaget i analysen, da der er stor forskel i opfølgningstiden.

Fagudvalget har ét forbehold for analyserne af dette effektmål:

- Som ved effektmålene "Klinisk remission, efter induktionsbehandling, uge 8" og " Systemisk steroidfri remission, efter vedligeholdelsesbehandling, uge 52", er der i forskel i måden, hvorpå den endoskopiske vurdering er foretaget (lokalt/centralt) i de inkluderede studier. Fagudvalget bemærker, at det er opgjort forskelligt, men vurderer, at effektmålet kan anvendes i vurderingen.

Ustekinumab sammenlignet med infliximab

I tabel 8 er angivet, hvor mange patienter, samt den procentvise andel, som opnåede mukosal heling, efter vedligeholdelsesbehandling, uge 52 i UNIFI-studiet og ACT1-studiet.

Tabel 8.

	ACT1 - infliximab		UNIFI - ustekinumab	
	n/N	Procent [95 % KI]	n/N	Procent [95 % KI]
Placebo	22/121	18,2 % [11,8; 26,2]	30/87	34,5 % [24,6; 45,4]
Lægemiddel	55/121	45,5 % [36,4; 54,8]	57/102	55,9 % [45,7; 65,7]

KI: Konfidensinterval; n: antal patienter som opnår hændelse; N: Totale antal patienter.

Den relative forskel (målt ved RR) mellem ustekinumab og infliximab er på 0,65 [0,38; 1,12]. Det relative effektestimat er til fordel for infliximab, men pga. det brede konfidensinterval kan værdien af ustekinumab sammenlignet med infliximab foreløbigt **ikke kategoriseres**.

Den absolutte forskel i andelen af bio-naive patienter, der opnår mukosal heling, vedligeholdelsesbehandling ved uge 52 er -16 procentpoint [-28,4; 5,3]. Pga. det brede konfidensinterval kan værdien af ustekinumab sammenlignet med infliximab foreløbigt **ikke kategoriseres**.

På aggregeret niveau kan værdien af ustekinumab **ikke kategoriseres** vedr. mukosal heling, vedligeholdelsesbehandling ved uge 52 sammenlignet med infliximab (meget lav evidenskvalitet).

Ustekinumab sammenlignet med vedolizumab

I tabel 9 er angivet hvor mange patienter, samt den procentvise andel, som opnåede mukosal heling, efter vedligeholdelsesbehandling, uge 52 i UNIFI-studiet og GEMINI-1-studiet.

Tabel 9.

	GEMINI-1 - vedolizumab		UNIFI - ustekinumab	
	n/N	Procent [95 % KI]	n/N	Procent [95 % KI]
Placebo	19/79	24,1 % [15,1; 35,0]	30/87	34,5 % [24,6; 45,4]
Lægemiddel	43/72	59,7 % [47,5; 71,1]	57/102	55,9 % [45,7; 65,7]

KI: Konfidensinterval; n: antal patienter som opnår hændelse; N: Totale antal patienter.

Den relative forskel (målt ved RR) mellem ustekinumab og vedolizumab er 0,68 [0,39; 1,17] til fordel for vedolizumab. Pga. det brede konfidensinterval kan værdien af ustekinumab sammenlignet med vedolizumab foreløbigt **ikke kategoriseres**.

Den absolutte forskel i andelen af bio-naive patienter, der opnår mukosal heling, vedligeholdelsesbehandling ved uge 52, er på -19,2 % [-36,3; 10,4]. Pga. det brede konfidensinterval kan værdien af ustekinumab sammenlignet med vedolizumab foreløbigt **ikke kategoriseres**.

På aggregeret niveau kan værdien af ustekinumab **ikke kategoriseres** vedr. mukosal heling, vedligeholdelsesbehandling ved uge 52 sammenlignet med vedolizumab (meget lav evidenskvalitet).

Bivirkninger (kritisk)

Andel patienter, der oplever en eller flere alvorlige uønskede hændelser

Bivirkninger belyser de negative konsekvenser, patienten kan opleve ved behandling med lægemidler. Fagudvalget ønsker at se på bivirkninger ud fra et kvantitativt mål, alvorlige uønskede hændelser og et kvalitativt mål i form af en narrativ beskrivelse af bivirkningsprofilerne for lægemidlerne.

Fagudvalget finder, at andelen af patienter, som oplever en eller flere alvorlige uønskede hændelser, er særligt relevant for vurderingen, da ustekinumab 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.

Ansøger har ikke udført indirekte statistiske analyser for effektmålet. Ansøger angiver, at de respektive studiedesigns i de inkluderede studier er meget forskellige, og at en indirekte sammenligning derfor vil være behæftet med betydelig usikkerhed. Fagudvalget accepterer denne antagelse. Fagudvalget har derfor baseret deres vurdering på frekvenserne for alvorlige uønskede hændelser som opgjort i studierne (se tabel 10.)

Tabel 10: Oversigt over andelen af patienter i behandling med ustekinumab, infliximab eller vedolizumab, som oplever alvorlige uønskede hændelser.

Lægemiddel Studie og reference	Opfølg-ningstid, uger	Intervention	Bionaive patienter		Bioerfarne patienter		Samlet patientpopulation	
			Andel patienter	Andel patienter, % [95 % KI]	Andel patienter	Andel patienter, % [95 % KI]	Andel patienter	Andel patienter, % [95% KI]
Ustekinumab UNIFI [10]	52	Ustekinumab	IA	IA	IA	IA	13/172	7,6 % [4,1; 12,6]
		Placebo	IA	IA	IA	IA	17/175	9,7 % [5,8; 15,1]
Infliximab ACT1 [11]	54	Infliximab	26/121	21,5 % [14,5; 29,99]	IA	IA	IA	IA
		Placebo	31/121	25,6 % [18,1; 34,4]	IA	IA	IA	IA
Infliximab ACT2 [11]	30	Infliximab	13/121	10,7 % [5,8; 17,7]	IA	IA	IA	IA
		Placebo	24/123	19,5 % [12,9; 27,6]	IA	IA	IA	IA
Vedolizumab GEMINI-1 [13,14]	52	Vedolizumab	28/309	9,1 % [6,1; 12,8]	44/266	16,5 % [12,3; 21,6]	10/122	8,2 % [4,0; 14,6]
		Placebo	12/76	15,8 % [8,4; 26,0]	7/63	11,1 % [4,6; 21,6]	20/126	15,9 % [10,0; 23,4]

IA: ikke angivet; KI: konfidensinterval.

Fagudvalget vurderer samlet set, at hyppigheden af alvorlige uønskede hændelser for ustekinumab, infliximab og vedolizumab er sammenlignelige.

Kvalitativ gennemgang af bivirkninger

Nedenstående kvalitative gennemgang er baseret på produktresuméerne for de tre lægemidler:

For ustekinumab er de hyppigst rapporterede bivirkninger (> 5 %) i de kontrollerede perioder i kliniske studier hos voksne med psoriasis, psoriasisartrit, Crohns sygdom og colitis ulcerosa: nasopharyngitis og hovedpine. De fleste bivirkninger blev anset som værende milde og resulterede ikke i behandlingsophør. De mest alvorlige bivirkninger er alvorlige overfølsomhedsreaktioner, herunder anafylaksi, forsinkede hypersensitivitetsreaktioner og angioødem [8].

For infliximab er de mest almindeligt forekommende bivirkninger rapporteret i kliniske studier: øvre luftvejsinfektioner, der blev registreret hos 25,3 % og 16,5 % af patienter behandlet med hhv. infliximab og placebo [18]. De mest alvorlige bivirkninger forbundet med brugen af TNF-hæmmere, som er blevet

rapporteret for infliximab, inkluderer: hepatitis B virus-reaktivering, kongestivt hjertesvigt, alvorlige infektioner (inklusive sepsis, opportunistiske infektioner og tuberkulose), serumsygdom (forsinkede overfølsomhedsreaktioner), hæmatologiske reaktioner, systemisk lupus erythematosus/lupus-lignende syndrom, demyeliniserende sygdomme, hepatobiliære bivirkninger, lymfomer, hepatosplenisk T-celle-lymphom, leukæmi, Merkelcellekarcinom, melanom, pædiatrisk malignitet, sarkoidose/sarkoid-lignende reaktion, byld i tarmen eller ved endetarmen (ved Crohns sygdom) og alvorlige infusionsreaktioner, herunder anafylaktisk chok og forsinkede hypersensitivitetsreaktioner [18].

For vedolizumab er de mest almindeligt forekommende bivirkninger: infektioner (f.eks. nasofaryngitis, infektion i de øvre luftveje, bronkitis, influenza og sinusitis) samt hovedpine, kvalme, feber, træthed, hoste og ledsmerter. Der er desuden rapporteret infusionsrelaterede reaktion (symptomerne var dyspnø, bronkospasme, urticaria, blussen, udslæt samt forhøjet blodtryk og hjertefrekvens) [19].

Da der ikke er udført analyser for alvorlige uønskede hændelser grundet forskelle i studiedesigns, lægges de opgjorte frekvenser af alvorlige uønskede hændelser i studierne til grund for vurderingen af ustekinumab, sammenholdt med den kvalitative gennemgang af bivirkninger.

Fagudvalget vurderer samlet set, at bivirkningsprofilerne for ustekinumab, infliximab og vedolizumab er sammenlignelige.

Samlet vurdering for effektmålet

Samlet set vurderer fagudvalget, at ustekinumab er sammenlignelig med infliximab og vedolizumab vedr. bivirkninger.

Livskvalitet (vigtig)

Til at måle livskvalitet blandt patienter med inflammatoriske tarmsygdomme anvendes Inflammatory Bowel Disease Questionnaire (IBDQ). 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 vurderer, at en forskel på 10 procentpoint i andelen af patienter, som opnår en samlet score på minimum 170, er klinisk relevant.

Fagudvalget ønsker også data for gennemsnitlig ændring fra baseline og vurderer, at den mindste klinisk relevante forskel er en ændring på ⩾ 16 point.

Livskvalitet, andel patienter, der opnår IBDQ score ≥ 170. Klinisk spørgsmål 1 (bionaive patienter)
Der er ikke publiceret relevante data for hverken ustekinumab, infliximab eller vedolizumab, som kan anvendes i besvarelsen af det kliniske spørgsmål.

Livskvalitet, forskel i ændring fra baseline på IBDQ. Klinisk spørgsmål 1 (bionaive patienter)
Fagudvalget har visse forbehold for analyserne af dette effektmål:

Livskvalitetsdata for ustekinumab:

- Data vedr. total IBDQ-score er kun publiceret for en patientpopulation bestående af bio-naive og bio-erfarne patienter ved uge 8.

Livskvalitetsdata for infliximab:

- Data vedr. total IBDQ-score er kun publiceret for bio-naive patienter og er opgjort efter 8 ugers opfølgningstid.
- Data vedr. total IBDQ-score for uge 54 er aflæst fra en graf og medtages derfor ikke i vurderingen.

Livskvalitetsdata for vedolizumab:

- Data vedr. total IBDQ-score er publiceret for en population bestående af bio-naive og bio-erfarne patienter efter 52 ugers opfølgningstid.
- På grund af forskelle i opfølgningstid for studier af ustekinumab og vedolizumab er der ikke foretaget en indirekte sammenlignende analyse for dette effektmål. Vurderingen vil derimod blive baseret på en narrativ fremstilling.

Ud fra de manglende sammenlignelige data vurderer fagudvalget, at det ikke er muligt at foretage en kvalificeret vurdering af eventuelle forskelle i effekt på livskvalitet mellem ustekinumab og hhv. infliximab og vedolizumab.

9.1.3 Evidensens kvalitet

Evidensens kvalitet for BMSL-behandlingsnaive patienter er samlet set vurderet som værende **meget lav**. Vurderingen af risiko for bias for de enkelte studier og evidensprofilerne kan ses i bilag 1. Indledningsvist blev lægemidlernes direkte sammenligning mod placebo vurderet. Der er udarbejdet separate evidensprofiler herfor (bilag 1). Der er for alle effektmål efterfølgende nedgraderet for "indirectness", da alle sammenligninger mellem ustekinumab og henholdsvis infliximab og vedolizumab er indirekte. Evidensens kvalitet er ikke vurderet for effektmålet "bivirkninger", da der grundet forskelle i studiedesigns ikke er udført en sammenlignende analyse af alvorlige uønskede hændelser.

Evidensens kvalitet er desuden nedgraderet på baggrund af følgende GRADE-domæner for de enkelte sammenligninger:

Ustekinumab

Evidensens kvalitet for ustekinumab sammenlignet med placebo er vurderet som værende lav.

- For effektmålene "systemisk steroidfri remission efter vedligeholdelsesbehandling" og "mukosal heling efter vedligeholdelsesbehandling" er der nedgraderet for "*risk of bias*", da risiko for bias er vurderet som værende høj grundet selektion af patienter, der efter uge 8 randomiseres til vedligeholdelsesbehandling.
- For effektmålet "livskvalitet" er der nedgraderet for "*indirectness*", da data i studiet er opgjort for den samlede population og ikke opdelt i BMSL-behandlingsnaive og -behandlingserfarne patienter. For samtlige effektmål er der nedgraderet for "*inconcistency*", da kun ét studie rapporterer relevante data. Det er derfor usikkert, om studiet estimerer den sande størrelsesorden af effekten, samt der er usikkerhed omkring effektestimatet.

Infliximab

Evidensens kvalitet for infliximab sammenlignet med placebo er vurderet som værende moderat.

- Der er nedgraderet for "*inconcistency*", da kun ét studie rapporterer data for den relevante opfølgningstid og er medtaget i analysen. Det er derfor usikkert, om studiet estimerer den sande størrelsesorden af effekten, samt der er usikkerhed omkring effektestimatet.

Vedolizumab

Evidensens kvalitet for vedolizumab sammenlignet med placebo er vurderet som værende meget lav.

- Der er nedgraderet for "*risiko for bias*" for effektmålene "systemisk steroidfri remission efter vedligeholdelsesbehandling", "mukosal heling efter vedligeholdelsesbehandling" og livskvalitet, da risiko for bias er vurderet værende høj grundet selektion af patienter samt inklusion af patienter, som har indgået i open-label-studiet, der efter uge 6 randomiseres til vedligeholdelsesbehandling.
- For samtlige effektmål er der nedgraderet for "*inconcistency*", da kun ét studie rapporterer relevante data. Det er derfor usikkert, om studiet estimerer den sande størrelsesorden af effekten, samt der er usikkerhed omkring effektestimatet.
- Der er nedgraderet for "*indirectness*" for effektmålet "klinisk remission efter induktionsbehandling" og "livskvalitet". For "klinisk remission efter induktionsbehandling" skyldes nedgraderingen, at opfølgningstiden i GEMINI-studiet er 6 uger og ikke 8 uger som efterspurgt i protokollen. For effektmålet "livskvalitet" er der nedgraderet for "*indirectness*", da data i studiet er opgjort for den samlede population og ikke opdelt i BMSL-behandlingsnaive og -behandlingserfarne patienter.
- Der er nedgraderet for "*imprecision*" på effektmålet "systemisk steroidfri remission", da konfidensintervallet for den relative værdi inkluderer 1 og dermed krydser den kliniske beslutningsgrænse for at anbefale eller ej.

9.2 Konklusion klinisk spørgsmål 2

Hvad er værdien af ustekinumab sammenlignet med hhv. infliximab og vedolizumab til behandling af voksne BMSL (biologiske og/eller målrettede syntetiske lægemiddel)-behandlingserfarne patienter med moderat til svær aktiv colitis ulcerosa?

Fagudvalget finder, at den samlede værdi af ustekinumab sammenlignet med vedolizumab ikke kan kategoriseres. Fagudvalget finder, at datagrundlaget for vurderingen er forbundet med stor usikkerhed. Værdien af ustekinumab sammenlignet med infliximab kan ikke vurderes.

I tabel 11 fremgår den samlede kategori for lægemidlet og kvaliteten af den samlede evidens. Derudover fremgår både absolutte og relative effektforskelle samt foreløbige og aggregerede værdier.

Tabel 11: Kategorier og resultater for vurdering af ustekinumab sammenlignet med vedolizumab (BMSL-behandlingserfarne patienter)

Effektmål	Måleenhed (MKRF)	Vigtighed	Absolutte forskelle mellem ustekinumab og komparatorer		Relative forskelle (RR) mellem ustekinumab og komparatorer		Aggregeret værdi pr. effektmål
			Forskel (95 % CI)	Foreløbig værdi	Forskel (95 % CI)	Foreløbig værdi	
Klinisk remission, efter induktions-behandling, uge 8	Andel patienter med total Mayo-score ≤ 2, ingen subscore > 1 og rektal blødning score = 0 (10 procentpoint)	Kritisk	22,7 procentpoint [-5,8; 251,6]	Kan ikke kategoriseres¤	3,31 [0,41; 26,67]	Kan ikke kategoriseres¤	Kan ikke kategoriseres¤
Systemisk steroidfri remission, efter vedligeholdelses-behandling, uge 52	Andel patienter, der ikke er i systemisk steroid-behandling efter 52 uger og har en total Mayo-score ≤ 2, ingen subscore > 1 og rektal blødning-score = 0 (10 procentpoint)	Kritisk	-16,8 procentpoint [-22,4; 30,1]	Kan ikke kategoriseres¤	0,27 [0,03;2,30]	Kan ikke kategoriseres¤	Kan ikke kategoriseres¤
Mukosal heling, vedligeholdelses-behandling, uge 52	Andel patienter med endoskopisk subscore ≤ 1 (10 procentpoint)	Vigtig	-33 procentpoint [-39,4;-10,1]	Negativ værdi	0,21 [0,06; 0,76]	Negativ værdi	Negativ værdi
Bivirkninger	Andel patienter, der oplever en alvorlig uønsket hændelse[#] (5 procentpoint)	Kritisk	UST: 7.6 %; PBO: 9,7 % VED: 8,2 %; PBO: 15,9 %	Kan ikke kategoriseres¤	Beregning ikke mulig	Kan ikke kategoriseres¤	Kan ikke kategoriseres¤
	Kvalitativ gennemgang af bivirkningsprofil. Se afsnit 9.1.2		Beregning ikke relevant	Kan ikke kategoriseres¤	Beregning ikke relevant	Kan ikke kategoriseres¤	
Livskvalitet	Andel patienter, der opnår score ≥ 170 på Inflammatory Bowel Disease Questionnaire (IBDQ) (10 procentpoint)	Vigtig	Data ikke opgjort	Kan ikke kategoriseres¤	Data ikke opgjort	Kan ikke kategoriseres¤	Kan ikke kategoriseres¤
	Forskel i ændring fra baseline på IBDQ (16 point)		Beregning ikke mulig	Kan ikke kategoriseres¤	Beregning ikke mulig	Kan ikke kategoriseres¤	Kan ikke kategoriseres¤
Samlet kategori for lægemidlets værdi		Kan ikke kategoriseres					
Kvalitet af den samlede evidens		Meget lav					

MKRF: Mindste klinisk relevante forskel; NA = Not applicable; PBO: Placebo; RR: Relativ risiko. UST: Ustekinumab; VED: Vedolizumab.

¤ På baggrund af den tilgængelige evidens er det ikke muligt at foretage en kategorisering baseret på resultaterne.
#: Naiv sammenligning. Estimaterne stammer fra UNIFI [10]og GEMINI-1[13]-studierne. Andelen er opgjort i en population bestående af både bionaive og -erfarne patienter.
* Gennemsnitlig forskel i ændring fra baseline IBDQ-score for ustekinumab sammenlignet med placebo i en population bestående af både bio-naive og bio-erfarne patienter [16].
** Gennemsnitlig forskel i ændring fra baseline IBDQ-score for vedolizumab sammenlignet med placebo i en population bestående af bio-naive patienter [15].
*** Gennemsnitlig forskel i ændring fra baseline IBDQ-score for vedolizumab sammenlignet med placebo i en population bestående af både bio-naive og bio-erfarne patienter [15].

9.2.1 Gennemgang af studier

Ansøger identificerede ét studie vedr. ustekinumab, som inkluderer BMSL-behandlingserfarne patienter, ingen studier vedr. infliximab og ét studie vedr. vedolizumab. Studiernes design og populationernes karakteristika er beskrevet i afsnit 9.1.1.

Studiedesign
Studierne, der indgår i analysen af klinisk spørgsmål 2, er beskrevet i afsnit 9.1.1. For ustekinumab omhandler det UNIFI, og for vedolizumab omhandler det GEMINI-1.

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

9.2.2 Resultater og vurdering

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

Klinisk remission, efter induktionsbehandling, uge 8 (kritisk)
Der er ikke publiceret data for bio-erfarne patienter i behandling med infliximab, og vurderingen af effektmålet vil derfor kun blive baseret på en sammenligning mellem ustekinumab og vedolizumab.

Ansøger har anvendt Buchers metode til at udarbejde en indirekte sammenligning mellem ustekinumab og vedolizumab. Der er i sammenligningen anvendt data for hhv. UNIFI-studiet og GEMINI-1-studiet.

Som fremhævet ved vurderingen af effektmålet "Klinisk remission, efter induktionsbehandling, uge 8" i klinisk spørgsmål 1 er der forskellige årsager til, at fagudvalget har forbehold for analyserne af dette effektmål:

- Ingen af de inkluderede studier for ustekinumab og vedolizumab [10,13] definerer klinisk remission som efterspurgt i protokollen. Fagudvalget bemærker denne forskel i definitionen, men finder, at effektmålet kan anvendes i sammenligningen, idet studierne er sammenlignelige.
- Effektmålet er i GEMINI 1-studiet opgjort efter 6 uger og ikke efter 8 uger som efterspurgt i protokollen. Den kortere opfølgningstid kan medføre, at andelen af patienter, som oplever klinisk remission ved behandling med vedolizumab, er lavere end ved behandling med ustekinumab.
- Der er forskel i måden, hvorpå den endoskopiske vurdering (lokal/central) er foretaget i de inkluderede studier. Fagudvalget bemærker denne forskel, men vurderer, at effektmålet kan anvendes i vurderingen.

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

Ustekinumab sammenlignet med vedolizumab

I tabel 12 er angivet, hvor mange patienter, samt den procentvise andel, som opnåede klinisk remission, efter induktionsbehandling, uge 8 i UNIFI-studiet og GEMINI-1-studiet.

Tabel 12.

	GEMINI-1 - vedolizumab		UNIFI - ustekinumab	
	n/N	Procent [95 % KI]	n/N	Procent [95 % KI]
Placebo	2/63	3,2 % [0,4; 11,0]	2/161	1,2 % [0,2; 4,4]
Lægemiddel	8/82	9,8 % [4,3; 18,3]	21/166	12,7 % [8,0; 18,7]

KI: Konfidensinterval; n: antal patienter som opnår hændelse; N: Totale antal patienter.

Den relative forskel (målt ved RR) mellem ustekinumab og vedolizumab på 3,31 [0,41; 26,67] er til fordel for ustekinumab, men der ses ingen statistisk signifikant forskel mellem lægemidlerne. Pga. det brede konfidensinterval kan værdien af ustekinumab sammenlignet med vedolizumab foreløbigt **ikke kategoriseres**.

Den absolutte forskel i andelen af bio-erfarne patienter, der opnår klinisk remission ved uge 8 er 22,7 procentpoint [-5,8; 251,6]. Pga. det brede konfidensinterval kan værdien af ustekinumab sammenlignet med vedolizumab foreløbigt **ikke kategoriseres**.

På aggregeret niveau kan værdien af ustekinumab **ikke kategoriseres** vedr. klinisk remission ved uge 8 sammenlignet med vedolizumab (lav evidenskvalitet).

Systemisk steroidfri remission, efter vedligeholdelsesbehandling, uge 52 (kritisk)

Der er ikke publiceret data for bioerfarne patienter i behandling med infliximab, og vurderingen af effektmålet vil derfor kun blive baseret på en sammenligning mellem ustekinumab og vedolizumab.

Ansøger har anvendt Buchers metode til at udarbejde en indirekte sammenligning mellem ustekinumab og vedolizumab. Der er i sammenligningen anvendt data for hhv. UNIFI-studiet og GEMINI-1-studiet.

Fagudvalget har et forbehold for analyserne af dette effektmål:

- Som ved effektmålet "Klinisk remission, efter induktionsbehandling, uge 8", er der i forskel i måden, hvorpå den endoskopiske vurdering er foretaget (lokal/central) i de inkluderede studier. Fagudvalget bemærker denne forskel, men vurderer, at effektmålet kan anvendes i vurderingen.

Ustekinumab sammenlignet med vedolizumab

I tabel 13 er angivet, hvor mange patienter, samt den procentvise andel, som opnåede systemisk steroidfri remission, efter vedligeholdelsesbehandling, uge 52 i UNIFI-studiet og GEMINI-1-studiet.

Tabel 13.

	GEMINI-1 - vedolizumab		UNIFI - ustekinumab	
	n/N	Procent [95 % KI]	n/N	Procent [95 % KI]
Placebo	1/23	4,3 % [0,1; 21,9]	14/88	15,9 % [9,0; 25,2]
Lægemiddel	6/26	23,1 % [9,0; 43,6]	16/70	22,9 % [13,7; 34,4]

KI: Konfidensinterval; n: antal patienter, som opnår hændelse; N: Totale antal patienter.

Den relative forskel (målt ved RR) mellem ustekinumab 90 mg SC og vedolizumab 300 mg IV er 0,27 [0,03;2,30]. Pga. det brede konfidensinterval kan værdien af ustekinumab sammenlignet med vedolizumab foreløbigt **ikke kategoriseres**.

Den absolutte forskel i andelen af bio-erfarne patienter, der opnår systemisk steroidfri remission, efter vedligeholdelsesbehandling ved uge 52, er på -16,8 procentpoint [-22,4; 30,1]. Pga. det brede konfidensinterval kan værdien af ustekinumab sammenlignet med vedolizumab foreløbigt **ikke kategoriseres**.

På aggregeret niveau kan værdien af ustekinumab **ikke kategoriseres** vedr. systemisk steroidfri remission, efter vedligeholdelsesbehandling ved uge 52 sammenlignet med vedolizumab (meget lav evidenskvalitet).

Mukosal heling, vedligeholdelsesbehandling, uge 52 (vigtig)

Der er ikke publiceret data for bioerfarne patienter i behandling med infliximab, og vurderingen af effektmålet vil derfor kun blive baseret på en sammenligning mellem ustekinumab og vedolizumab.

Ansøger har anvendt Buchers metode til at udarbejde en indirekte sammenligning mellem ustekinumab og vedolizumab. Der er i sammenligningen anvendt data for hhv. UNIFI-studiet og GEMINI-1-studiet.

Fagudvalget har et forbehold for analyserne af dette effektmål:

- Som ved effektmålene "Klinisk remission, efter induktionsbehandling, uge 8" og " Systemisk steroidfri remission, efter vedligeholdelsesbehandling, uge 52", er der i forskel i måden, hvorpå den endoskopiske vurdering er foretaget (lokalt/centralt) i de inkluderede studier. Fagudvalget bemærker denne forskel, men vurderer, at effektmålet kan anvendes i vurderingen.

Ustekinumab sammenlignet med vedolizumab

I tabel 14 er angivet hvor mange patienter, samt den procentvise andel, som opnåede mukosal heling efter vedligeholdelsesbehandling, uge 52 i UNIFI-studiet og GEMINI-1-studiet.

Tabel 14.

	GEMINI-1 - vedolizumab		UNIFI - ustekinumab	
	n/N	Procent [95 % KI]	n/N	Procent [95 % KI]
Placebo	3/38	7,9 % [1,7; 21,4]	20/88	22,7 % [14,5; 32,9]
Lægemiddel	18/43	41,9 % [27,0; 57,9]	18/70	25,7 % [16,0; 37,6]

KI: Konfidensinterval; n: antal patienter, som opnår hændelse; N: Totale antal patienter.

Den relative forskel (målt ved RR) mellem ustekinumab og vedolizumab på 0,21 [0,06; 0,76] er til fordel for vedolizumab, og forskellen er statistisk signifikant. Baseret på den relative effektforskel har ustekinumab foreløbigt en **negativ værdi** sammenlignet med vedolizumab vedr. mukosal heling ved uge 52.

Den absolutte forskel i andelen af bio-erfarne patienter, der opnår mukosal heling efter vedligeholdelsesbehandling ved uge 52, er på -33 procentpoint [-39,4;-10,1]. Forskellen mellem lægemidlerne overstiger den prædefinerede mindste klinisk relevante forskel og er til fordel for vedolizumab. Baseret på den absolutte forskel har ustekinumab foreløbigt en **negativ værdi** sammenlignet med vedolizumab.

På aggregeret niveau har ustekinumab en **negativ værdi** sammenlignet med vedolizumab vedr. mukosal heling ved uge 52 (meget lav evidenskvalitet).

Bivirkninger (kritisk)
Se afsnit 9.1.2., da BMSL-behandlingsnaive og -erfarne patienter vurderes samlet for dette effektmål.

Livskvalitet (vigtig)
Se afsnit 9.1.2., da BMSL-behandlingsnaive og -erfarne patienter vurderes samlet for dette effektmål.

9.2.3 Evidensens kvalitet

Evidensens kvalitet for BMSL-behandlingserfarne patienter er samlet set vurderet som værende **meget lav**. Overvejelser vedrørende evidensens kvalitet og risiko for bias kan ses i bilag 1. Indledningsvist blev lægemidlernes direkte sammenligning mod placebo vurderet. Der er udarbejdet separate evidensprofiler herfor. Der er for alle effektmål efterfølgende nedgraderet for "indirectness", da alle sammenligninger mellem ustekinumab og vedolizumab er indirekte. Evidensens kvalitet er ikke vurderet for effektmålet "bivirkninger", da der grundet forskelle i studiedesigns ikke er udført en sammenlignende analyse af alvorlige uønskede hændelser mellem ustekinumab og vedolizumab.

Evidensens kvalitet er desuden nedgraderet på baggrund af følgende GRADE-domæner for de enkelte sammenligninger:

Ustekinumab

Evidensens kvalitet for ustekinumab sammenlignet med placebo er vurderet som værende lav.

- For samtlige effektmål er der nedgraderet for "*inconcistency*", da kun ét studie rapporterer relevante data. Det er derfor usikkert, om studiet estimerer den sande størrelsesorden af effekten, samt der er usikkerhed omkring effektestimatet.
- For effektmålene "systemisk steroidfri remission efter vedligeholdelsesbehandling" og "mukosal heling efter vedligeholdelsesbehandling" er der nedgraderet for "*risk of bias*", da risiko for bias er vurderet som værende høj grundet selektion af patienter, der efter uge 8 randomiseres til vedligeholdelsesbehandling.
- Der er nedgraderet for "*imprecision*" på effektmålene "systemisk steroidfri remission" og "mukosal heling", da konfidensintervallet for den relative værdi inkluderer 1 og dermed krydser den kliniske beslutningsgrænse for at anbefale eller ej.
- For effektmålet "livskvalitet" er der nedgraderet for "*indirectness*", da data i studiet er opgjort for den samlede population og ikke opdelt i BMSL-behandlingsnaive og -behandlingserfarne patienter.

Vedolizumab

Evidensens kvalitet for vedolizumab sammenlignet med placebo er vurderet som værende meget lav.

- For samtlige effektmål er der nedgraderet for "*inconcistency*", da kun ét studie rapporterer relevante data. Det er derfor usikkert, om studiet estimerer den sande størrelsesorden af effekten, samt der er usikkerhed omkring effektestimatet.
- Der er nedgraderet for "*indirectness*" for effektmålet "klinisk remission efter induktionsbehandling" og "livskvalitet". For "klinisk remission efter induktionsbehandling" skyldes nedgraderingen, at opfølgningstiden i GEMINI-studiet er 6 uger og ikke 8 uger, som efterspurgt i protokollen. For effektmålet "livskvalitet" skyldes nedgraderingen, at data i studiet er opgjort for den samlede population og ikke opdelt i BMSL-behandlingsnaive og -behandlingserfarne patienter.

- Der er nedgraderet for "*risk of bias*" for effektmålene "systemisk steroidfri remission efter vedligeholdelsesbehandling" og "mukosal heling efter vedligeholdelsesbehandling", da risiko for bias er vurderet værende høj grundet selektion af patienter samt inklusion af patienter, som har indgået i open-label-studiet, der efter uge 6 randomiseres til vedligeholdelsesbehandling.
- Der er nedgraderet for "*imprecision*" på effektmålene "klinisk remission efter induktionsbehandling" og "systemisk steroidfri remission", da konfidensintervallerne for den relative værdi inkluderer 1 og dermed krydser den kliniske beslutningsgrænse for at anbefale eller ej.

10 Fagudvalgets vurdering af samlet værdi og samlet evidensniveau

For BMSL-naive patienter finder fagudvalget, at den samlede værdi af ustekinumab sammenlignet med hhv. infliximab og vedolizumab ikke kan kategoriseres. Fagudvalget bemærker, at ustekinumab har en tendens til at udvise ringere effekt på klinisk remission ved uge 8, systemisk steroidfri remission ved uge 52 og mukosal heling vurderet ved uge 52. Ingen af disse forskelle var statistisk signifikante. Da der ikke er påvist forskelle mellem ustekinumab og komparatorerne, vurderer fagudvalget samlet set, at ustekinumab har en sammenlignelig effekt og sikkerhedsprofil med infliximab og vedolizumab.

For BMSL-erfarne patienter finder fagudvalget, at den samlede værdi af ustekinumab sammenlignet med vedolizumab ikke kan kategoriseres. Fagudvalget lægger vægt på, at der for de kritiske effektmål, klinisk remission ved uge 8 og steroidfri remission ved uge 52 er stor usikkerhed omkring estimatet af effekten. Samtidig vurderer fagudvalget, at sikkerhedsprofilen mellem ustekinumab og vedolizumab er sammenlignelig. For det vigtige effektmål mukosal heling ved 52-uger er ustekinumab statistisk signifikant dårligere sammenlignet med vedolizumab. Datagrundlaget for dette effektmål er dog baseret på få hændelser. Samlet set vægter fagudvalget usikkerheden omkring effekten af ustekinumab og finder derfor ikke, at der på baggrund af nuværende data er en påviselig forskel mellem ustekinumab og vedolizumab. Værdien af ustekinumab sammenlignet med infliximab kan ikke vurderes.

På denne baggrund vurderer fagudvalget, at:

- Værdien af ustekinumab til BMSL-behandlingsnaive patienter med moderat til svær colitis ulcerosa sammenlignet med hhv. infliximab og vedolizumab **kan ikke kategoriseres**. Fagudvalget vurderer dog, at ustekinumab samlet set har en sammenlignelig effekt og sikkerhedsprofil med infliximab og vedolizumab.

- Værdien af ustekinumab til BMSL-behandlingserfarne patienter med moderat til svær colitis ulcerosa sammenlignet med vedolizumab **kan ikke kategoriseres**. Fagudvalget finder, at datagrundlaget for vurderingen er forbundet med stor usikkerhed. Værdien af ustekinumab sammenlignet med infliximab kan ikke vurderes.

11 Rådets vurdering af samlet værdi og samlet evidensniveau

Medicinrådet finder, at den samlede værdi af ustekinumab til BMSL-behandlingsnaive patienter med moderat til svær colitis ulcerosa sammenlignet med hhv. infliximab og vedolizumab ikke kan kategoriseres. Rådet vurderer dog, at ustekinumab samlet set har en sammenlignelig effekt og sikkerhedsprofil med infliximab og vedolizumab.

Medicinrådet finder, at den samlede værdi af ustekinumab til BMSL-behandlingserfarne patienter med moderat til svær colitis ulcerosa sammenlignet med vedolizumab ikke kan kategoriseres. Rådet finder, at datagrundlaget for vurderingen er forbundet med stor usikkerhed. Værdien af ustekinumab sammenlignet med infliximab kan ikke vurderes.

12 Relation til eksisterende behandlingsvejledning

Der foreligger en RADS-behandlingsvejledning vedrørende dyre lægemidler til behandling af kroniske inflammatoriske tarmsygdomme, inklusive behandling af moderat til svær aktiv colitis ulcerosa. Fagudvalget vurderer, at ustekinumab kan ligestilles med nuværende førstelinjebehandlinger (infliximab, vedolizumab og golimumab) til patienter, som ikke tidligere har været behandlet med et biologisk eller målrettet syntetisk lægemiddel (BMSL-behandlingsnaive patienter). Fagudvalget vurderer, at ustekinumab på foreliggende datagrundlag ikke kan indplaceres i behandlingsrækkefølgen til patienter, som tidligere har været i behandling med et BMSL (BMSL-behandlingserfarne patienter).

Medicinrådet har besluttet at udarbejde en behandlingsvejledning for colitis ulcerosa i 2020. Her vil fagudvalget vurdere lægemidler med indikationen moderat til svær colitis ulcerosa.

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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15 Versionslog

Version	Dato	Ændring
1.0	19. februar 2020	Godkendt af Medicinrådet.

16 Bilag 1: GRADE-evidensprofiler

16.1 Cochrane Risk of Bias

Ustekinumab NCT02407236 (UNIFI)

(Ustekinumab as Induction and Maintenance Therapy for Ulcerative Colitis, Sands et al., 2019)

Bias	Risk of bias	Elaboration
Selection bias		
Random sequence generation	**High**	Randomization was performed with the use of permuted blocks, with stratification according to status with respect to previous treatment failure with biologic agents (yes or no) and geographic region (eastern Europe, Asia, or rest of world). For the induction therapy, the risk of bias regarding the random sequence generation is judged as unclear, since the block design is not described. 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 ustekinumab at week 8 of the induction therapy, were randomly assigned in this part. Also, patients who did not have a response to intravenous placebo and who then received an induction dose of intravenous ustekinumab (6 mg per kilogram) at week 8 and had a response at week 16 entered the maintenance trail. Those, that were receiving placebo and had a clinical response to placebo, continued with that.
Allocation concealment	**Unclear**	Central randomisation for treatment allocation was implemented in the induction study. A computer-generated randomization schedule was prepared for this study under the supervision of the sponsor or delegate. At each call to the interactive web response system (IWRS) for a treatment assignment, the IWRS assigned a treatment code that dictated the treatment assignment and matching study agent kit for each subject (stated in the EPAR for ustekinumab). No description of the method used to guarantee allocation concealment in the maintenance study. Risk of bias is judged as unclear.
Deviations from intended interventions	**Low**	No concerns.
Performance bias: blinding of participants and personnel. Assessment made for class of outcomes.		
Patient-reported outcomes	**Low**	Blinding was maintained (for both the induction and maintenance studies) for investigative sites, site monitors, and subjects participating in this protocol until the Week 44 analyses were completed. Because subjects in this study were assigned to different dosing frequencies, all subjects received study agent (ie, ustekinumab or placebo) at all scheduled study agent administration visits to maintain the blind. Risk of bias is judged as low
Objective outcomes	**Low**	Ibid.
Detection bias: blinding of outcome assessment. Assessment made for class of outcomes.		
Patient-reported outcomes	**Low**	Blinding was maintained (for both the induction and maintenance studies) for investigative sites, site monitors, and subjects participating in this protocol until the Week 44 analyses were completed.
Objective outcomes	**Low**	Ibid.

Attrition bias: incomplete outcome data. Assessment made for class of outcomes.	**Low**	For subjects with missing data the last observation was carried forward for continuous endpoints. An exception to this was with the Mayo and partial Mayo scores, where the last available Mayo subscores were carried forward. For dichotomous endpoints, subjects with missing data were considered not to have achieved the respective endpoints. Treatment failure rules overrode missing data rules. This meant that if a subject had an event of treatment failure, baseline values were assigned from the point of treatment failure onward for continuous endpoints, and subjects were not considered to have achieved the respective endpoints for dichotomous endpoints, regardless of whether the data were observed or missing.
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 selection of patients that are randomized in the maintenance phase and the non-randomized patients.

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 low.. 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. Moreover, patients from an open-label cohort receiving induction dose of ustekinumab was enrolled in the randomization for the maintenance study.
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 judged as unclear.
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 is judged as unclear.
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 unclear.
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 unclear.
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.

16.2 GRADE-evaluering af evidenskvaliteten

Klinisk spørgsmål 1/BMSL-behandlingsnaive patienter

Ustekinumab sammenlignet med placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ustekinumab	placebo	Relative (95% CI)	Absolute (95% CI)		
Klinisk remission, efter induktionsbehandling (follow up: mean 8 weeks)												
1	randomised trials	not serious	serious [a]	not serious	not serious	none	29/156 (18.6%)	15/158 (9.5%)	**RR 1.96** (1.09 to 3.51)	**91 more per 1.000** (from 9 more to 238 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Systemisk steroidfri remission, efter vedligeholdelsesbehandling (follow up: mean 44 weeks)												
1	randomised trials	serious [b]	serious [a]	not serious	not serious	none	49/102 (48.0%)	27/87 (31.0%)	**RR 1.55** (1.07 to 2.25)	**171 more per 1.000** (from 22 more to 388 more)	⨁⨁◯◯ LOW	CRITICAL
Mukosal heling, efter vedligeholdelsesbehandling (follow up: mean 44 weeks)												
1	randomised trials	serious [b]	serious [a]	not serious	not serious	none	57/102 (55.9%)	30/87 (34.5%)	**RR 1.62** (1.16 to 2.27)	**214 more per 1.000** (from 55 more to 438 more)	⨁⨁◯◯ LOW	IMPORTANT
Livskvalitet, IBDQ (follow up: mean 8 weeks; Scale from: 32 to 224)												
1	randomised trials	not serious	serious [a]	serious [c]	not serious	none	Absolut effektforskel (gennemsnitlig ændring fra baseline) 18,9 [13,99;23,81]				⨁⨁◯◯ LOW	IMPORTANT

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

Forklaring:
a. Kun ét studie indgår i vurderingen af dette effektmål.
b. Risiko for bias er vurderet høj primært pga. selektion af randomiserede patienter, som indgår i studiet for vedligeholdelsesbehandling.
c. Der er ikke publiceret særskilte data for BMSL-behandlingsnaive og -erfarne patienter. Vurderingen af dette effektmål er foretaget for den samlede population.

Infliximab sammenlignet med placebo

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, efter induktionsbehandling (follow up: mean 8 weeks)												
2	randomised trials	not serious	not serious	not serious	not serious	none	88/242 (36.4%)	25/244 (10.2%)	**RR 3.732** (1.676 to 8.311)	**280 more per 1.000** (from 69 more to 749 more)	⨁⨁⨁⨁ HIGH	CRITICAL
Systemisk steroidfri remission, efter vedligeholdelsesbehandling (follow up: mean 54 weeks)												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	18/70 (25.7%)	7/79 (8.9%)	**RR 2.90** (1.29 to 6.53)	**168 more per 1.000** (from 26 more to 490 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Mukosal heling, efter vedligeholdelsesbehandling (follow up: mean 54 weeks)												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	55/121 (45.5%)	22/121 (18.2%)	**RR 2.50** (1.63 to 3.83)	**273 more per 1.000** (from 115 more to 515 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Livskvalitet, IBDQ (follow up: mean 8 weeks; Scale from: 32 to 224)												
2	randomised trials	not serious	not serious	not serious	not serious	none			-	**0** (0 to 0)	⨁⨁⨁⨁ HIGH	IMPORTANT

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

Forklaring:
a. Kun ét studie indgår i vurderingen af dette effektmål.

Vedolizumab sammenlignet med placebo

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, efter induktionsbehandling (follow up: mean 6 weeks)												
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
Systemisk steroidfri remission, efter vedligeholdelsesbehandling (follow up: mean 46 weeks)												
1	randomised trials	serious [c]	serious [a]	not serious	serious [d]	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)	⨁◯◯◯ VERY LOW	CRITICAL
Mukosal heling, efter vedligeholdelsesbehandling (follow up: mean 46 weeks)												
1	randomised trials	serious [c]	serious [a]	not serious	not serious	none	43/72 (59.7%)	19/79 (24.1%)	**RR 2.39** (1.55 to 3.68)	**334 more per 1.000** (from 132 more to 645 more)	⨁⨁◯◯ LOW	IMPORTANT
Livskvalitet (follow up: mean 46 weeks; Scale from: 32 to 224)												
1	randomised trials	serious [c]	serious [a]	serious [e]	not serious	none			-	**0** (0 to 0)	⨁◯◯◯ VERY LOW	IMPORTANT

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

Forklaring:
a. Kun ét studie indgår i vurderingen af dette effektmål.
b. GEMINI-studiet havde kun 6 ugers opfølgningstid. Der var bedt om 8 ugers opfølgning i induktionsperioden.
c. Risiko for bias er vurderet høj primært pga. selektion af randomiserede patienter, som indgår i studiet for vedligeholdelsesbehandling, samt at patienter, der indgik i open-label studiet i induktionsperioden, indgår i vedligeholdelsesstudiet.
d. Konfidensintervallet for den relative forskel inkluderer 1.
e. Der er ikke publiceret særskilte data for BMSL-behandlingsnaive og -erfarne patienter. Vurdering af dette effektmål er foretaget for den samlede population.

Ustekinumab sammenlignet med placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ustekinumab	placebo	Relative (95% CI)	Absolute (95% CI)		
Klinisk remission, efter induktionsbehandling (follow up: mean 8 weeks)												
1	randomised trials	not serious	serious [a]	not serious	not serious	none	21/166 (12.7%)	2/161 (1.2%)	**RR 10.18** (2.43 to 42.73)	**114 more per 1.000** (from 18 more to 518 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Systemisk steroidfri remission, efter vedligeholdelsesbehandling (follow up: mean 44 weeks)												
1	randomised trials	serious [b]	serious [a]	not serious	serious [c]	none	16/70 (22.9%)	14/88 (15.9%)	**RR 1.44** (0.75 to 2.74)	**70 more per 1.000** (from 40 fewer to 277 more)	⨁◯◯◯ VERY LOW	CRITICAL
Mukosal heling, efter vedligeholdelsesbehandling (follow up: mean 44 weeks)												
1	randomised trials	serious [b]	serious [a]	not serious	serious [c]	none	18/70 (25.7%)	20/88 (22.7%)	**RR 1.13** (0.65 to 1.97)	**30 more per 1.000** (from 80 fewer to 220 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Livskvalitet, IBDQ (follow up: mean 8 weeks; Scale from: 32 to 224)												
1	randomised trials	not serious	serious [a]	serious [d]	not serious	none	Absolut effektforskel (gennemsnitlig ændring fra baseline) 18,9 [13,99;23,81]				⨁⨁◯◯ LOW	IMPORTANT

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

Forklaring:
a. Kun ét studie indgår i vurderingen af dette effektmål.
b. Risiko for bias er vurderet høj primært pga. selektion af randomiserede patienter, som indgår i studiet for vedligeholdelsesbehandling.
c. Konfidensintervallet for den relative forskel inkluderer 1.
d. Der er ikke publiceret særskilte data for BMSL-behandlingsnaive og -erfarne patienter. Vurderingen af dette effektmål er foretaget for den samlede population.

Vedolizumab sammenlignet med placebo

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, efter induktionsbehandling (follow up: mean 6 weeks)												
1	randomised trials	not serious	serious [a]	serious [b]	serious [c]	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)	⨁◯◯◯ VERY LOW	CRITICAL
Systemisk steroidfri remission, efter vedligeholdelsesbehandling (follow up: mean 46 weeks)												
1	randomised trials	serious [d]	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)	⨁◯◯◯ VERY LOW	CRITICAL
Mukosal heling, efter vedligeholdelsesbehandling (follow up: mean 46 weeks)												
1	randomised trials	serious [d]	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)	⨁⨁◯◯ LOW	IMPORTANT
Livskvalitet (follow up: mean 46 weeks; Scale from: 32 to 224)												
1	randomised trials	serious [d]	serious [a]	serious [c]	not serious	none			-	**0** (0 to 0)	⨁◯◯◯ VERY LOW	IMPORTANT

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

Forklaring:
a. Kun ét studie indgår i vurderingen af dette effektmål.
b. GEMINI-studiet havde kun 6 ugers opfølgningstid. Der var i protokollen bedt om 8 ugers opfølgning i induktionsperioden.
c. Konfidensintervallet for den relative forskel inkluderer 1.
d. Risiko for bias er vurderet høj primært pga. selektion af randomiserede patienter, som indgår i studiet for vedligeholdelsesbehandling, samt at patienter, der indgik i open-label studiet i induktionsperioden, indgår i vedligeholdelsesstudiet
e. Der er ikke publiceret særskilte data for BMSL-behandlingsnaive og -erfarne patienter. Vurdering af dette effektmål er foretaget for den samlede population.

Application for the assessment of clinically added value of Stelara® (ustekinumab) for moderate to severe ulcerative colitis

Contents

1 Basic information

Table 1 Contact information.

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Title	Health economics, market access and reimbursement specialist
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Table 2 Overview of the pharmaceutical (1).

Proprietary name	STELARA®
Generic name	Ustekinumab
Marketing authorization holder in Denmark	Janssen-Cilag A/S Bregnerødvej 133 DK-3460 Birkerød
ATC code	L04AC05
Pharmacotherapeutic group	Immunosuppressants, interleukin inhibitors
Active substance(s)	Ustekinumab
Pharmaceutical form(s)	130 mg concentrate for solution for infusion ustekinumab and 90 mg solution for injection in pre-filled syringe ustekinumab.
Mechanism of action	Ustekinumab is a fully human IgG1κ monoclonal antibody that binds with specificity to the shared p40 protein subunit of human cytokines interleukin (IL)-12 and IL-23. Ustekinumab inhibits the bioactivity of human IL-12 and IL-23 by preventing p40 from binding to the IL-12Rβ1 receptor protein expressed on the surface of immune cells. Ustekinumab cannot bind to IL-12 or IL-23 that is already bound to IL-12Rβ1 cell surface receptors. Thus, ustekinumab is not likely to contribute to complement- or antibody-mediated cytotoxicity of cells with IL-12 and/or IL-23 receptors. IL-12 and IL-23 are heterodimeric cytokines secreted by activated antigen presenting cells, such as macrophages and dendritic cells, and both cytokines participate in immune functions; IL-12 stimulates natural killer (NK) cells and drives the differentiation of CD4+ T cells toward the T helper 1 (Th1) phenotype, IL-23 induces the T helper 17 (Th17) pathway. However, abnormal regulation of IL-12 and IL-23 has been associated with immune mediated diseases, such as psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis. By binding the shared p40 subunit of IL-12 and IL-23, ustekinumab may exert its clinical effects in psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis through interruption of the Th1 and Th17 cytokine pathways, which are central to the pathology of these diseases.
Dosage regimen	STELARA® treatment is to be initiated with a single intravenous dose based on body weight. The infusion solution is to be composed of the number of vials of STELARA® 130 mg as specified in SmPC section 4.2. The first subcutaneous administration of 90 mg STELARA® should take place at week 8 after the intravenous dose. After this, dosing every 12 weeks is recommended. Patients who have not shown adequate response at 8 weeks after the first subcutaneous dose, may receive a second subcutaneous dose at this time.

	Patients who lose response on dosing every 12 weeks may benefit from an increase in dosing frequency to every 8 weeks.
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	STELARA® is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic or have medical contraindications to such therapies.
Other approved therapeutic indications	Plaque psoriasis STELARA® is indicated for the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate (MTX) or PUVA (psoralen and ultraviolet A). Paediatric plaque psoriasis STELARA® is indicated for the treatment of moderate to severe plaque psoriasis in adolescent patients from the age of 12 years and older, who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies. Psoriatic arthritis (PsA) STELARA®, alone or in combination with MTX, is indicated for the treatment of active psoriatic arthritis in adult patients when the response to previous non-biological disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate. Crohn's disease (CD) STELARA® is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNFα antagonist or have medical contraindications to such therapies.
Will dispensing be restricted to hospitals?	Yes for STELARA® 130mg - dispensing code is BEGR (2) Yes for STELARA® 90mg - dispensing code is NBS (3)
Combination therapy and/or co-medication	No
Packaging – types, sizes/number of units, and concentrations	STELARA® 130 mg concentrate for solution for infusion Each vial contains 130 mg of ustekinumab in 26 ml (5 mg / ml). STELARA® 90 mg solution for injection 1 ml solution in type 1 vial with 2 ml closed with a coated butyl rubber stopper
Orphan drug designation	No

2 Abbreviations

AE	adverse event
CD	Crohn's disease
CI	confidence interval
DMARD	disease-modifying anti-rheumatic drug
IBD	inflammatory bowel disease
IBDQ	inflammatory bowel disease questionnaire
IFX	infliximab
IL	Interleukin
IV	intravenous
LL	lower limit
MTX	methotrexate
NCT	National Clinical Trial
PBO	placebo
PSA	Psoriatic arthritis
PUVA	psoralen and ultraviolet A
Q12W	every 12 weeks
Q4W	every 4 weeks
Q8W	every 8 weeks
RR	risk ratio
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SE	standard error
TNF	tumor necrosis factor
UC	Ulcerative Colitis
UL	upper limit
UST	ustekinumab
VDZ	vedolizumab

3 Summary

Ustekinumab (Stelara®) is an innovative treatment approved by the European Commission on September 3th, 2019 for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic or have medical contraindications to such therapies.

This application presents the basis for the evaluation of the clinically added value of ustekinumab for adult biological and targeted synthetic drug treatment-naïve and treatment-experienced patients with moderate to severe active ulcerative colitis compared to infliximab and vedolizumab. The efficacy measures which the evaluation is based on is clinical remission at week 8, corticosteroid-free clinical remission at week 52, serious adverse events, mucosal healing at week 52, change from baseline in total Inflammatory Bowel Disease questionnaire (IBDQ) score and IBDQ remission.

Ustekinumab has not been directly compared to either infliximab or vedolizumab in any published randomized trials. Consequently, an indirect comparison between ustekinumab and infliximab as well as ustekinumab and vedolizumab has been performed utilizing Bucher's methodology.

The efficacy and safety of ustekinumab in the treatment of patients with moderately to severely active UC was demonstrated in the phase III, randomized, double-blind, placebo-controlled, parallel-group, multicenter UNIFI trial. Ustekinumab demonstrated rapid and sustained improvement of disease activity in patients who demonstrated an inadequate response or failure or intolerance to conventional therapy or biologic therapy.

Summary of results on the critical efficacy endpoints:

- For bio-naïve and bio-experienced patients, 18.6% and 12.7%, respectively, achieved clinical remission at week 8 when treated with the ~6 mg/kg ustekinumab IV induction.
- For bio-naïve and bio-experienced patients, 48% and 22.9%, respectively, achieved corticosteroid-free clinical remission at week 52 when treated with 90 mg SC ustekinumab q12w.

The safety profile of ustekinumab in the UNIFI trial was similar to placebo and consistent with clinical experience in established indications, as demonstrated in Crohn's disease, plaque psoriasis, and psoriasis arthritis clinical trials.

Results for the indirect comparisons on all efficacy measures for both the adult biological and targeted synthetic drug treatment-naïve and treatment-experienced patients showed that there was no significant difference between ustekinumab and vedolizumab. In addition, there was no significant difference between ustekinumab and infliximab in adult biological and targeted synthetic drug treatment-naïve patients. The indirect comparison between ustekinumab and infliximab as well as ustekinumab and vedolizumab resulted in relative differences and absolute differences with uncertainty as indicated by broad confidence intervals and accordingly no clinically relevant differences were determined.

Conclusively, the evaluation of clinically added value presented in this application shows that ustekinumab has comparable efficacy to infliximab and vedolizumab for treatment of adult biological and targeted synthetic drug treatment-naïve and treatment-experienced patients with moderate to severe active ulcerative colitis.

3.1 Introduction

Ulcerative colitis (UC) is an idiopathic inflammatory disease, affecting mainly adults between the ages of 30 and 40 years, and resulting in significant disability (4). Changes in regulators of inflammation in the intestinal cells as well as altered response to mucosal injury are key drivers of disease pathology (4).
Type and severity of symptoms depend on the extent of the disease but generally include rectal bleeding, bowel urgency, proctitis plus diarrhoea, abdominal cramping, fatigue and fever (4). Nearly 70% of patients experience UC symptom flare-ups every few months and more than 70% report inability to enjoy leisure activities (5).
High symptoms burden associated with increased disease activity is shown to be an independent predictor of decreased physical and mental health-related quality of life (HRQoL) (6, 7). Fast response and long-term maintenance of response to therapy and disease remission are therapeutic goals which are still not achieved by many UC patients. It is the reason why patients with UC usually undergo multiple lines of treatments in order to control the symptoms of their disease (8).
This highlights patients´ need for a new effective treatment with ustekinumab, which provides rapid induction remission, as well as long-term maintenance thereof, with improvement in mucosal healing and quality of life (9).

Blocking of the cytokines IL-12 and IL-23 by ustekinumab, related to the pathogenesis and symptoms of inflammatory bowel disease, presents a new and unique option for patients suffering from ulcerative colitis. The mode of action of ustekinumab is to neutralize key cytokines in the maturation of naïve T-cells to critical concentrations of T helper 1 and 17 cells acting upstream in the inflammation cascade. That inhibition may lead to fast-acting symptom relieve and a sustained control of symptoms important in ulcerative colitis.
The efficacy of ustekinumab for ulcerative colitis is evaluated in the phase 3 trial, UNIFI, where patients refractory to vedolizumab were included for the first time, endoscopies were evaluated centrally, and the measure of histological healing was introduced. For the full randomized population, six out of ten patients achieved clinical response after 8 weeks, almost eight out ten patients cumulatively achieved response at week 16, and out of the patients in clinical remission to ustekinumab at week 52 of the maintenance trial, 97.2% were also corticosteroid free.
The safety profile of ustekinumab for ulcerative colitis is similar to the profile reported for other approved indications as stated in the Summary of Product Characteristics, and among 505 patients who received ustekinumab during both induction and maintenance, antidrug antibodies developed in 4.6% (1, 9). Furthermore, this is illustrated in the integrated safety data across the indications psoriasis, psoriatic arthritis, and Crohn's disease which have recently been published (10). In 12 clinical studies among 6280 enrolled patients, 5884 ustekinumab-treated patients (psoriasis: 3117; PsA: 1018; CD: 1749) contributed 4521 patient years (PY) versus 674 PYs in placebo-treated patients through year 1 (829 PYs and 385 PYs during 8- to 16-week controlled periods). Ustekinumab demonstrated a consistent safety profile across registrational trials and was comparable with that of placebo when integrated across indications, with no evidence of a dose effect in the occurrence of AEs, SAEs, or infections (10).

Given the efficacy and safety profile demonstrated in the UNIFI clinical trial programme, the supporting clinical trial evidence in CD, PsO and PsA, the comparative efficacy and safety, as well as the convenient dosing regimen, ustekinumab provides a much needed innovative (the first IL12/23 inhibitor treatment) treatment for moderately to severely active UC patients refractory to both conventional and biologic therapies (1, 9, 11).

4 Literature search

A systematic literature search was conducted according to the search strings and criteria which the secretariat has prepared to be used in MEDLINE (via PubMed) and CENTRAL (via Cochrane Library) as specified in the Medicines Council protocol for evaluation of ustekinumab for the treatment of moderate to severe ulcerative colitis (12). This was done to extract data answering the clinical questions:

1. What is the value of ustekinumab compared to infliximab and vedolizumab for the treatment of adult biological and targeted synthetic drug treatment-naïve patients with moderate to severe active ulcerative colitis?
2. What is the value of ustekinumab compared to infliximab and vedolizumab for the treatment of adult biological and targeted synthetic drug treatment-experienced patients with moderate to severe active ulcerative colitis?

For both clinical questions, the selection of relevant studies were based on the inclusion and exclusion criteria specified by the medicine council in the protocol (12). Consequently, the included studies had to be phase 3 RCT with a follow-up of at least 8 weeks and include the relevant populations i.e. bio-naïve and bio-experienced patients with moderate to severe ulcerative colitis. In addition, the studies had to evaluate ustekinumab, infliximab or vedolizumab and include minimum one of the relevant efficacy endpoints specified in the protocol.

The literature search identified in 333 potentially relevant publications through MEDLINE (via PubMed) and CENTRAL (via Cochrane library) according to the search strings specified in the protocol, see the appendix 7.1.2. However, after removal of duplicates 247 records were eligible for systematic review. These records were screened on title and abstract based on the PICO, which resulted in the exclusion of 237 records. The remaining 10 records were retrieved for full-text screening which further resulted in the exclusion of 4 publication. Consequently, 6 publication addressing the clinical questions for relevant patient populations with moderate to severe UC that are either bio-naïve or bio-experienced and treated with ustekinumab, infliximab or vedolizumab at the relevant doses were included. The PRISMA flow diagram showing the number of references identified and the number of included and excluded references is available in appendix 7.1.3 and a list of references excluded after full-text screening is provided in the appendix 7.1.4 including the reasons for exclusion of each reference.

4.1 Relevant studies

Table 3 Relevant studies included in the assessment.

Reference (title, author, journal, year)	Trial name	National Clinical Trial (NCT) Identifier	Dates of study (start and expected completion date)	Relevant for clinical question
Ustekinumab as Induction and Maintenance Therapy for Ulcerative Colitis. Sands BE et al., NEJM, 2019. (9)	UNIFI	NCT02407236	July 2015- November 2021	Clinical question 1 & 2
Infliximab for induction and maintenance therapy for ulcerative colitis. Rutgeerts P et al., NEJM, 2005. (13)	ACT 1 & ACT 2	NCT00036439 NCT00096655	Feb 2002- jan 2007 May 2002- Aug 2007	Clinical question 1
The effects of infliximab therapy on health-related quality of life in ulcerative colitis patients. Feagan BG et al., Am J Gastroenterol, 2007. (14)	ACT 1 & ACT 2	NCT00036439 NCT00096655	Feb 2002- jan 2007 May 2002- Aug 2007	Clinical question 1
Vedolizumab as induction and maintenance therapy for ulcerative colitis. Feagan BG et al., NEJM, 2013. (15)	GEMINI 1	NCT00783718	Jan 2009- March 2012	Clinical question 1 & 2
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. (16)	GEMINI 1	NCT00783718	Jan 2009- March 2012	Clinical question 1 & 2
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. (17)	GEMINI 1	NCT00783718	Jan 2009- March 2012	Clinical question 1 & 2

4.2 Main characteristics of included studies

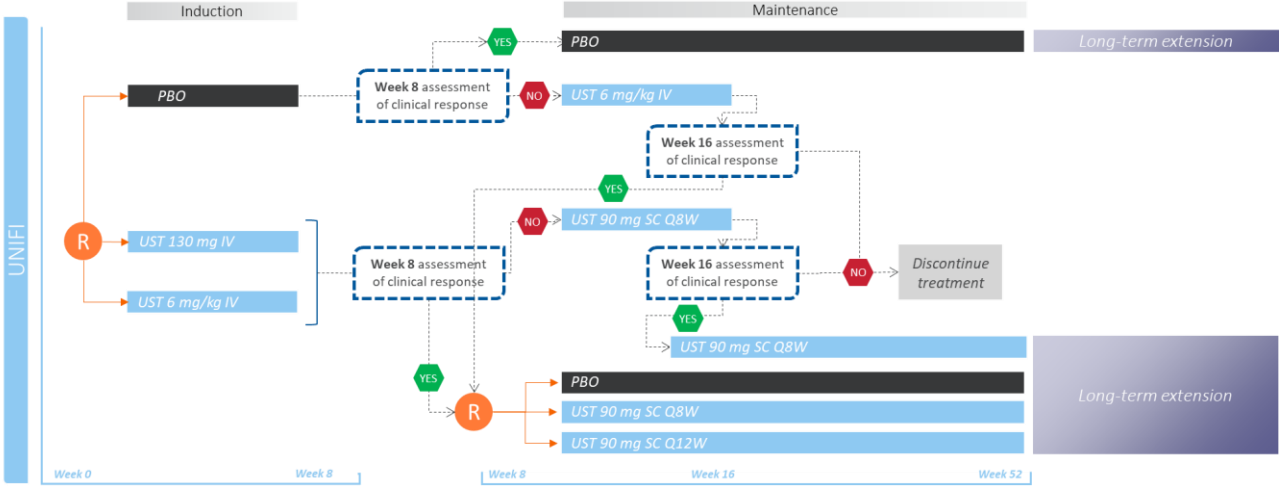
4.2.1 UNIFI – Ustekinumab

Ulcerative colitis is progressive debilitating disease and the symptoms can be severe with profound impact on patients' lives, thus rapid onset of action of treatment is particularly important (5, 18). Therefore, the UNIFI induction study was conducted to evaluate the clinical efficacy of ustekinumab at week 8 by testing the hypothesis that ustekinumab is superior to placebo at induction at week 8. The induction study targeted patients with active UC who had demonstrated an inadequate response or failure to tolerate conventional or biologic therapy (19).

In addition, the durable efficacy of treatment is particularly important due to the chronic nature of ulcerative colitis (20, 21). Therefore, the UNIFI maintenance study was conducted to evaluate the clinical efficacy of ustekinumab through week 44 (representing 52 weeks of treatment) (9). To avoid confusion the results which is presented as week 44 in the UNIFI study will from this point onwards be described as week 52 in this application. The maintenance study was designed to test the hypothesis that ustekinumab maintenance therapy is superior to placebo in patients with moderate to severely active UC who was induced to respond with ustekinumab during the induction phase. Patients were evaluated for at least 1 year of induction and maintenance therapy; after completion of the maintenance study (9). Figure 1 illustrates the response-based re-randomization study design that UNIFI has. Randomization was used to minimize bias in the assignment of subjects to groups, to increase the likelihood that known and unknown subject attributes (e.g., demographic and baseline characteristics) were evenly balanced across all treatment groups, and to enhance the validity of statistical comparisons across all treatment groups (11). Blinded treatment was used to reduce potential bias during data collection and evaluation of clinical endpoints (11). Central randomization for treatment allocation was implemented in the induction study (11).

The study included a total of 961 patients who were randomized to receive an IV induction dose of ustekinumab of either 130 mg (320 patients) or weight-based dose that approximated 6 mg/kg (322 patients) or placebo (319 patients) (9). Patients who achieved a response to induction therapy 8 weeks after administration of IV ustekinumab were subsequently re-randomized to receive SC maintenance injections of 90 mg of ustekinumab either every 12 weeks (172 patients) or every 8 weeks (176 patients) or placebo (175 patients) (9).
The study population by region in the induction and maintenance trials was: Asia 13.8 %, Eastern Europe 38.3 % and rest of the world 47.9 % (11). The subject population enrolled into this study is reflective of a contemporary population of patients with moderately to severely active UC who have previously failed or were intolerant of conventional and/or biologic therapies, including tumor necrosis factor (TNF) antagonists and/or vedolizumab.

Figure 1 UNIFI study design with initial randomization of patients to the induction phase, after which patients responding are re-randomized to the maintenance phase. After completing the maintenance study week 52, patients are evaluated for at least 3 years.



Abbreviations: UST (ustekinumab); PBO (placebo); R (randomization); SC (subcutaneous); Q8W (every 8 weeks); Q12W (every 12 weeks); IV (intravenous)

UNIFI trial design

UNIFI is a phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study evaluating the safety and efficacy of ustekinumab induction and maintenance therapy in patients with moderately to severely active UC (9, 19).
For extensive description of UNIFI main characteristics please see appendix 7.1.5, table A2.

UNIFI was conducted under a single protocol, but was designed and analyzed as two separate studies; an induction study to evaluate the onset of action by clinical efficacy at week 8, and a maintenance study to evaluate the durable efficacy (9, 11).
The induction study was designed to evaluate the efficacy and safety of IV ustekinumab in patients with moderately to severely active UC (11). See table 4 for primary and secondary objectives. The endoscopic healing endpoint is equal to the mucosal healing endpoint defined by the Medicine council. Thus, to avoid confusion mucosal healing will be used from this point onwards.

Table 4 Primary and secondary objectives for the induction study (9, 11).

Primary Objective	**Major secondary objectives**
Clinical remission at week 8	Mucosal healing at week 8
	Clinical response at week 8
	Change from baseline in the total IBDQ score at week 8

In the induction study patients were randomized in a 1:1:1 ratio to 1 of 3 treatment groups (11):

- Placebo IV
- Ustekinumab 130 mg IV
- Weight-range-based ustekinumab doses approximating ustekinumab 6 mg/kg IV (i.e., ustekinumab ~6 mg/kg IV):
  - Ustekinumab 260 mg (weight ≤55 kg)
  - Ustekinumab 390 mg (weight >55 kg but ≤85 kg)
  - Ustekinumab 520 mg (weight >85 kg)

Eligible patients were allocated to a treatment group using permuted block randomization with biologic failure status (yes or no) and region (Eastern Europe, Asia, or rest of world) as stratification variables.
In the induction phase, randomized patients received their assigned IV dose of ustekinumab or placebo at Week 0. At Week 8, all patients were evaluated for the primary endpoint of clinical remission. All patients were also assessed for clinical response at week 8. Further study agent administration was determined by clinical response status (using the Mayo endoscopy sub-score assigned by the local endoscopist) at Week 8, as follows (11):

- Patients who were in clinical response at week 8 are eligible to enter the maintenance study.
- Patients who were not in clinical response at week 8 received ustekinumab as follows:
  - Patients who were randomized to placebo at week 0 will receive 1 dose of ustekinumab ~6 mg/kg IV plus placebo SC (to maintain the blind) at week 8
  - Patients who were randomized to ustekinumab at week 0 will receive 1 dose of ustekinumab 90 mg SC plus placebo IV (to maintain the blind) at week 8.

At week 16, the patients who were not initially in clinical response at week 8 were re-evaluated for clinical response (clinical response status was based on the Mayo endoscopy sub score assigned by the local endoscopist) (11):

- Patients who achieved clinical response at week 16 were eligible to enter the maintenance study. However, these patients were not included in the primary population.
- Patients who did not achieve clinical response at week 16 did not enter the maintenance study and had a safety follow-up visit approximately 20 weeks after their last (i.e. week 8) administration of study agent.

All UC-specific medical therapies must have been maintained at a stable dose through to the end of the induction study and could only be discontinued or reduced in dose if investigator judgment required it because of toxicity or medical necessity. The initiation or increase in dose of UC-specific therapies (or any restricted/prohibited medication or therapy) during the induction study prohibited a subject from entering the maintenance study (11).
The maintenance study was designed to evaluate clinical remission and safety for SC maintenance regimens of ustekinumab in patients with moderately to severely active UC (9). See table 5 for primary and secondary objectives.

Table 5 Primary and secondary objectives for the maintenance study (9, 11).

Primary Objective	**Major secondary Objectives**
Clinical remission at week 52	Maintenance of clinical response at week 52
	Mucosal healing at week 52
	Clinical remission and not receiving concomitant corticosteroids (corticosteroid-free clinical remission) at week 52
	Maintenance of clinical remission at week 52 among the subjects who had achieved clinical remission at maintenance baseline

In the randomized-withdrawal maintenance study, the study population was composed by patients with moderately to severely active UC who were in clinical response to IV ustekinumab during induction. This population will include the following (11):

- Patients who were randomized to receive ustekinumab at week 0 of the induction study and were in clinical response at induction week 8.
- Patients who were randomized to receive placebo at week 0 of the induction study and were not in clinical response at induction week 8 but were in clinical response at induction week 16 after receiving an induction dose of IV ustekinumab (~6 mg/kg) at induction week 8.

Patients who were in clinical response to IV ustekinumab induction were randomized in a 1:1:1 ratio to 1 of 3 treatment groups at the maintenance week 0/baseline (M-0) visit of the maintenance study (11):

- Placebo SC
- Ustekinumab 90 mg SC every 12 weeks (q12w)
- Ustekinumab 90 mg SC every 8 weeks (q8w)

Eligible patients were allocated to a treatment group using a permuted block randomization with clinical remission status at maintenance baseline (yes/no), oral corticosteroid use at maintenance baseline (yes/no), and induction treatment (placebo IV [I-0]→ ustekinumab ~6 mg/kg IV [I-8], ustekinumab 130 mg IV [I-0], or ustekinumab ~6 mg/kg IV [I-0]) as stratification variables (11).

Additional patients entering the maintenance study included the following (these patients were not part of the primary population) (11):

- Patients who are in clinical response to placebo IV induction will receive placebo SC.
- Patients who were delayed responders to ustekinumab induction (i.e., were not in clinical response to ustekinumab at induction week 8 but were in clinical response at induction week 16) will receive ustekinumab 90 mg SC q8w.

All patients received their assigned dose of SC study agent at the first maintenance visit (M-0). Thereafter, to maintain the blind, all patients received the study agent at all scheduled administration visits. Patients were assessed for clinical flare at every visit and, if loss of response was confirmed (based on the Mayo score that includes the endoscopy subscore assigned by the local endoscopist), may have been eligible for rescue medication. Patients who met the following criteria were considered to be in clinical flare (11):

- an increase from maintenance baseline in the partial Mayo score at least 2 points and an absolute partial Mayo score ≥4;
- an absolute partial Mayo score ≥7 points

Patients in clinical flare who had not previously met the criteria for loss of clinical response in the maintenance study underwent endoscopy and were evaluated for loss of clinical response. These patients maintained stable doses of their UC medications after meeting clinical flare criteria and while waiting for their endoscopy score to establish loss of clinical response (11).

Patients who had lost response were eligible to receive rescue medication while continuing to receive study agent administration as scheduled. These patients were assessed 16 weeks after the visit at which the loss of clinical response criteria was met. During this interval, clinical flare criteria was not be applied. Patients who had not achieved a partial Mayo response (i.e., a decrease from induction baseline of ≥ 2 in the partial Mayo score) at 16 weeks after loss of response were discontinued from study agent administration and returned for a final safety visit approximately 20 weeks after their last study agent administration. A subject

who meets the criteria of clinical flare on more than 2 occasions during the maintenance study will be discontinued from study agent administration (11).
Concomitant medical therapy for UC was stable from the I-0 (Induction week 0) visit through the M-0 (Maintenance week 0) visit unless, in the judgment of the investigator, the therapy had to be discontinued or reduced in dose because of toxicity or medical necessity. Patients who initiated or increased the dose of a UC-specific medication (or any restricted/prohibited medication) during the induction study were prohibited from entering the maintenance study (11).

With the exception of corticosteroids, which were tapered (to decrease in a gradual or progressive fashion the dosage of a medication or the intensity of another form of treatment), UC-specific medical therapies (i.e. oral 5-ASA compounds, or the immunomodulators 6-MP, AZA, or MTX) were maintained at stable doses through the maintenance phase unless investigator judgment required that the therapy was discontinued or the dose reduced because of toxicity or medical necessity, or unless there was a documented loss of response that makes the subject eligible for rescue medication. Corticosteroids were tapered beginning at the M-0 visit for all patients who enter the maintenance study (11).

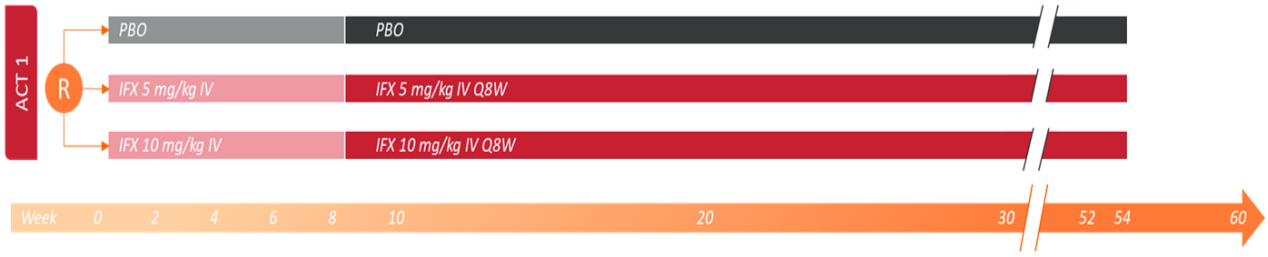
4.2.2 ACT 1 and ACT 2 - Infliximab

ACT 1 and ACT 2 are multicenter, phase 3, randomized, blinded, placebo-controlled studies in patients with moderately to severely active ulcerative colitis (13). For extensive description of ACT 1 and ACT 2 main characteristics please see appendix 7.1.5, table A2.2 and table A2.3, respectively.

ACT 1 and ACT 2 has a treat-through study design as illustrated in *figure 2*. With this study design the patients randomized to induction phase continue with the same treatment to the maintenance phase. The included patients were randomized in a 1:1:1 ratio to receive IV infliximab at a dose of 5mg/kg or 10mg/kg or placebo at week 0, 2 and 6. Hereafter administration every 8 weeks through week 22 for ACT 2 and week 46 for ACT 1. Follow-up in ACT 2 were through week 30 and ACT 1 through week 54. 364 patients underwent randomization in ACT 1 of these 121 patients received placebo, 121 received 5mg/kg infliximab and 122 received 10mg/kg infliximab. In ACT 2, 364 patients were randomized of which 123 were allocated to receive placebo, 121 received 5mg/kg infliximab and 120 received 10mg/kg infliximab (13).

For both ACT 1 and ACT 2 the evaluation of efficacy was performed with the primary outcome measure being the proportion of patients with a clinical response at week 8. Clinical response was 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. The secondary outcome measure was the proportion of patients in clinical remission defined as a Mayo score of = 2 points, with no individual subscore > 1, at week 8 (22, 23).

Figure 2 ACT 1 and 2 treat-through study design with initial randomization of patients to the induction phase, after which patients continue in assigned treatment arm in the maintenance phase.



Abbreviations: IFX (infliximab); PBO (placebo); R (randomization); Q8W (every 8 weeks); IV (intravenous)

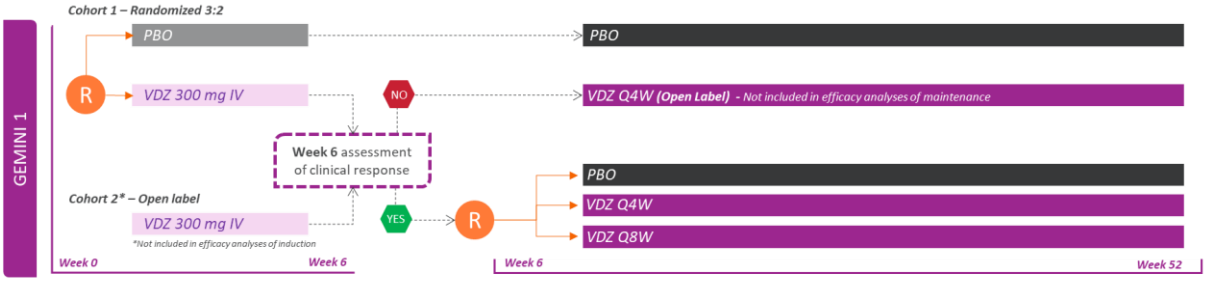
4.2.3 GEMINI 1 - Vedolizumab

GEMINI I is a multicenter, phase 3, randomized, blinded, placebo-controlled study in patients with moderately to severely active ulcerative colitis (15, 24). For extensive description of GEMINI I main characteristics please see appendix 7.1.5, table A2.4

The induction phase of the study had two cohorts of which cohort 1 consisted of 374 patients receiving IV vedolizumab at a dose of 300 mg or IV placebo at weeks 0 and 2. Cohort 2 consisted of 521 patients who received open-label vedolizumab at weeks 0 and 2 (15).

In the maintenance phase patients from both Cohort 1 and Cohort 2 treated with vedolizumab 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. Patients treated with vedolizumab 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 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 (15, 24). The GEMINI I has a similar response-based re-randomization study design as UNIFI which is demonstrated in figure 3:

Figure 3 GEMINI I study design with initial randomization of patients to the induction phase, after which patients responding are re-randomized to the maintenance phase.



Abbreviations: VDZ (vedolizumab); PBO (placebo); R (randomization); Q8W (every 8 weeks); Q4W (every 4 weeks): IV (intravenous)

5 Clinical questions

5.1 Clinical question 1: What is the clinical added value of ustekinumab for adult biological and targeted synthetic drug treatment-naïve patients with moderate to severe active ulcerative colitis compared to infliximab and vedolizumab?

5.1.1 Presentation of relevant studies

The studies used in the assessment of the added clinical value of ustekinumab for bio-naïve patients compared to infliximab and vedolizumab consist of UNIFI, ACT 1-2 and GEMINI I for ustekinumab, infliximab and vedolizumab, respectively. Furthermore, the EMA assessment report (EPAR) of STELARA® will be used due to the results for bio-naïve and bio-experienced patients being published in the EPAR.

For ustekinumab induction therapy results will only be presented for patient population receiving ~6 mg/kg IV as this is the EMA approved induction dose (11). However, for the maintenance dose of ustekinumab, both results for administration every 12 weeks, which is the standard dosing regimen, and every 8 weeks which may be used according to clinical judgement (11).

Overall, UNIFI evaluating ustekinumab, ACT 1-2 evaluating infliximab and GEMINI I evaluating vedolizumab as therapy in patients with moderately to severely active UC, have certain important characteristics in common. The following characteristics were assessed and deemed comparable across trials: duration of disease, age and weight at baseline, proportion of males/females, C-reactive protein level and Mayo score at baseline. The characteristics are available in appendix 7.1.5, table A2.1, A2.2.1 and A2.4.1.

However, small difference between the studies were found. Different time points of assessment were found across the induction trials. Induction endpoints were reported at 6 weeks for vedolizumab, whereas endpoints at 8 weeks were reported for infliximab and ustekinumab (9, 13, 15). However, results have been considered comparable between 6 weeks and 8 weeks. Furthermore, the endoscopic score was in ACT 1-2 and GEMINI I assessed by a local endoscopist whereas in UNIFI both a local reading and a central reading (performed by a reader who reviewed the video of endoscopy) were conducted (9, 11, 13, 15). The efficacy analyses presented for the induction and maintenance study is based on central review of endoscopies (11).

Besides timepoint of assessment, the studies differentiated regarding the populations included in UNIFI, ACT 1-2 and GEMINI I. ACT1-2 only included bio-naïve patients whereas UNIFI and GEMINI I included both bio-naïve and bio-experienced (9, 13, 15). How associated population definitions corresponds are available in *table 6*.

Table 6 Stratification definition across the UNIFI, GEMINI I, ACT1 and ACT 2 studies (9, 11, 13, 16).

Trial	Population	Definition	Population corresponding to UNIFI
UNIFI	• Biologic failure • Non-biologic failure	• Patients who have received treatment with 1 or more TNF antagonists or vedolizumab • Subjects who may be biologic-naive or may have been exposed to biologic therapy but not demonstrated an inadequate response or intolerance to treatment with a biologic agent	N/A
GEMINI I	• TNF-naïve • Prior TNF antagonist failure • No prior TNF antagonist failure	• Prior anti-TNF therapy • Prior failure of anti-TNF therapy • No prior failure of anti-TNF therapy	• Prior anti-TNF failure corresponds to biologic failure patients from UNIFI • No prior anti-TNF failure corresponds to non-biologic failure patients from UNIFI
ACT 1 & 2	• Bio-naïve patients	• Patients previously exposed to infliximab or any other anti-TNF agent were excluded.	• Corresponds to non-biologic failure patients from UNIFI

In addition to the differences described above, the study design of ACT 1-2 differentiates compared to UNIFI and GEMINI 1. Study designs conducted in UC have evolved over time from treat-through designs, for anti-TNF therapies including infliximab to designs based on response to treatment, for the newer therapies (9, 13, 15). Essentially all trials in UC can be classified as being in either one of these two broad categories of designs.

The studies ACT 1-2 evaluating infliximab are based on the treat-through design were patients randomized to induction phase continue with the same treatment to the maintenance phase (13). This design is conventional and allows for a straight forward interpretation of the efficacy of a continued 1-year regimen versus placebo.

In contrast, GEMINI 1 and UNIFI are based on re-randomized response based designs where responders to active treatment during the induction phase are re-randomized to the treatment or placebo arm for the maintenance phase; non-responders are treated-through for the maintenance phase up to 1 year (9, 15). Furthermore, patients either remain on placebo from induction to maintenance regardless of response (as depicted above for GEMINI I in *figure 3*) or continued to receive placebo maintenance treatment based on response at the end of induction (UNIFI in *figure 1*) (9, 15).

5.1.2 Results per study

UNIFI – Ustekinumab

Ustekinumab efficacy results for induction and maintenance endpoints for bio-naïve patients with moderate to severe UC defined in the Medicine Council protocol is presented in the following section and summarized in table 9 and 10, at the end of this section. Further detailed description of results is summarized in appendix 7.1.6 table A3. Some of the endpoints defined in the Medicine Council protocol are not published for the bio-naïve patient population. However, published data based on the primary efficacy analysis set which consist of both bio-naïve and bio-experienced patients are available. Results and analyses are therefore presented for total patient population where data is missing for the defined sub-populations.

Clinical remission at week 8

For patients without a history of biologic failure, a significantly greater proportions of patients in the ~6 mg/kg (18.6%), achieved clinical remission at week 8, compared with patients in the placebo group (9.5%; p<0.022) (11).

Corticosteroid-free clinical remission at week 52

A significantly greater proportions of patients in ustekinumab q8w and q12w groups (47.1% and 48.0%, respectively) who did not have a history of biologic failure, achieved corticosteroid-free clinical remission at week 52 compared with patients in the placebo group (31.0%); p<0.05 and p<0.05, respectively (11).

Safety

Serious adverse events

Data for serious adverse events stratified on bio-naïve and bio-experienced patients is unfortunately not published. However, data for the primary efficacy analysis set consisting of both bio-naïve and bio-experienced patients is available and presented in following section.

Intravenous ustekinumab dose of ~6 mg/kg was generally well-tolerated through week 8 with a safety profile that was consistent with the known safety profile of ustekinumab. Serious AEs occurred at a low frequency overall reflected by the results through week 8 as 3.4% (11 of 320 patients) and 6.9% of the patients (22 of 319) had a SAEs in the ~6 mg/kg and placebo group, respectively (9).

Furthermore, the subcutaneous maintenance regimens of ustekinumab 90 mg administered q12w or q8w were generally well tolerated and also consistent with the known safety profile of ustekinumab. Serious AEs were uncommon as reported in 8.5% (15 of 176), 7.6% (13 of 172), and 9.7% (17 of 175) of patients in the ustekinumab q8w, ustekinumab q12w, and placebo groups, respectively (9). Results were similar across all treatment groups, with the exception of ulcerative colitis, which was reported more frequently among patients in the placebo group (4.6%) than in the ustekinumab q8w and q12w groups (1.1% and 0.6%, respectively) (11).

Adverse events

Overall, the AE profile in patients treated with ustekinumab was generally comparable with that reported in patients receiving placebo. No new safety signals were observed compared with the known safety profile of ustekinumab in Crohn's disease and the psoriatic indications. The proportions of patients reporting AEs in the ustekinumab ~6 mg/kg group was generally comparable with the placebo group. Proportions of

patients reporting infections through week 8 were similar across treatment groups 15.9%, and 15.4% in the ~6 mg/kg and placebo group, respectively (9, 11). AEs of special interest e.g. the proportion serious infections through week 8 were similar comparing placebo IV (1.6%) with UST IV 6mg/kg (0.3%) (9, 11).

Table 71 Summary of key safety findings through week 8 (9, 11).

	Placebo IV	UST IV ~6mg/kg
Safety Analysis Set	319	320
Subjects with 1 or more		
Adverse events, n (%)	153 (48.0%)	162 (50.6%)
Serious adverse events, n (%)	22 (6.9%)	11 (3.4%)
Infections, n (%)	49 (15.4%)	51 (15.9%)
Serious Infections, n (%)	5 (1.6%)	1 (0.3%)

For the maintenance study the proportions of subjects reporting AEs and infections in the ustekinumab q8w group were generally comparable with the placebo group, see table 8. However, a lower proportion of subjects reported AEs in the ustekinumab q12w group than in either the ustekinumab q8w or placebo groups (9, 11). Overall, the data do not suggest that there is a meaningful difference in the safety profile of ustekinumab administered q8w and q12w.
AEs were reported in 77.3%, 69.2%, and 78.9% of subjects in the ustekinumab q8w, ustekinumab q12w, and placebo groups, respectively. Serious infections were infrequent among randomized patients and were reported in 1.7%, 3.5%, and 2.3% in the ustekinumab q8w, ustekinumab q12w, and placebo groups, respectively. The proportion of randomized patients with AEs leading to discontinuation of study agent was higher in the placebo group than in the q12w and q8w groups and the most frequent AEs leading to discontinuation in the placebo group was worsening UC. Adverse events leading to discontinuation of ustekinumab in randomized patients were reported in 5 (2.8%), 9 (5.2%), and 20 (11.4%) subjects in the ustekinumab q8w, ustekinumab q12w, and placebo groups, respectively (9, 11). Ulcerative colitis was the most frequently reported AE that resulted in discontinuation of study agent among randomized subjects, in 15 (8.6%) subjects in the placebo group, 4 (2.3%) subjects in the q12w group, and none in the q8w group (11).

Table 8 Summary of key safety findings at week 52 (9, 11).

	Placebo SC	UST 90 mg SC q12w	UST 90 mg SC q8w	UST SC (combined)
Safety Analysis Set	175	172	176	348
Subjects with 1 or more				
Adverse events, n (%)	138 (78.9%)	119 (69.2%)	136 (77.3%)	255 (73.3%)
Serious adverse events, n (%)	17 (9.7%)	13 (7.6%)	15 (8.5%)	28 (8.0%)
Infections, n (%)	81 (46.3%)	58 (33.7%)	86 (48.9%)	144 (41.4%)
Serious Infections, n (%)	4 (2.3%)	6 (3.5%)	3 (1.7%)	9 (2.6%)
Adverse events leading to discontinuation	20 (11.4%)	9 (5.2%)	5 (2.8%)	14 (4.0%)

The q12w and q8w dosing regimens of ustekinumab were generally well tolerated in the maintenance phase of the UNIFI study and were consistent with the previously established safety profile of ustekinumab. Among randomized patients, the proportions reporting AEs and infections in the ustekinumab q8w group were generally comparable with the placebo group. However, a lower proportion of patients reported AEs and infections in the ustekinumab q12w group than in the ustekinumab q8w or placebo groups. Of note, compared with patients in the ustekinumab q8w and placebo groups, patients randomized to the ustekinumab q12w group were less likely to have entered the study receiving concomitant corticosteroids and were more likely to be biologic-naïve; these findings may contribute to some of the differences noted in the proportions of patients reporting AEs and infections. Overall, these data do not suggest that there is a meaningful difference in the safety profile of ustekinumab administered q8w or q12w.

As stated in the Summary of Product Characteristics, the overall safety profile was similar for patients with psoriasis, psoriatic arthritis, and Crohn's disease and ulcerative colitis (1).

Mucosal healing at week 52

Of the patients who did not have a history of biologic failure, significantly greater proportions of patients in the ustekinumab q8w and q12w groups (57.6% and 55.9%, respectively) achieved mucosal healing at week 52 compared with patients in the placebo group (34.5%; $p<0.05$ and $p<0.05$, respectively) (11).

Change from Baseline in Total IBDQ Score

Unfortunately results for change from baseline in total IBDQ score for bio-naïve patients treated with ustekinumab have not been published.

However, for the primary efficacy analysis set consisting of all subjects randomized in the induction study results are available. At baseline, median IBDQ scores were similar across all treatment groups with placebo IV median IBDQ score of 126, and ustekinumab ~6 mg/kg of 126. At week 8, the median improvements from baseline in the IBDQ scores were significantly greater in the ~6 mg/kg group (31.0) compared with the placebo group (10.0; $p<0.001$) (9). Furthermore, the baseline mean total IBDQ score for the ustekinumab ~6 mg/kg group was 127 and the mean change from baseline at week 8 was reported to be 35.0 (confidence interval (CI);31.51-38.49), see table 10 (9). In contrast the baseline mean total IBDQ score for the placebo IV group was 127.4 and the mean change from baseline was reported to be 16.1 (CI;12.64-19.56) (9).

The confidence intervals were calculated assuming normal distribution and by utilizing the reported standard deviation 31.39 and 31.86 for placebo and ustekinumab, respectively. The SD was converted to a standard error (SE) which e.g. for ustekinumab was calculated to be 1.78 using following formula (SE) = SD/√N = 31.86/√321 = 1.78. Furthermore, the confidence interval of ustekinumab was calculated using following formula: Lower CI= 35-1.96*1.78 = 31.51 and upper CI= 35+1.96*1.78 = 38.49

In addition, the mean difference between ustekinumab and placebo is estimated to be 18.9 (13.99-23.81)

This difference between the two means was calculated using following formula (25):

- Mean difference = Mean1 − Mean2
- Standard error of the mean difference (SE) = $\sqrt{(SD_1^2 / N_1 + SD_2^2 / N_2)}$
- 95% CI = mean difference ± 1.96 × SE

IBDQ remission i.e. a total IBDQ score ≥ 170

Unfortunately results of the UNIFI study regarding the proportions of patients achieving a total IBDQ score ≥ 170 have not been published for either bio-naïve or the primary efficacy analysis set. Consequently, comparative analyses cannot be conducted.

Table 9 Efficacy of ustekinumab in the bio-naïve population for endpoints defined in the Medicine Council protocol (9, 11).

Induction results at week 8			
Endpoint	**Placebo IV**	**Ustekinumab IV**	
		6mg/kg	
Analysis set	158	156	
Clinical remission	31 (9.5%)	29 (18.6%) †	
Maintenance results at week 52			
Endpoint	**Placebo SC[a]**	**Ustekinumab SC**	
		90 mg q12w	**90 mg q8w**
Analysis set	87	102	85
Corticosteroid-free clinical remission[b]	27 (31.0%)	49 (48.0%) †	40 (47.1%) †
Mucosal healing[c]	30 (34.5%)	57 (55.9%) †	49 (57.6%) †

† p<0.05.
IV=intravenous; q8w=every 8 weeks; q12w=every 12 weeks; SC=subcutaneous.
a: Subjects who were in clinical response to ustekinumab IV induction dosing and were randomized to placebo SC on entry into this maintenance study.
b: A Mayo score ≤2 points, with no individual subscore >1.
c: A Mayo endoscopy subscore of 0 or 1.

Table 10 Mean change in IBDQ total score from baseline at week 8 in the primary efficacy analysis set consisting of bio-naïve and bio-experienced population (9).

Endpoint	**Placebo IV**	**Ustekinumab IV**
		6 mg/kg
Analysis set	317	321
Mean change in IBDQ total score from baseline	16.1 (CI;12.64-19.56)	35.0 (CI;31.51-38.49)

ACT 1 and ACT 2 – Infliximab

Infliximab efficacy results for induction and maintenance endpoints for bio-naïve patients with moderate to severe UC defined in the Medicine Council protocol is presented in the following section and summarized in table 13 and 14, at the end of this section. Further detailed description of results is summarized in appendix 7.1.6 table A3c and A3d.

Clinical remission at week 8

In ACT 1 38.8% (47 of 121) of the patients in the group receiving 5mg/kg infliximab were in clinical remission at week 8 compared to 14.9% (18 of 121) in the placebo group. In ACT 2 33.9% (41 of 121) of the bio-naïve patients were in clinical remission whereas 5.7% (7 of 123) in the placebo group reached clinical remission (13).

Corticosteroid-free clinical remission at week 54 and week 30

Among patients treated with 5mg/kg infliximab in ACT-1, 25.7% (18 of 70) of bio-naive patients were in corticosteroid-free remission following infliximab maintenance treatment at week 54. In contrast 8.9% (7 of 79) of bio-naïve patients receiving placebo reached corticosteroid-free remission at week 54. Furthermore, in ACT-2 18.3% (11 of 60) of the patients treated with 5mg/kg infliximab reached corticosteroid-free remission compared to 3.3% (2 of 60) in the placebo group at week 30 (13).

Safety

Serious adverse events

Serious adverse events at week 54 occurred in 25.6% of the bio-naive patients in the placebo group and 21.5% of patients receiving 5 mg/kg of infliximab, see table 11. Furthermore, the proportion of patients having a serious adverse event was 19.5% and 10.7% for the placebo and 5mg/kg infliximab population in ACT 2, respectively (13). For ACT 2 safety results see table 12.

Adverse events

The proportion of adverse events were similar in the placebo and 5mg/kg infliximab population, however the proportion of AE reported in the active infliximab treatment were numerically higher compared to placebo in both ACT 1 and ACT 2, see table 11 and 12. Infection were reported for a higher proportion of patients treated with infliximab compared to placebo in both ACT 1 and ACT 2 and serious infections were reported in 4.1% of the patients in the placebo group and 2.5 % in the infliximab group in ACT 1 whereas 0.8% and 1.7% were reported for the respective groups in ACT 2.
The proportion of randomized patients with AEs leading to discontinuation of treatment was higher in the placebo group than in the 5mg/kg infliximab group. Adverse events leading to discontinuation of infliximab were reported in 10 (8.3%) and 2 (1.7%), in ACT 1 and ACT 2, respectively (13).

Table 11 Summary of key safety findings through week 54 (13).

Safety endpoint	ACT 1 Non-biologic failure Maintenance (Week 54)	
	PBO (N=121)	IFX 5mg/kg (N=121)
Adverse events, n (%)	103 (85.1)	106 (87.6)
Serious adverse events, n (%)	31 (25.6)	26 (21.5)
Any infection, n (%)	47 (38.8)	53 (43.8)
Serious infection, n (%)	5 (4.1)	3 (2.5)
Adverse events leading to discontinuation, n (%)	11 (9.1)	10 (8.3)

Table 12 Summary of key safety findings through week 30.

Safety endpoint	ACT 2 Non-biologic failure Maintenance (Week 30)	
	PBO (N=123)	IFX 5mg/kg (N=121)
Adverse events, n (%)	90 (73.2)	99 (81.8)
Serious adverse events, n (%)	24 (19.5)	13 (10.7)
Any infection, n (%)	29 (23.6)	33 (27.3)
Serious infection, n (%)	1 (0.8)	2 (1.7)
Adverse events leading to discontinuation, n (%)	12 (9.8)	2 (1.7)

Mucosal healing at week 54 and week 30

At week 54 a higher percentage of patients treated with infliximab 5mg/kg had mucosal healing (45.5%) compared to patients assigned to placebo (18.2%) in ACT-1 (13). In ACT-2 46.3% (56 of 121) of the patients receiving 5mg/kg infliximab and 30.1% (37 of 123) in the placebo group had mucosal healing (13).

Change from Baseline in Total IBDQ Score

IBDQ mean change from baseline at week 54 would need to be read by graph which creates a high uncertainty. Due to this and to increase the comparability to results related to ustekinumab the change from baseline in total IBDQ score is reported at week 8 for infliximab. The change from baseline in total IBDQ score is reported for infliximab 5mg/kg at week 8 in the pooled data from the ACT 1 and ACT 2 patient populations (N=242). The baseline mean total IBDQ score for the infliximab 5mg/kg was 125 and the mean change from baseline was reported to be 40 (CI;35.72-44.28) at week 8 (14).
In contrast the baseline mean total IBDQ score for the placebo IV group was 124 and the mean change from baseline was reported to be 21 (CI;17.49-24.51) (14).

The confidence intervals were calculated assuming normal distribution and by utilizing the reported standard deviation 28 and 34 for placebo and infliximab, respectively (14). The SD was converted to a standard error (SE) which e.g. for infliximab was calculated to be 2.19 using following formula (SE) = SD/√N = 34/√242 = 2.19. Furthermore, the confidence interval of infliximab was calculated using following formula: Lower CI= 40-1.96*2.19= 35.72 and upper CI= 40+1.96*2.19 = 44.28

In addition, the mean difference between infliximab and placebo was estimated to be 19 (13.46-24.54)

IBDQ remission i.e. a total IBDQ score ≥ 170

IBDQ remission for bio-naïve patients treated with infliximab have not been published. Consequently, comparative analyses cannot be conducted.

Table 13 Efficacy of infliximab in the bio-naïve population for endpoints defined in the Medicine Council protocol (13).

Induction results at week 8				
Endpoint	**Placebo IV**		**Infliximab 5mg/kg IV**	
	ACT 1	ACT 2	ACT 1	ACT 2
Analysis set	121	123	121	121
Clinical remission	18 (14.9%)	7 (5.7%)	47 (38.8 %)	41 (33.9%)
Maintenance results at week 54 (ACT 1) and week 30 (ACT 2)				
Endpoint	**Placebo IV**		**Infliximab 5mg/kg IV**	
	ACT 1	ACT 2	ACT 1	ACT 2
Analysis set	121	123	121	121
Mucosal healing	22 (18.2%)	37 (30.1%)	55 (45.5%)	56 (46.3%)
Analysis set	79	60	70	60
Corticosteroid-free clinical remission	7 (8.9%)	2 (3.3%)	18 (25.7%)	11 (18.3%)

Table 14 Mean change in IBDQ total score from baseline at week 8 in the pooled data from the ACT 1 and ACT 2 bio-naïve patient populations (14).

Endpoint	**Placebo IV ACT 1 and ACT 2**	**Infliximab 5mg/kg IV ACT 1 and ACT 2**
Analysis set	244	242
Mean change in IBDQ total score from baseline	21 (CI;17.49-24.51).	40.0 (CI;35.72-44.28)

GEMINI I – Vedolizumab

Vedolizumab efficacy results for induction and maintenance endpoints for bio-naïve patients with moderate to severe UC defined in the Medicine Council protocol is presented in the following section and summarized in table 16 and 17, at the end of this section. Further detailed description of results is summarized in appendix 7.1.6 table A3d.

Clinical remission at week 6

In the bio-naïve patient population receiving induction treatment with vedolizumab 300mg 23.1% (30 out 130) achieved clinical remission at week 6. This resulted in higher percentages of patients in clinical remission compared to placebo with 6.6% (5 out of 76) patients being in clinical remission (16).

Corticosteroid-free clinical remission at week 52

Among patients in the population receiving corticosteroids at baseline, 35.9% of TNF-naive patients were in corticosteroid-free remission following vedolizumab maintenance treatment. In contrast 18.6% of bio-naïve patients receiving placebo reached corticosteroid-free remission at week 52 (16).

Serious adverse events

Serious adverse events at week 52 occurred in 16% (12 of 76) of the bio-naive patients in the placebo group and 9% (28 of 309) of patients receiving vedolizumab (16).

To increase the comparability to the safety of ustekinumab, data for the full population consisting of bio-naïve and bio-experienced is also presented, see table 15. In the patient population being vedolizumab induction responders and receiving vedolizumab every 8 weeks 8% (10 of 122) had a serious adverse event compared to 16% (20 of 126) in the placebo group (15).

Adverse events

The proportion of adverse events were similar in the placebo and vedolizumab, with AE reported in the active vedolizumab treatment of 74% compared to placebo (75%) in the bio-naive patient population. Serious infections were reported in 4% of the patients in the placebo group and 1% in the vedolizumab group (16).

To increase the comparability to the safety of ustekinumab, data for the full population consisting of bio-naïve and bio-experienced is also presented. Adverse events were reported in 84% (106 of 126) in the placebo group and in the active vedolizumab population of 82% (100 of 122) had an adverse event, see table 15. The rate of infection were similar in proportion of patients treated with vedolizumab every 8 weeks (71%) (87 of 122) compared to placebo 71% (89 of 126). Serious infections were reported in 3% of the patients in the placebo group and 2% in the vedolizumab group (15).

Table 15 Summary of key safety findings through week 52.

Safety endpoint	Vedolizumab Bio-naïve and bio-experienced Maintenance (Week 52)	
	PBO (N=126)	Vedolizumab (N=122)
Adverse events, n (%)	106 (84)	100 (82)
Serious adverse events, n (%)	20 (16)	10 (8)
Any infection, n (%)	89 (71)	87 (71)
Serious infection, n (%)	4 (3)	3 (2)

Mucosal healing at week 52

At week 52 a higher percentage of bio-naïve patients treated with vedolizumab 300mg q8w had mucosal healing (59.7%) compared to patients assigned to placebo (24.1%) (16).

Change from Baseline in Total IBDQ Score

Bio-naïve patients treated with vedolizumab q8w had a mean difference of 25.9 (CI; 14.6-37.3) compared to placebo at week 52. The mean baseline score and change from baseline in this subgroup treated with vedolizumab is not availble (17). However, for the total patient population cosisting of bio-naïve and bio-experienced patients treated with vedolizumab q8w the baseline mean IBDQ score was 124.5 with a mean change of 48.4 (CI; 41.7-55.1) at week 52 (17).
In contrast the baseline mean IBDQ score was 122.2 with a mean change of 27.3 (CI; 20.8-33.8) for the placebo group at week 52 (17). The confidence intervals were calculated assuming normal distribution and by utilizing the reported standard error of 3.3 and 3.4 for placebo and vedolizumab, respectively (17). Example given for the calculation of vedolizumab confidence interval: Lower CI= 48.4-1.96*3.4 = 41.7 and upper CI= 48.4+1.96*3.4 = 55.1

In addition, the mean difference between vedolizumab and placebo at week 52 was 21.1 (11.8-30.4) (17).

IBDQ remission i.e. a total IBDQ score ≥ 170

IBDQ remission for bio-naïve patients treated with vedolizumab have not been published. Consequently, comparative analyses cannot be conducted.

Table 16 Efficacy of vedolizuamb in the bio-naïve population for endpoints defined in the Medicine Council protocol (16).

Induction results at week 6		
Endpoint	**Placebo IV**	**Vedolizumab**
		300mg IV
Analysis set	76	130
Clinical remission	5 (6.6%)	30 (23.1%)
Maintenance results at week 52		
Endpoint	**Placebo SC**	**Vedolizumab**
		300mg IV q8w
Analysis set	43	39
Corticosteroid-free clinical remission	8 (18.6%)	14 (35.9%)
Analysis set	79	72
Mucosal healing	19 (24.1%)	43 (59.7%)

Table 17 Mean change in IBDQ total score from baseline at week 52 in the pooled bio-naïve and bio-experienced population (17).

Endpoint	**Placebo IV**	**Vedolizimab**
		300mg IV q8w
Analysis set	126	121
Mean change in IBDQ total score from baseline	27.3 (CI;20.8-33.8)	48.4 (CI;41.7-55.1)

5.1.3 Comparative analyses

Ustekinumab has not been directly compared to either infliximab or vedolizumab in any published randomized trials. Consequently, an indirect comparison between ustekinumab and infliximab as well as ustekinumab and vedolizumab has been performed utilizing Bucher's methodology. Furthermore, meta-analysis was used to combine the results of the ACT 1 and ACT 2 studies of infliximab using random effects models in OpenMetaAnalyst (26). Indirect comparison between ustekinumab and infliximab has been performed based on Bucher´s methodology using the results from the meta-analyses. See section 7.4 (27). Absolute difference in effect were calculated using the estimated risk ratio from the meta-analyses and the formula provided in the Handbook of the Medicines Council's process and methodologies version 2.4 (28). Secondary analysis with indirect comparison between ustekinumab and infliximab using only ACT 1 has also been performed based on Bucher´s methodology for the endpoints corticosteroid-free clinical remission and mucosal at week 52. The indirect comparison between ustekinumab and vedolizumab was likewise performed utilizing Bucher´s methodology. The relative difference, absolute difference and event rates used to calculate the absolute difference is available in section 7.2, *table A4* and *table A4.1*.

Clinical remission at week 8

Ustekinumab vs Infliximab

The relative difference in risk ratio (RR) between ustekinumab 6mg/kg and 5mg/kg infliximab in the proportion of patients achieving clinical remission at week 8 is 0.52 (0.19-1.41) utilizing the meta-analysis results of ACT1 and ACT2, see appendix 7.4.1. In addition the absolute difference in effect following induction is -17.30% (-29.31%-15.01%). The RR point estimate of 0.52 is in favor of infliximab however as the confidence interval of the relative difference is quite broad and contains 1 the difference is statistically non-significant and therefore the estimate is associated with a high uncertainty. Furthermore, due to the confidence interval overlapping the prespecified classifications of clinical value applying to relative differences, as described in the Handbook of the Medicine councils process and methodologies for new pharmaceuticals and indication expansions version 2.4, the preliminary clinical value cannot be categorized. The absolute effect point difference in favor of infliximab might be higher than the 10%-point difference defined as being the least clinical relevant difference, however the same conclusion regarding the high uncertainty and preliminary categorization of clinically added value applies to the absolute difference as the relative difference. This is evident when the confidence interval around the absolute effect difference is compared with the adjusted least clinically relevant difference of 5%-point and the criteria for the different preliminary categorize. More specifically the lower bound of -29.31% is neither equal to; lower limit (LL) > -5%-point nor is it equal to; LL ≥ 5%-point and the upper bound of 15.01% is not equal to; upper limit (UL) < -5%-point. Conclusively, the results are associated with a high uncertainty and suggests that there is no difference in clinical remission at week 8 between ustekinumab and infliximab.

Ustekinumab vs vedolizumab

The relative difference in RR between ustekinumab 6mg/kg and 300mg vedolizumab in the proportion of bio-naïve patients achieving clinical remission at week 8 is 0.56 (0.19-1.64). In addition, the absolute difference in effect following induction is -10.20% (-18.70%-14.69%). The RR point estimate of 0.56 is in

favor of vedolizumab however as described above for the comparison with infliximab the confidence interval of the relative difference indicates that the result is statistically non-significant and therefore the estimate is associated with a high uncertainty. In addition, the confidence interval around the absolute point difference between ustekinumab and vedolizumab is so broad that it cannot be concluded that ustekinumab is neither better nor worse and therefore the clinically efficacy of the two treatments could be viewed as being similar.

Corticosteroid-free clinical remission at week 52

Ustekinumab vs infliximab

The relative difference in RR between ustekinumab 90mg SC and 5mg/kg infliximab IV in the proportion of patients achieving corticosteroid-free clinical remission at week 52 is 0.46 (0.21-1.02) utilizing the meta-analysis results of ACT1 and ACT2, see appendix 7.4.2. In addition the absolute difference in effect following maintenance therapy is -12.1% (-17.7%-0.51%). The confidence interval of the relative difference is quite broad as it contains 1 the difference is statistically non-significant and therefore the estimate is associated with a high uncertainty. Consequently, the clinically added value cannot be categorized based on the results due to the same reasons as described above for clinical remission at week 8. However, a secondary analysis between ustekinumab and infliximab was conducted utilizing only the ACT 1 study which have follow-up of 54 weeks compared to 52 weeks in the UNIFI study. This was done as conducting NMAs requires making important assumptions regarding clinical heterogeneity which e.g. can be defined by differences in or follow-up time, and the meta-analysis contains results on infliximab at week 54 and week 30. The relative difference in RR between ustekinumab 90mg SC and 5mg/kg infliximab IV in ACT 1 in the proportion of patients achieving corticosteroid-free clinical remission at week 52 is 0.53 (0.22-1.30). In addition, the absolute difference in effect following maintenance therapy is -11.99% (-20.09%-7.78%). Consequently, the same conclusion as for the comparison with the meta-analysis results can be drawn.

It is important to highlight that the results are highly driven due to the difference in the proportion of patients achieving steroid free clinical remission in the placebo-arm of the ACT1 (8.9%) and ACT2 (3.3%) study compared to the UNIFI study (31%) (11, 13). This differences in the placebo arms are of great importance for the indirect comparison of both the absolute and relative differences since Bucher's method is based on the relative effects of the treatments in relation to placebo.

Hence a narrative comparison on the proportion of patients which achieved corticosteroid-free clinical remission at week 52 is conducted. In the ustekinumab q12w group 48% achieved corticosteroid-free clinical remission at week 52 compared with 25.7% at week 54 in ACT1 in the group receiving 5mg/kg infliximab (11, 13). This clearly shows that the efficacy of ustekinumab is higher as there is a percentage point difference of 22.3. Furthermore, if the result of ustekinumab is compared to the results of the meta-analysis on ACT 1 and ACT 2 there is a difference of 25.7%-points. This is well above the least clinically relevant difference of 10%-point defined by the medicine council (12).

Ustekinumab vs vedolizumab

The relative difference in RR between ustekinumab 90mg SC and 300mg IV vedolizumab in the proportion of patients achieving corticosteroid-free clinical remission at week 52 is 0.80 (0.35-1.86). In addition the absolute difference in effect following maintenance therapy is -7.1% (-23.5%-30.8%). The confidence interval of the relative difference is quite broad and contains 1. Thus, the difference is statistically non-significant and therefore the estimate is associated with a high uncertainty. Consequently, the clinically added value cannot be categorized based on the results due to the same reasons as described above for infliximab. The absolute effect point difference in favor of vedolizumab is not more than the 10%-point difference defined as being the least clinical relevant difference. In addition conclusion regarding the high uncertainty and preliminary categorization of clinically added value applies to the absolute difference as the relative difference.

Conclusively, the results are associated with uncertainty but suggests that there is no difference in steroid-free clinical remission at week 52 between ustekinumab and vedolizumab.

Safety

See the section safety 5.3.

Mucosal healing at week 52

Ustekinumab vs infliximab

As for clinical remission a comparison with infliximab is done based on meta-analysis results, see appendix. Furthermore, a secondary analysis between ustekinumab and infliximab was conducted utilizing only the ACT 1 study as the ACT 2 study only have a follow-up of 30 weeks and heterogeneity was suspected as the I^2 of the meta-analysis was higher than 50% (29).

The relative difference in RR between ustekinumab 90mg SC and 5mg/kg IV infliximab in the proportion of patients achieving mucosal at week 52 is 0.84 (0.47-1.51) utilizing the meta-analysis results of ACT 1 and ACT 2, see appendix 7.4.3. In addition the absolute difference in effect following maintenance therapy is -7.2% (-24.3%-23.3%). The RR point estimate of 0.84 is in favor of infliximab however as the confidence interval of the relative difference is quite broad and contains 1 the difference is statistically non-significant and therefore the estimate is associated with a high uncertainty. The absolute effect point difference in favor of infliximab is not higher than the 10%-point difference defined as being the least clinical relevant difference. Consequently, this suggest that there is no difference in mucosal healing at week 52 between ustekinumab and infliximab. The secondary analysis between ustekinumab and infliximab was conducted utilizing only the ACT 1 study and had comparable results to that of the meta-analysis with RR of 0.65 (0.38-1.12) and absolute difference of -16% (-28.4%-5.3%)

Ustekinumab vs vedolizumab

The relative difference in RR between ustekinumab 90mg SC and vedolizumab 300mg IV in the proportion of bio-naive patients achieving mucosal healing at week 52 is 0.68 (0.39-1.17). In addition, the absolute difference in effect following maintenance therapy is -19.2% (-36.3%-10.4%). The RR point estimate of 0.68

is in favor of vedolizumab however as the confidence interval of the relative difference is quite broad and contains 1 the difference is statistically non-significant. The absolute effect point difference in favor of vedolizumab might be higher than the 10%-point difference defined as being the least clinically relevant difference, however the same conclusion regarding the high uncertainty applies to the absolute difference as for the relative difference. Consequently, the clinically added value for both the relative and absolute difference cannot be categorized.

The results are as for the other efficacy endpoints associated with uncertainty but suggests that there is no difference in mucosal healing at week 52 between ustekinumab and vedolizumab.

Change from Baseline in Total IBDQ Score

Ustekinumab vs Infliximab

Change from baseline in total IBDQ score is only published for the the primary efficacy analysis set consisting of bio-naïve and bio-experienced patients in the induction study of UNIFI. Thus, ustekinumab is compared to results of infliximab at week 8 in only bio-naïve patients.

The mean difference in change from baseline in total IBDQ score at week 8 between ustekinumab and placebo of 18.9 (13.99-23.81) points demonstrate a clinically relevant improvement of quality of life in patients with moderate to severe ulcerative colitis. This is evident as the point estimate difference of 18.9 points is well above the least clinically relevant difference of 16 points defined in the protocol and the lower confidence value is 5.99 points above the adjusted least clinically relevant difference of 8 point when ustekinumab is compared to placebo (12). However, the mean difference in change from baseline in total IBDQ score at week 8 between ustekinumab and infliximab of -5 (-10.52-0.52) points suggest that ustekinumab and infliximab have comparable impact on the change in total IBDQ score. This is also illustrated when conducting a narrative comparison of the mean difference between infliximab and placebo of 19 (13.46-24.54) points with that of ustekinumab and placebo of 18.9 (13.99-23.81) points (9, 13). Furthermore, with reference to the Medicines Council´s process and methodologies for new pharmaceuticals and indication expansions version 2.4 the confidence interval around the mean point difference of the between ustekinumab and infliximab is so broad that it cannot be concluded that ustekinumab is neither better nor worse (28).

This difference between the two means was calculated using following formula:

- Mean difference = Mean1 − Mean2
- Standard error of the mean difference (SE) = $\sqrt{(SD_1^2 / N_1 + SD_2^2 / N_2)}$
- 95% CI = mean difference ± 1.96 × SE

Ustekinumab vs vedolizumab

A narrative comparison between ustekinumab and vedolizumab will be conducted as the results are reported at week 8 and week 52, respectively. Due to this a comparison should be interpreted with caution as the clinical heterogeneity is present.

As described above ustekinumab demonstrate a clinically relevant improvement of quality of life in the combined bio-naïve and bio-experienced patient population with moderate to severe ulcerative colitis compared to placebo with a difference of 18.9 (13.99-23.81) points (9).

Vedolizumab 300mg q8w also showed a clinically relevant improvement of quality of life in the bio-naïve patient population with mean difference of 25.9 (CI; 14.6-37.3) compared to placebo at week 52 (17). However, to increase the comparabilty the result for ustekinumab is compared to the patient population cosisting of bio-naïve and bio-experienced patients treated with vedolizumab 300mg q8w. This population had a mean change of 48.4 (CI; 41.7-55.1) at week 52 and the mean difference between vedolizumab and placebo at week 52 was 21.1 (11.8-30.4) (17).

Consequently, there is a mean difference of 4.8 in favor of ustekinumab when comparing the mean difference between ustekinumab and placebo at week 8 with the mean difference between vedolizumab and placebo at week 52. However, the results suggest that there is no difference in change from baseline in total IBDQ score between ustekinumab and vedolizumab as the point difference result is not higher than the least clinically relevant difference of 16 points and the lower bound difference between ustekinumab and vedolizumab is not above the adjusted least clinically relevant difference of 8 points.

IBDQ remission i.e. a total IBDQ score ≥ 170

Ustekinumab vs infliximab

Unfortunately data regarding the proportions of patients achieving IBDQ remission i.e. a total IBDQ score ≥ 170 could not be identified for any of the studies for either the bio-naïve population or the population consisting of both bio-naïve and bio-experienced patients. Consequently, comparative analyses cannot be conducted.

Ustekinumab vs vedolizumab

Unfortunately data regarding the proportions of patients achieving IBDQ remission i.e. a total IBDQ score ≥ 170 could not be identified for any of the studies for either the bio-naïve population or the population consisting of both bio-naïve and bio-experienced patients. Consequently, comparative analyses cannot be conducted.

5.2 Clinical question 2: What is the clinical added value of ustekinumab for adult biological and targeted synthetic drug treatment-experienced patients with moderate to severe active ulcerative colitis compared to infliximab and vedolizumab?

5.2.1 Presentation of relevant studies

The studies used in the assessment of the added clinical value of ustekinumab for bio-experienced patients compared to vedolizumab consist of UNIFI and GEMINI I for ustekinumab and vedolizumab, respectively. . Furthermore, the EPAR of STELARA® will be used due to the results for bio-naïve and bio-experienced patients being published here. As described in section 5.1.1., the background characteristics are generally comparable, but some differences in the history of failure with biologics can be noted for the populations to be discussed in the clinical question 2 (see tables A2.1 and A2.4.1 for details). For GEMINI I, the history of failure with a biologic was in the range of 36.4-42.6% and for UNIFI; 50.5-51.6%. The biologics treatment failures in GEMINI I were all from the anti-TNF class, while UNIFI included patients who had failed on vedolizumab (15.4% and 18.6% in the placebo and ustekinumab ~6 mg/kg groups, respectively). For further presentation of the relevant studies see section 5.1.1. These studies will be used for the indirect comparison.

5.2.2 Results per study

UNIFI – Ustekinumab

Ustekinumab efficacy results for induction and maintenance endpoints for bio-experienced patients with moderate to severe UC defined in the Medicine Council protocol is presented in the following section and summarized in table 18, at the end of this section. Further detailed description of results is summarized in appendix 7.1.6 table A3a. Some of the endpoints defined in the Medicine Council protocol are not published for the bio-experienced patient population. However, published data based on the primary efficacy analysis set which consist of both bio-naïve and bio-experienced patients are available. Results and analyses are therefore presented for the total patient population where data is missing for the defined sub-populations.

Clinical remission at week 8

Of the patients who had a history of biologic failure, significantly greater proportions of patients in the ~6 mg/kg group (12.7%), achieved clinical remission at Week 8 compared with patients in the placebo group (1.2%; p<0.001) (11).

Corticosteroid-free clinical remission at week 52

A significantly greater proportion of patients with a history of biologic failure in the ustekinumab q8w and q12w groups (37.4% and 22.9%, respectively) achieved corticosteroid-free clinical remission at week 52 compared with patients in the placebo group (15.9%; p<0.001 and p<0.05) (11).

Mucosal healing at week 52

For the patients who had a history of biologic failure, a significantly greater proportion of patients in the ustekinumab q8w group (45.1%) and a numerically greater proportion of patients in the q12w groups (25.7%) achieved mucosal healing at week 52 compared with patients in the placebo group (22.7%; p<0.001 for q8w) (11).

Change from Baseline in Total IBDQ Score

Unfortunately results for change from baseline in total IBDQ score for bio-experienced patients treated with ustekinumab have not been published. However, results for the primary efficacy analysis set consisting of all subjects randomized in the induction study are presented in section 5.1.2 and table 10.

IBDQ remission i.e. a total IBDQ score ≥ 170

Unfortunately results of the UNIFI study regarding the proportions of patients achieving IBDQ a total IBDQ score ≥ 170 have not been published for either bio-experienced or the primary efficacy analysis set. Consequently, comparative analyses cannot be conducted.

Table 18 Efficacy of ustekinumab in the bio-experienced population for endpoints defined in the Medicine Council protocol (11).

Induction results at week 8			
Endpoint	**Placebo IV**	**Ustekinumab IV**	
		6mg/kg	
Analysis set	161	166	
Clinical remission[a]	1.2%	12.7%*	
Maintenance results at week 52			
Endpoint	**Placebo SC[a]**	**Ustekinumab SC**	
		90 mg q12w	**90 mg q8w**
Analysis set	88	70	91
Corticosteroid-free clinical remission[b]	14 (15.9%)	16 (22.9%)†	34 (37.4%)*
Mucosal healing[c]	20 (22.7%)	18 (25.7%)	41 (45.1%)*

*p<0.001
† p<0.05.
IV=intravenous; q8w=every 8 weeks; q12w=every 12 weeks; SC=subcutaneous.
b: Subjects who were in clinical response to ustekinumab IV induction dosing and were randomized to placebo SC on entry into this maintenance study.
c: A Mayo score ≤2 points, with no individual subscore >1.
d: A Mayo endoscopy subscore of 0 or 1.

GEMINI I – Vedolizumab

Vedolizumab efficacy results for induction and maintenance endpoints for bio-experienced patients with moderate to severe UC defined in the Medicine Council protocol is presented in the following section and summarized in table 19, at the end of this section. Further detailed description of results is summarized in appendix 7.1.6, table A3e.

Clinical remission at week 6

In the bio-experienced patient population receiving induction treatment with vedolizumab 300mg, 9.8% (8 out 82) achieved clinical remission at week 6. This resulted in higher percentages of patients in clinical remission compared to placebo with 3.2% (2 out of 63) patients being in clinical remission (16).

Corticosteroid-free clinical remission at week 52

Among patients receiving corticosteroids at baseline, 23.1% (6 of 26) of bio-experienced patients were in corticosteroid-free remission following vedolizumab maintenance treatment. In contrast 4.3% (1 of23) of bio-experienced patients receiving placebo reached corticosteroid-free remission at week 52 (16).

Safety

Serious adverse events

Serious adverse events at week 52 occurred in 11% of the bio-experienced patients (7 of 63) in the placebo group and 17% (44 of 266) of patients receiving vedolizumab (16). However, to increase the comparability to the safety of ustekinumab, data for the full population consisting of bio-naïve and bio-experienced is also presented, see section 5.1.2, *table 15*.

Adverse events

The proportion of adverse events were similar in the placebo and vedolizumab population, however the proportion of AE reported in the active vedolizumab treatment of 88% (233 of 266) were numerically higher compared to placebo 84% (53 of 63) in the bio-experienced patient population. Serious infections were reported in 3% (2 of 63) of the patients in the placebo group and 3% (8 of 266) in the vedolizumab group (16). However, to increase the comparability to the safety of ustekinumab, data for the full population consisting of bio-naïve and bio-experienced is also presented, see section 5.1.2, *table 15*.

Mucosal healing at week 52

At week 52 a higher percentage of patients treated with vedolizumab 300mg q8w had mucosal healing, 41.9% (18 of 43) compared to patients assigned to placebo 7.9% (3 of 38) (16).

Change from Baseline in Total IBDQ Score

Bio-experienced patients treated with vedolizumab q8w had a mean difference of 14.1 (CI; -2.5-30.7) compared to placebo. The mean baseline score and change from baseline in the bio-experienced group treated with vedolizumab is not availble (17). However, results for the total patient population cosisting of bio-naïve and bio-experienced is presented in section 5.1.2, *table 17*.

IBDQ remission i.e. a total IBDQ score ≥ 170

IBDQ remission for bio-experienced patients treated with vedolizumab have not been published. Consequently, comparative analyses cannot be conducted.

Table 19 Efficacy of vedolizuamb in the bio-experienced population for endpoints defined in the Medicine Council´s protocol (16).

Induction results at week 6		
Endpoint	**Placebo IV**	**Vedolizumab 300mg**
Analysis set	63	82
Clinical remission	2 (3.2%)	8 (9.8%)
Maintenance results at week 52		
Endpoint	**Placebo SC**	**Vedolizumab 300mg q8w**
Analysis set	23	26
Corticosteroid-free clinical remission	1 (4.3%)	6 (23.1%)
Analysis set	38	43
Mucosal healing	3 (7.9%)	18 (41.9%)

5.2.3 Comparative analyses

A comparative analysis will only be conducted between ustekinumab and vedolizumab as efficacy results for bio-experienced patients has been published for the respective treatments whereas there is no published data evaluating infliximab in bio-experienced patients. Indirect comparison between ustekinumab and vedolizumab has been performed based on Bucher's methodology (27). Absolute difference in effect were calculated using the estimated risk ratio and the formula provided in the Handbook of the Medicines Council's process and methodologies version 2.4 (28). The relative difference, absolute difference and event rates used to calculate the absolute difference is available in section 7.2, *table A4.2.*

Clinical remission at week 8

Ustekinumab vs vedolizumab

The relative difference in RR between ustekinumab 6mg/kg and vedolizumab 300mg in the proportion of patients achieving clinical remission at week 8 is 3.31 (0.41-26.67). In addition, the absolute difference in effect following induction is 22.7% (-5.8%-251.6%) The RR point estimate of 3.31 is in favor of ustekinumab suggesting that the chance of having clinical remission at week 8 is 3.31 times higher when treated with ustekinumab compared to vedolizumab. However, as the confidence interval of the relative difference is quite broad and contains 1 the difference is statistically non-significant and therefore the estimate is associated with uncertainty. Furthermore, due to the confidence interval overlapping the prespecified classifications of clinical value applying to relative differences, as described in the Handbook of the Medicine councils process and methodologies for new pharmaceuticals and indication expansions version 2.4, the preliminary clinical value cannot be categorized (28). The absolute effect point difference in favor of ustekinumab is well above the 10%-point difference defined as being the least clinically relevant difference, however the same conclusion regarding the uncertainty and preliminary categorization of clinically added value applies to the absolute difference as for the relative difference (12). This is evident when the confidence interval around the absolute effect difference is compared with the adjusted least clinically relevant difference of 5%-point and the criteria for the different preliminary categorize (12). More specifically the lower bound of -5.8% is neither equal to LL > -5%-point nor is it equal to LL ≥ 5%-point and the upper bound of 251.6% is not equal to UL < -5%-point. Conclusively, the results are suggests that there is no difference in clinical remission at week 8 between ustekinumab and vedolizumab even though the point estimate shows that ustekinumab achieves a clinically relevant difference.

Corticosteroid-free clinical remission at week 52

Ustekinumab vs vedolizumab

The relative difference in RR between ustekinumab 90mg SC and 300mg vedolizumab IV in the proportion of patients achieving corticosteroid-free clinical remission at week 52 is 0.27 (0.03-2.30). In addition, the absolute difference in effect following maintenance therapy is -16.8% (-22.4%-30.1%). The confidence interval of the relative difference is again quite broad and contains 1 thus the difference is statistically non-significant and therefore the estimate is associated with a high uncertainty. Consequently, the clinically added value cannot be categorized based on the results due to the same reasons as described above for clinical remission at week 8. In addition, the conclusion regarding high uncertainty and preliminary categorization of clinically added value applies to the absolute difference as for the relative difference.

It is important to highlight that the results are highly driven due to the difference in the proportion of patients achieving steroid free clinical remission in the placebo-arm of GEMINI 1 study (4.3%) compared to the UNIFI study (15.9%) (11, 16). This differences in the placebo arms are of great importance for the indirect comparison of both the absolute ones and relative differences since Bucher's method is based on the relative effects of the treatments in relation to placebo.

Hence a narrative comparison on the proportion of patients which achieved corticosteroid-free clinical remission at week 52 is also conducted. In the ustekinumab 90mg SC q12w group 22.9% achieved corticosteroid-free clinical remission at week 52 compared with 23.1% at week 52 in the group receiving 300mg IV vedolizumab q8w (11, 16). This clearly shows that the efficacy of ustekinumab is equal to that of vedolizumab.

Conclusively, the results are associated with uncertainty but suggests that there is no difference in steroid-free clinical remission at week 52 between ustekinumab and vedolizumab in bio-experienced patients.

Safety

See the section safety 5.3.

Mucosal healing at week 52

Ustekinumab vs vedolizumab

The relative difference in RR between ustekinumab 90mg SC and vedolizumab 300mg IV in the proportion of bio-experienced patients achieving mucosal healing at week 52 is 0.21 (0.06-0.76). In addition, the absolute difference in effect following maintenance therapy is -33% (-39.4%-(-10.1%)). The RR estimate is in favor of vedolizumab as well as the absolute effect point difference. However, even though the results suggest that vedolizumab is favorable regarding mucosal healing, the results should be interpreted very carefully as they are associated with a high uncertainty. Consequently, it is important to highlight that the results are highly driven due to the difference in the proportion of patients achieving mucosal healing in the placebo-arm of GEMINI 1 study (7.9%) compared to the UNIFI study (22.7%).

Furthermore, conducting NMAs requires making important assumptions which are governed by two overlapping yet considerably different concepts: clinical and statistical heterogeneity. Clinical heterogeneity can be defined by differences in study design, baseline population characteristics, endpoint definitions used across studies, follow-up time, prior treatment exposure, etc. Statistical heterogeneity can be detected by specific tests in order to have an idea of whether the treatment effects observed in individual trials are different from those that would be expected if there was no heterogeneity. The presence of any type of heterogeneity can introduce bias in the relative treatment effect estimates obtained. Due to a high difference observed in the proportion of patients with mucosal healing in the bio-experienced placebo-group (22.7%) of the UNIFI study compared to the placebo group (7.9%) of GEMINI 1, a chi-squared test was conducted based on the mucosal healing data (11, 16). The chi-square statistic result was 3.91 with a p-value of 0.048. Thus, the p-value was significant indicating the outcome data for the common comparator arm not being comparable. In addition, the sample size difference should be considered as the sample size of the vedolizumab population is 38.5% smaller than that of ustekinumab.

Consequently, a narrative comparison will also be presented.

For the patients who had a history of biologic failure, a numerically greater proportion of patients in the ustekinumab q12w group 25.7% (CI; 15.5%-36%) achieved mucosal healing at week 52 compared with patients in the placebo group 22.7% (CI14%-31.5%) (11). The risk ratio between ustekinumab and placebo of 1.13 (CI; 0.65-1.97) indicates that the difference is not significant, however the point estimate is higher than one indicating a higher likelihood of achieving mucosal healing when treated with ustekinumab. In the UNIFI trial, there is evidence of a carry-over effect of induction therapy with ustekinumab affecting maintenance outcomes for patients who receive placebo. Evidence of carry-over effects are also found in the trials for other biologic treatments for UC, however the magnitude of the carry-over effects differs across studies. Consequently, this potentially drives the high placebo effect in the regards to mucosal healing and the difference to be not significant.

Comparing the results of ustekinumab to the proportion of patients achieving mucosal healing when treated with vedolizumab 41.9% shows that there is a different of 16.2% in favor of vedolizumab, which is substantially lower than that calculated based on the RR between ustekinumab and vedolizumab (16).

Furthermore, a sensitivity analyses is presented to illustrate the significance of the high proportion patients achieving mucosal healing in the UNIFI placebo group. The sensitivity analysis is conducted assuming a rate between ustekinumab and placebo equal to that between vedolizumab and placebo observed in the GEMINI 1 study.
The rate between vedolizumab and placebo is calculated dividing 7.9 with 41.9 which equals 0.189. This rate is multiplied with the proportion of ustekinumab treated patients which achieved mucosal healing to get the same placebo rate as observed in the GEMINI 1 study. Consequently, 0.189 is multiplied with 25.7 which equals 4.8. Utilizing this proportion of patients with mucosal healing in the bio-experienced placebo-group (4.8%) compared with the ustekinumab group 25.7% in an indirect comparison to vedolizumab a quite different results presents.
The relative difference in RR between ustekinumab 90mg SC and vedolizumab 300mg IV in the proportion of bio-experienced patients achieving mucosal healing at week 52 is 1.0 (0.22-4.59). In addition, the absolute difference in effect following maintenance therapy is 0.0% (-32.8%-150.4%). The RR estimate and absolute effect difference is no longer in favor of vedolizumab. However, as the confidence interval of the relative difference is quite broad and contains 1 the difference is statistically non-significant and the same conclusion regarding the high uncertainty applies to the absolute difference as for the relative difference. Consequently, the clinically added value for both the relative and absolute difference cannot be categorized. Conclusively, using an equal rate between ustekinumab and placebo as observed between vedolizumab and placebo the results are as for the other efficacy endpoints associated with uncertainty but suggests that there is no difference in mucosal healing at week 52 between ustekinumab and vedolizumab.

Change from Baseline in Total IBDQ Score

Ustekinumab vs vedolizumab

Please see clinical question 1 in section 5.1.3 where a comparative analysis on the pooled patient population of bio-naïve and bio-experienced patients is presented.

IBDQ remission i.e. a total IBDQ score ≥ 170

Ustekinumab vs vedolizumab

Unfortunately data regarding the proportions of patients achieving IBDQ remission i.e. a total IBDQ score ≥ 170 could not be identified for any of the studies for either the bio-experienced population or the population consisting on both bio-naïve and bio-experienced patients. Consequently, comparative analyses cannot be conducted.

5.3 Comparative safety analysis of ustekinumab for bio-naïve and bio-experienced patients with moderate to severe UC compared to infliximab and vedolizumab.

The following section outlines reasons why an indirect comparison of safety in maintenance is not appropriate.
As mentioned previously two main types of trial designs exist in UC: On the on hand, treat-through trials in which patients are assigned to placebo or active treatment for the full length of the trial (ACT 1 and ACT 2), on the other hand, trials in which patients responding to active treatment after induction are re-randomised to active treatment, or placebo (withdrawal). Importantly, in order to limit the exposure to inactive placebo, there are variations in these re-randomised trials to what maintenance treatment of the patients induced with placebo.

- Placebo induction responders are continued on placebo (UNIFI)
- Placebo responders and non-responders continue on placebo (GEMINI)

As a result, the 'placebo' safety population of these trials consist of various 'placebo' patients consisting of the above mentioned placebo patients.

The below section describes multiple examples of how various safety comparison versus '*placebo'* in the different trials can lead to different conclusions, describes how these conclusions differ from conclusions drawn after detailed analyses from regulators, and provide an overall conclusion on why a comparison of conclusions by regulators may provide a more adequate comparison of the safety profile than a indirect treatment conmparison.

1) The re-randomised trial designs have different, non-homogeneous placebo arms that all form part of the overall placebo safety population. More importantly, the trials do not have consistent placebo definitions for their safety population. The below examples demonstrate how this can influence conclusions.

a. **Infections in the GEMINI-1 trial** (15).

In the GEMINI-1 trial, the rate of infections is similar in the combined active treatment arms (60%) versus the combined placebo arms (56%). Similarly, in the re-randomised portion of the trial, the rate of infections is similar in the placebo arms (71%) versus the two active arms (71% and 72%). However, in the non-re-randomised arms, the rate seems to differ, with 44% in the placebo arm, and 56% in the non-re-randomised active arm. More importantly, despite the apparent similarity in the infection rates between active and placebo, EMA/CHMP concluded that there is a "difference of 11% in the infection rate between the vedolizumab combined group (42%) versus the non-ITT placebo group (31%) " and concluded that infections are a risk associated with treatment with vedolizumab (30).

b. **SAEs in the GEMINI-1 trial** (15).

The proportion of SAEs in the overall safety population of the trial seems similar between placebo (13.5% and active arms (12.4%). There are more SAEs in the re-randomised placebo arm (16%) compared to the active arms (8% and 9%), but the opposite is true in the non-randomised part, with 11% for placebo and 15% for active treatment. This difference is pointed out in the EMA/CHMP EPAR noting that "*the frequency of SAEs was higher (15%) in patients who had not responded to vedolizumab during induction (non-ITT VDZ Q4w dose group) than in the ITT VDZ Q8w and in the ITT VDZ Q4w*" (30).

2) Integration of safety of the re-randomised trials is not always available for the complete treatment of induction and maintenance, whereas the safety analysis for the treat-through trials covers induction and maintenance.

Overall, the above examples clearly indicate that a number of factors influence safety results. Different definitions of the placebo safety population, comprising of non-homogeneous placebo arms with different efficacy and exposure can result in spurious conclusions about safety, both for SAEs and infections. Differences exist in inclusion criteria which may influence results on infections. These examples illustrate that unadjusted analysis may lead to conclusions that do not correspond to the conclusions of regulators after detailed analysis. More importantly, while a number of examples are provided above, insufficient information is available for all comparators to enable attempting to correct for these factors.
As a result, safety indirect analysis was not conducted. A comparison of the conclusions of regulators, after their detailed analysis (i.e. the respective labels) is thought to be more meaningful to compare the safety profiles of the different comparators. In addition to comparisons of infections (the most relevant AEs for this class), this enables to compare adverse events that are relevant to specific comparators.

5.3.1 Narrative comparison of safety profiles for the comparator treatments based on data provided in the included studies.

Serious adverse events

The known safety profile of ustekinumab is also present for the ulcerative colitis indication as the frequency of serious AEs were uncommon as reported in 7.6% (13 of 172), of the pooled bio-naïve and bio-experienced patients in ustekinumab q12w, see table 20 (9, 11). Furthermore, the safety profile shows to be better compared to 21.5% of patients receiving 5 mg/kg of infliximab and similar with that of vedolizumab as 8% (10 of 122) of patients receiving vedolizumab had a serious adverse event (13, 15). The difference between ustekinumab and infliximab of 13.9% indicates that there is a clinical meaningful difference as the difference is higher than the least clinically relevant difference of 5% defined by the medicine's council. However, this should be interpreted with caution due to the narrative comparison and difference in patient population.

Adverse events

Comparing the proportion of adverse events reported in the studies for ustekinumab, infliximab and vedolizumab side by side shows that the safety profile of ustekinumab is superior to that of infliximab and vedolizumab, see *table 20*. The proportion of patients experiencing an adverse events or infections when treated with ustekinumab is lower than compared to infliximab and vedolizumab. Furthermore, adverse events leading to discountinuation is lower in ustekinumab compared to infliximab and the results regarding serious infection is similar.

Conclusively, ustekinumab for the treatment of patientes with moderate to severe ulcerative colitis is consistent with the previously established safety profile of ustekinumab in other indications.

Table 20 Comparison of the safety profile of ustekinumab, infliximab and vedolizumab (9, 13, 15).

	UST 90 mg SC q12w	**IFX 5mg/kg (ACT 1)**	**IFX 5mg/kg (ACT 2)**	**Vedolizumab**
Safety Analysis Set	172	121	121	122
Subjects with 1 or more				
Adverse events, n (%)	119 (69.2%)	106 (87.6%)	99 (81.8%)	100 (82%)
Serious adverse events, n (%)	13 (7.6%)	26 (21.5%)	13 (10.7%)	10 (8%)
Infections, n (%)	58 (33.7%)	53 (43.8%)	33 (27.3%)	87 (71%)
Serious Infections, n (%)	6 (3.5%)	3 (2.5%)	2 (1.7%)	3 (2%)
Adverse events leading to discontinuation, n (%)	9 (5.2%)	10 (8.3%)	2 (1.7%)	-

5.3.2 Comparison of safety profiles for the comparator treatments based on SmPC.

The safety assessments of the EMA are summarized in the SmPCs (1, 31, 32). The relative amount and content of safety information in the SmPCs of the technology and comparator treatments is an important aspect of the safety evidence for ustekinumab and its comparator treatments. This is summarized in appendix 7.3 due to size limitations, and these tables provide an overview of adverse events, infections and warnings and precautions with regard to infections associated with ustekinumab and the comparators as assessed by the EMA. The comparison of the SmPCs obtained after assessment of detailed data from regulators suggests ustekinumab has an acceptable safety profile compared to infliximab and vedolizumab.

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7 Appendices

7.1 Literature search

7.1.1 Inclusion and exclusion criteria

Table A1 Inclusion and exclusion criteria.

Inclusion criteria	Population: Adult biological and targeted synthetic drug treatment-naïve and treatment-experienced patients with moderate to severe active ulcerative colitis Intervention(s): Ustekinumab 6mg/kg (i.v) infusion week 0: 260 mg [≤55 kg]; 390 mg [55 kg - 85 kg];520 mg [>85 kg]. Subcutaneous (s.c.) injection 90 mg week 8 and thereafter every 12. week. Comparator(s): Infliximab (i.v) infusion 5mg/kg week 0, 2 og 6, thereafter every 8. Week. Vedolizumab (i.v) infusion 300 mg week 0, 2 og 6, thereafter every 8. week Outcomes: Minimum one of the following: Clinical remission week 8, steroid free remission week 52, SAEs, mucosal healing week 52, IBDQ change and remission in bio-naïve and bio-experienced patients Settings (if applicable): n/a Study design: Randomized controlled trials, minimum 8 weeks Language restrictions: English, Danish, Norwegian or Swedish Other search limits or restrictions applied: No
Exclusion criteria	Population: Other than the populations defined in inclusion criteria Intervention(s): Other interventions than defined in inclusion criteria Comparator(s): Other interventions than defined in inclusion criteria Outcomes: Other interventions than defined in inclusion criteria Settings (if applicable): n/a Study design: other study designs than randomised controlled trials and phase 1 and 2a studies Language restrictions: Other languages than defined in inclusion criteria Other search limits or restrictions applied: n/a

7.1.2 Search strings

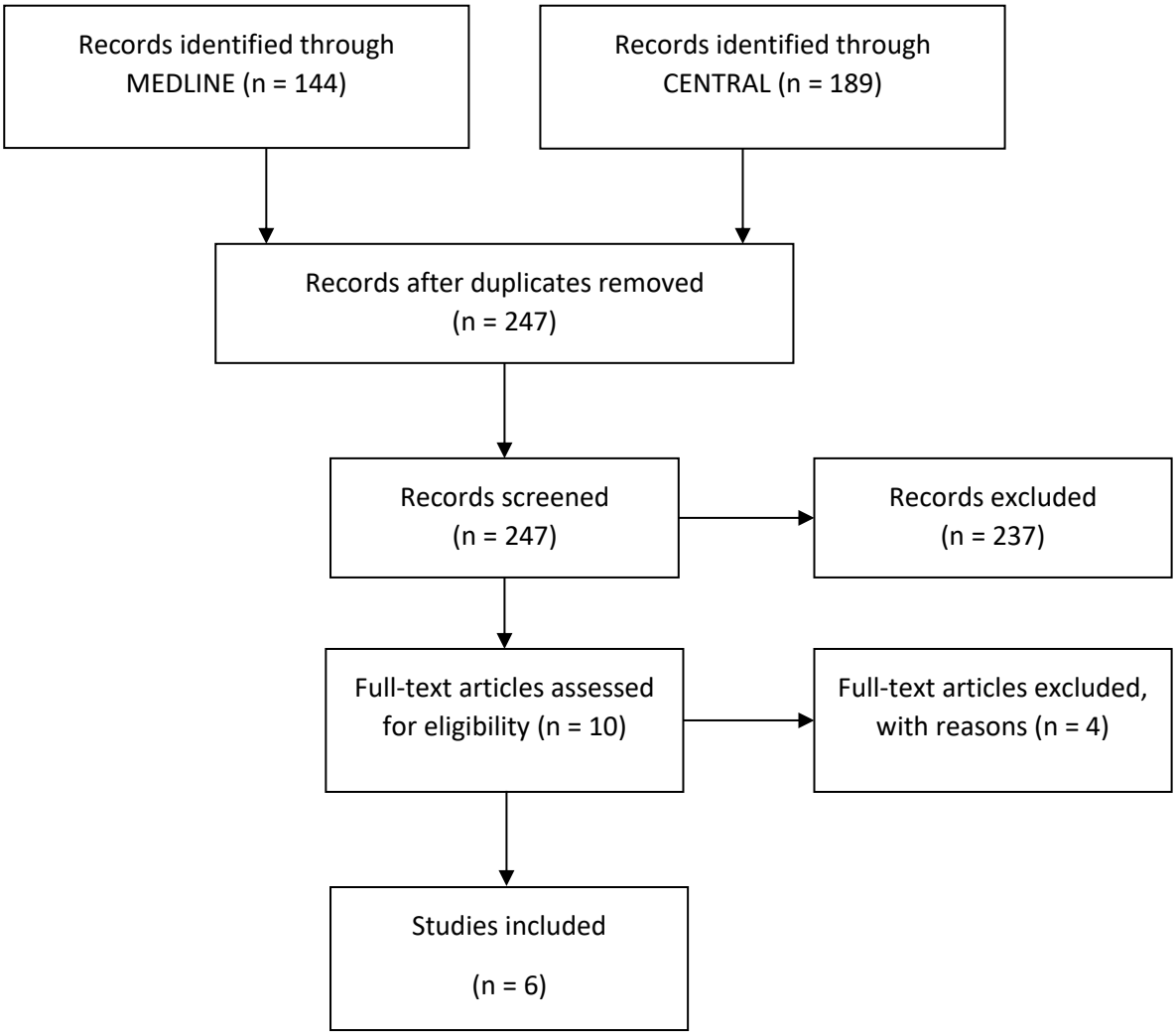
Table A1.1 MEDLINE search string conducted 18-11-2019.

Search	Query	Items found
#18	Search **(((((((((("Colitis, Ulcerative"[mh]) OR ((ulcerative[tiab] OR ulcerosa[tiab]) AND colitis[tiab]))) AND (((((((Ustekinumab[mh]) OR (ustekinumab[tiab] OR Stelara*[tiab] OR CNTO1275[tiab] OR CNTO-1275[tiab])) OR Infliximab[mh]) OR SB2 infliximab[nm]) OR (infliximab[tiab] OR PF-06438179[tiab] OR Remicade*[tiab] OR Inflectra*[tiab] OR Remsima*[tiab] OR CT-P13[tiab] OR Renflexis*[tiab] OR Flixabi*[tiab])) OR vedolizumab[nm]) OR (vedolizumab[tiab] OR Entyvio*[tiab] OR MLN0002[tiab]))))) AND (("Randomized Controlled Trial"[pt] OR "Controlled Clinical Trial"[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR "Clinical Trials as Topic"[mh:noexp] OR randomly[tiab] OR trial[ti]) NOT ("Animals"[mh] NOT "Humans"[mh]))))) NOT (Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Guideline[pt] OR Letter[pt] OR News[pt] OR Observational Study[pt] OR Practice Guideline[pt] OR Review[pt] OR Systematic Review[pt])))) AND (English[la] OR Danish[la] OR Norwegian[la] OR Swedish[la])**	144
#17	Search **English[la] OR Danish[la] OR Norwegian[la] OR Swedish[la]**	25784072
#16	Search **(((((((("Colitis, Ulcerative"[mh]) OR ((ulcerative[tiab] OR ulcerosa[tiab]) AND colitis[tiab]))) AND (((((((Ustekinumab[mh]) OR (ustekinumab[tiab] OR Stelara*[tiab] OR CNTO1275[tiab] OR CNTO-1275[tiab])) OR Infliximab[mh]) OR SB2 infliximab[nm]) OR (infliximab[tiab] OR PF-06438179[tiab] OR Remicade*[tiab] OR Inflectra*[tiab] OR Remsima*[tiab] OR CT-P13[tiab] OR Renflexis*[tiab] OR Flixabi*[tiab])) OR vedolizumab[nm]) OR (vedolizumab[tiab] OR Entyvio*[tiab] OR MLN0002[tiab]))))) AND (("Randomized Controlled Trial"[pt] OR "Controlled Clinical Trial"[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR "Clinical Trials as Topic"[mh:noexp] OR randomly[tiab] OR trial[ti]) NOT ("Animals"[mh] NOT "Humans"[mh]))))) NOT (Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Guideline[pt] OR Letter[pt] OR News[pt] OR Observational Study[pt] OR Practice Guideline[pt] OR Review[pt] OR Systematic Review[pt])**	155
#15	Search **Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Guideline[pt] OR Letter[pt] OR News[pt] OR Observational Study[pt] OR Practice Guideline[pt] OR Review[pt] OR Systematic Review[pt]**	6350661
#14	Search **(((((("Colitis, Ulcerative"[mh]) OR ((ulcerative[tiab] OR ulcerosa[tiab]) AND colitis[tiab]))) AND (((((((Ustekinumab[mh]) OR (ustekinumab[tiab] OR Stelara*[tiab] OR CNTO1275[tiab] OR CNTO-1275[tiab])) OR Infliximab[mh]) OR SB2 infliximab[nm]) OR (infliximab[tiab] OR PF-06438179[tiab] OR Remicade*[tiab] OR Inflectra*[tiab] OR Remsima*[tiab] OR CT-P13[tiab] OR Renflexis*[tiab] OR Flixabi*[tiab])) OR vedolizumab[nm]) OR (vedolizumab[tiab] OR Entyvio*[tiab] OR MLN0002[tiab]))))) AND (("Randomized Controlled Trial"[pt] OR "Controlled Clinical Trial"[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR "Clinical Trials as Topic"[mh:noexp] OR randomly[tiab] OR trial[ti]) NOT ("Animals"[mh] NOT "Humans"[mh]))**	347
#13	Search **("Randomized Controlled Trial"[pt] OR "Controlled Clinical Trial"[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR "Clinical Trials as Topic"[mh:noexp] OR randomly[tiab] OR trial[ti]) NOT ("Animals"[mh] NOT "Humans"[mh])**	1193078
#12	Search **(((("Colitis, Ulcerative"[mh]) OR ((ulcerative[tiab] OR ulcerosa[tiab]) AND colitis[tiab]))) AND (((((((Ustekinumab[mh]) OR (ustekinumab[tiab] OR Stelara*[tiab] OR CNTO1275[tiab] OR CNTO-1275[tiab])) OR Infliximab[mh]) OR SB2 infliximab[nm]) OR (infliximab[tiab] OR PF-06438179[tiab] OR Remicade*[tiab] OR Inflectra*[tiab] OR Remsima*[tiab] OR CT-P13[tiab] OR Renflexis*[tiab] OR Flixabi*[tiab])) OR vedolizumab[nm]) OR (vedolizumab[tiab] OR Entyvio*[tiab] OR MLN0002[tiab]))**	2528
#11	Search **((((((Ustekinumab[mh]) OR (ustekinumab[tiab] OR Stelara*[tiab] OR CNTO1275[tiab] OR CNTO-1275[tiab])) OR Infliximab[mh]) OR SB2 infliximab[nm]) OR (infliximab[tiab] OR PF-06438179[tiab] OR Remicade*[tiab] OR Inflectra*[tiab] OR Remsima*[tiab] OR CT-P13[tiab] OR Renflexis*[tiab] OR Flixabi*[tiab])) OR vedolizumab[nm]) OR (vedolizumab[tiab] OR Entyvio*[tiab] OR MLN0002[tiab])**	16009
#10	Search **vedolizumab[tiab] OR Entyvio*[tiab] OR MLN0002[tiab]**	742
#9	Search **vedolizumab[nm]**	394
#8	Search **infliximab[tiab] OR PF-06438179[tiab] OR Remicade*[tiab] OR Inflectra*[tiab] OR Remsima*[tiab] OR CT-P13[tiab] OR Renflexis*[tiab] OR Flixabi*[tiab]**	11837
#7	Search **SB2 infliximab[nm]**	2
#6	Search **Infliximab[mh]**	9822
#5	Search **ustekinumab[tiab] OR Stelara*[tiab] OR CNTO1275[tiab] OR CNTO-1275[tiab]**	1593
#4	Search **Ustekinumab[mh]**	911
#3	Search **("Colitis, Ulcerative"[mh]) OR ((ulcerative[tiab] OR ulcerosa[tiab]) AND colitis[tiab])**	47072
#2	Search **(ulcerative[tiab] OR ulcerosa[tiab]) AND colitis[tiab]**	39121
#1	Search **"Colitis, Ulcerative"[mh]**	33569

Table A1.2 Cochrane search string conducted 18-11-2019.

−	+	#1	[mh "Colitis, Ulcerative"]	S	MeSH	Limits	1415
−	+	#2	ulcerative colitis:kw			Limits	3263
−	+	#3	((ulcerative OR ulcerosa) NEAR/2 colitis):ti,ab			Limits	4242
−	+	#4	#1 OR #2 OR #3			Limits	4641
−	+	#5	[mh Ustekinumab]			Limits	131
−	+	#6	(ustekinumab OR Stelara* OR CNTO1275 OR "CNTO 1275"):ti,ab,kw			Limits	703
−	+	#7	[mh Infliximab]			Limits	662
−	+	#8	(infliximab OR "PF 06438179" OR Remicade* OR Inflectra* OR Remsima* OR "CT P13" OR Renflexis* OR Flixabi*):ti,ab,kw			Limits	2454
−	+	#9	(vedolizumab OR Entyvio* OR MLN0002):ti,ab,kw			Limits	371
−	+	#10	#5 OR #6 OR #7 OR #8 OR #9			Limits	3349
−	+	#11	#4 AND #10			Limits	626
−	+	#12	("conference abstract" OR review):pt			Limits	180210
−	+	#13	NCT*:au			Limits	145577
−	+	#14	("clinicaltrials gov" OR trialsearch):so			Limits	275249
−	+	#15	#12 OR #13 OR #14			Limits	455556
−	+	#16	#11 NOT #15 in Trials			Limits	189
−	+	#17	Type a search term or use the S or MeSH buttons to compose	S	MeSH	Limits	N/A

7.1.3 PRISMA Flow diagram



7.1.4 Excluded references

Table A1.3 References excluded after full-text screening.

Reference (title, author, journal, year)	*Reason for exclusion*
Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis. Panaccione R, et al., Gastroenterology. 2014 (UC-SUCCESS)	The study does not include a placebo arm which can be used as a common comparator to connect the included studies in an indirect comparison
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	The exclusion of Kobayashi et al. and Jiang et al. was due to the studies only investigating infliximab in Asian patient population. Consequently, these studies had a patient population which baseline characteristics presented clinical heterogeneity compared to the included studies regarding e.g. age and duration of disease.
Low-dose Infliximab for Induction and Maintenance Treatment in Chinese Patients With Moderate to Severe Active Ulcerative Colitis. Jiang et al., J Clin Gastroenterol, 2015	
Vedolizumab versus adalimumab for Moderate- to-Severe Ulcerative Colitis. Sands BE et al., NEJM, 2019	The study does not include a placebo arm which can be used as a common comparator to connect the study with the UNIFI study in an indirect comparison. Furthermore, the lack of a placebo-arm result in the fact that a meta-analysis with the GEMINI 1 study cannot be conducted.

7.1.5 Main characteristics of included studies

Table A2 Main study characteristics of UNIFI (9).

Trial name	*A study to Evaluate the Safety and Efficacy of Ustekinumab Induction and Maintenance Therapy (UNIFI) (19).*
NCT number	*NCT02407236*
Objective	*The purpose of this study is to evaluate the efficacy and safety of ustekinumab as intravenous (IV: into the vein) infusion in induction study in participants with moderately to severely active Ulcerative Colitis (UC) and as subcutaneous (SC) administration in maintenance study in participants with moderately to severely active Ulcerative Colitis (UC) who have demonstrated a clinical response to Induction treatment with IV ustekinumab (19).*
Publications – title, author, journal, year	*Ustekinumab as Induction and Maintenance Therapy for Ulcerative Colitis. Sands BE et al., NEJM, 2019 (9).*
Study type and design	*Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicentre study evaluating the safety and efficacy of ustekinumab induction and maintenance therapy in patients with moderately to severely active UC (9).*
Follow-up time	*<u>Induction:</u> Average duration of follow-up for randomly assigned patients to receive Ustekinumab 6 mg/kg in induction study was 8.6 weeks.* *Average duration of follow-up for randomly assigned patients to receive placebo in induction study was 8.7 weeks* *<u>Maintenance:</u> Average duration of follow-up for the randomized population of patients with response to IV Ustekinumab in induction study and receiving 90mg/12week Ustekinumab in maintenance study was 41.8 weeks.* *Average duration of follow-up for the randomized population of patients with response to IV Ustekinumab in induction study and receiving placebo in maintenance study was 42.3 weeks*
Population (inclusion and exclusion criteria)	*Inclusion Criteria:* • *Has a clinical diagnosis of Ulcerative Colitis (UC) at least 3 months before Screening* • *Has moderately to severely active UC, defined as a Baseline (Week 0) Mayo score of 6 to 12, including a Screening endoscopy subscore of the Mayo score greater than or equal to (>=) 2 as determined by a central reading of the video endoscopy* • *Have failed biologic therapy, that is, have received treatment with 1 or more tumour necrosis factor (TNF) antagonists or vedolizumab at a dose approved for the treatment of UC, and have a documented history of failure to respond to or tolerate such treatment; OR Be naïve to biologic therapy (TNF antagonists or vedolizumab) or have received biologic therapy but have not demonstrated a history of failure to respond to, or tolerate, a biologic therapy and have a prior or current UC medication history that includes at least 1 of the following: a. Inadequate response to or failure to tolerate current treatment with oral corticosteroids or immunomodulators (6-mercaptopurine [6-MP] or azathioprine [AZA]) OR b. History of failure to respond to, or tolerate, at least 1 of the following therapies: oral or IV corticosteroids or immunomodulators (6-MP or AZA) OR c. History of corticosteroid dependence (that is, an inability to successfully taper corticosteroids without a return of the symptoms of UC)*

	• *Before the first administration of study agent, the following conditions must be met: vedolizumab must have been discontinued for at least 4 months and anti-tumor necrosis factors (TNFs) for at least 8 weeks* *Exclusion Criteria:* • *Has severe extensive colitis and is at imminent risk of colectomy* • *Has UC limited to the rectum only or to < 20 centimeters (cm) of the colon* • *Presence of a stoma or history of a fistula* • *Participants with history of extensive colonic resection (for example, less than 30 cm of colon remaining) that would prevent adequate evaluation of the effect of study agent on clinical disease activity* • *Participants with history of colonic mucosal dysplasia. Participants will not be excluded from the study because of a pathology finding of "indefinite dysplasia with reactive atypia''*
Intervention	*Induction:* • *Ustekinumab 130mg (n=321)* • *Ustekinumab 6mg/kg (n=320)* • *Placebo (n=319)* *Maintenance:* • *Ustekinumab 90mg q12w (n=172)* • *Ustekinumab 90mg q8w (n=176)* • *Placebo (n=175)*
Baseline characteristics	*See table A2.1*
Primary and secondary endpoints	*The primary outcome for the induction trial was clinical remission, defined as a total Mayo score of ≤2 and no subscore >1, at week 8. The major secondary outcomes in the induction trial at week 8 were endoscopic improvement (defined as a Mayo endoscopic subscore of 0 or 1), clinical response (decrease from baseline in the Mayo score ≥ 30% and ≥ 3 points with either a decrease in rectal bleeding subscore from baseline or or rectal bleeding subscore = 0 or 1) and changes in the IBDQ score.* *The primary outcome for the maintenance trial was clinical remission at week 52. The major secondary endpoints at week 52 were maintenance of clinical response, endoscopic improvement, maintenance of clinical remission through week 52 among patients in clinical remission at baseline in the maintenance trial and corticosteroid-free clinical remission at week 52.*
Method of analysis	*Dichotomous end points were compared between each ustekinumab group and the placebo group with the use of a two-sided, Cochran–Mantel–Haenszel chi-square test with adjustment for stratification variables. Continuous end points were analyzed by means of analysis of covariance or analysis of covariance on van der Waerden normal scores with adjustment for baseline value and stratification variables.* *Analyses of other end points were not adjusted for multiple comparisons, and results are reported with 95% confidence intervals not adjusted for multiple comparisons. All efficacy analyses were based on the ITT principle; therefore, subjects were analyzed according to the group to which they were assigned regardless of the treatment received* (11).
Subgroup analyses	*In prespecified exploratory and post-hoc analyses, efficacy outcomes were evaluated in the bio-experienced and bio-naïve intention-to-treat populations (11).*

Table A2.1 UNIFI baseline characteristics in the induction trial (9).

Characteristics	Placebo (N=319)	Ustekinumab 130mg (N=320)	Ustekinumab 6mg/kg† (N=322)
Male sex — no. (%)	197 (61.8)	190 (59.4)	195 (60.6)
Age — yr	41.2±13.5	42.2±13.9	41.7±13.7
Weight — kg	72.9±16.8	73.7±16.8	73.0±19.3
Duration of disease — yr	8.0±7.2	8.1±7.2	8.2±7.8
Total Mayo score‡	8.9±1.6	8.9±1.6	8.9±1.5
Score of 6–10, indicating moderate disease— no./total no. (%)	263/319 (82.4)	271/320 (84.7)	276/321 (86.0)
Disease limited to left side of colon — no./total no. (%)	167/316 (52.8)	183/318 (57.5)	168/320 (52.5)
C-reactive protein — mg/liter§			
Median	4.7	4.5	4.8
IQR	1.4–10.0	1.6–9.9	1.8–13.7
Fecal calprotectin — mg/kg¶			
Median	1224.0	1382.0	1506.5
IQR	496.0–2224.0	564.5–2681.0	621.5–3192.5
Medications for ulcerative colitis taken at baseline			
≥1 Medication — no. (%)	283 (88.7)	290 (90.6)	294 (91.3)
Aminosalicylates — no. (%)	207 (64.9)	215 (67.2)	238 (73.9)
Corticosteroids — no. (%)‖	157 (49.2)	173 (54.1)	168 (52.2)
Median dose (IQR) — mg/day	20.0 (10.0–20.0)	20.0 (10.0–20.0)	20.0 (10.0–20.0)
Immunomodulator — no. (%)**	89 (27.9)	93 (29.1)	89 (27.6)
No history of disease refractory to treatment with biologic agents — no. (%)	158 (49.5)	156 (48.8)	156 (48.4)
Had not received biologics	151 (47.3)	145 (45.3)	147 (45.7)
Had received biologics but did not have documented treatment failure	7 (2.2)	11 (3.4)	9 (2.8)
History of treatment failure with biologics — no. (%)††	161 (50.5)	164 (51.2)	166 (51.6)
Only TNF antagonist	112 (35.1)	107 (33.4)	106 (32.9)
Vedolizumab	49 (15.4)	57 (17.8)	60 (18.6)
≥1 TNF antagonist, regardless of vedolizumab	159 (49.8)	162 (50.6)	164 (50.9)
Any TNF antagonist and vedolizumab	47 (14.7)	55 (17.2)	58 (18.0)

* Plus–minus values are means ±SD. IQR denotes interquartile range, and TNF tumor necrosis factor.
† Weight-range–based doses of ustekinumab approximate 6 mg per kilogram of body weight (with 260 mg prescribed for patients weighing ≤55 kg, 390 mg for patients weighing >55 kg and ≤85 kg, and 520 mg for patients weighing >85 kg).
‡ Total scores on the Mayo scale range from 0 to 12, with higher scores indicating more severe disease.
§ Data for C-reactive protein concentrations were available for 951 patients: 316 receiving placebo, 315 receiving 130 mg of ustekinumab, and 320 receiving 6 mg of ustekinumab per kilogram.
¶ Data for fecal calprotectin concentrations were available for 855 patients: 289 receiving placebo, 296 receiving 130 mg of ustekinumab, and 300 receiving 6 mg of ustekinumab per kilogram.
‖ Corticosteroids included budesonide and beclomethasone dipropionate. Shown is the prednisone-equivalent dose. Data on corticosteroid dose were available for 418 patients: 133 receiving placebo, 143 receiving 130 mg of ustekinumab, and 142 receiving 6 mg of ustekinumab per kilogram.
** Immunomodulators included azathioprine, mercaptopurine, and methotrexate.
†† Patients may have reported more than one reason for treatment failure with a TNF antagonist.

Table A2.2 Main study characteristics of ACT 1 (13, 22).

Trial name	*A Safety and Efficacy Study for Infliximab (Remicade) in Patients with Active Ulcerative colitis (ACT 1)*
NCT number	*NCT00036439*
Objective	*Investigate the safety and effectiveness of a medication called infliximab in adult patients with active ulcerative colitis.(clinical trials)*
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 et al., Am J Gastroenterol, 2007*
Study type and design	*ACT 1 is a multicenter, phase 3, randomized, blinded, placebo-controlled studies in patients with moderately to severely active ulcerative colitis.*
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* iv at week 0, 2, 6 and then every 8 weeks* • *Infliximab* 5 mg/kg iv at week 0, 2, 6 and then every 8 weeks* • *Infliximab* 10 mg/kg iv at week 0, 2, 6 and then every 8 weeks* **with optional 5-ASA, immunnosuppressors and background Glucocorticoids of which the latter to be tapered after week 8.*
Baseline characteristics	*See table A2.2.1*
Primary and secondary endpoints	*The primary end point was a clinical response at week 8. Clinical response is 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.* *Secondary end points were a clinical response or clinical remission 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. Clinical remission is defined as a Mayo score of = 2 points, with no individual subscore > 1*
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	*No subgroup analysis*

Table A2.2.1 Baseline characteristics of ACT 1 and ACT 2 (13).

Characteristics	ACT 1				ACT 2			
	Placebo (N=121)	5 mg of infliximab (N=121)	10 mg of infliximab (N=122)	P value †	Placebo (N=123)	5 mg of infliximab (N=121)	10 mg of infliximab (N=120)	P value †
Male sex — no. (%)	72 (59.5)	78 (64.5)	72 (59.0)	0.63	71 (57.7)	76 (62.8)	68 (56.7)	0.58
White race — no. (%)	111 (91.7)	116 (95.9)	113 (92.6)	0.62	117 (95.1)	116 (95.9)	111 (92.5)	0.03
Age — yr	41.4±13.7	42.4±14.3	41.8±14.9	0.86	39.3±13.5	40.5±13.1	40.3±13.3	0.68
Weight — kg	76.8±16.2	80.0±17.8	76.9±17.1	0.25	76.1±17.4	78.4±17.8	79.6±20.6	0.34
Duration of disease — yr	6.2±5.9	5.9±5.4	8.4±8.1	0.03	6.5±6.7	6.7±5.3	6.5±5.8	0.18
Colonic area involved								
Total no. of patients	120	119	121		120	118	120	
Left side — no. (%)	66 (55.0)	63 (52.9)	67 (55.4)	0.92	70 (58.3)	70 (59.3)	75 (62.5)	0.79
Extensive — no. (%)	54 (45.0)	56 (47.1)	54 (44.6)		50 (41.7)	48 (40.7)	45 (37.5)	
Mayo score‡	8.4±1.8	8.5±1.7	8.4±1.4	0.86	8.5±1.5	8.3±1.5	8.3±1.6	0.58
C-reactive protein§								
Total no. of patients	119	120	121		121	120	119	
Mean — mg/dl	1.7±2.7	1.4±1.9	1.6±2.3	0.82	1.6±2.9	1.3±2.3	1.4±2.2	0.86
Median — mg/dl	0.8	0.9	1.0		0.6	0.8	0.6	
Elevated — no. (%)	74 (62.2)	78 (65.0)	81 (66.9)	0.74	72 (59.5)	76 (63.3)	64 (53.8)	0.32
Concomitant medication — no. (%)								
Corticosteroids	79 (65.3)	70 (57.9)	73 (59.8)	0.47	60 (48.8)	60 (49.6)	66 (55.0)	0.58
≥20 mg/day	54 (44.6)	45 (37.2)	46 (37.7)		43 (35.0)	40 (33.1)	47 (39.2)	
5-Aminosalicylates	85 (70.2)	82 (67.8)	86 (70.5)	0.88	89 (72.4)	92 (76.0)	91 (75.8)	0.76
Immuno-suppressants	53 (43.8)	66 (54.5)	59 (48.4)	0.25	54 (43.9)	52 (43.0)	50 (41.7)	0.94
Azathioprine	36 (29.8)	45 (37.2)	44 (36.1)		35 (28.5)	41 (33.9)	37 (30.8)	
Mercaptopurine	17 (14.0)	21 (17.4)	15 (12.3)		19 (15.4)	11 (9.1)	13 (10.8)	
Corticosteroid-refractory disease — no. (%)	38 (31.4)	36 (29.8)	38 (31.1)	0.96	36 (29.3)	35 (28.9)	34 (28.3)	0.99
Smoking status — no. (%)				0.50				0.95
Current smoker	7 (5.8)	2 (1.7)	3 (2.5)		6 (4.9)	8 (6.6)	6 (5.0)	
Nonsmoker	60 (49.6)	65 (53.7)	66 (54.1)		63 (51.2)	65 (53.7)	63 (52.5)	
Former smoker	54 (44.6)	54 (44.6)	53 (43.4)		54 (43.9)	48 (39.7)	51 (42.5)	

Table A2.3 Main study characteristics of ACT 2 (13, 23).

Trial name	*A Safety and Efficacy Study for Infliximab (Remicade) in Patients with Active Ulcerative colitis (ACT-2)*
NCT number	*NCT00096655*
Objective	*Investigate the safety and effectiveness of a medication called infliximab in adult patients with active ulcerative colitis.*
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 et al., Am J Gastroenterol, 2007*
Study type and design	*ACT 2 is a multicenter, phase 3, randomized, blinded, placebo-controlled studies in patients with moderately to severely active ulcerative colitis.*
Follow-up time	*30 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* iv at week 0, 2, 6 and then every 8 weeks* • *Infliximab* 5 mg/kg iv at week 0, 2, 6 and then every 8 weeks* • *Infliximab* 10 mg/kg iv at week 0, 2, 6 and then every 8 weeks* **with optional 5-ASA, immunnosuppressors and background Glucocorticoids of which the latter to be tapered after week 8.*
Baseline characteristics	*See table A2.2.1*
Primary and secondary endpoints	*The primary end point was a clinical response at week 8. Clinical response is 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.* *Secondary end points were a clinical response or clinical remission with discontinuation of corticosteroids at week 30, clinical remission and mucosal healing at weeks 8 and week 30, and a clinical response at week 8 in patients with a history of disease refractory to corticosteroids. Clinical remission is defined as a Mayo score of = 2 points, with no individual subscore > 1*
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	*No subgroup analysis*

Table A2.4 Main study characteristics of GEMINI I (15, 24).

Trial name	*Study of Vedolizumab (MLN0002) in Patients with Moderate to Severe Ulcerative Colitis (GEMINI I)*
NCT number	*NCT00783718*
Objective	*The overall objective of the study was to determine the effect of vedolizumab induction treatment on clinical response at 6 weeks and to determine the effect of vedolizumab maintenance treatment on clinical remission at 52 weeks.*
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 Gastroenterol Hepatol, 2017.* • *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.*
Study type and design	*This multicenter, phase 3, randomized, blinded, placebo-controlled study in patients with moderately to severely active ulcerative colitis comprises two phases:* *The Induction Phase, designed to establish the efficacy and safety of vedolizumab for the induction of clinical response and remission.* *The Maintenance Phase, designed to establish the efficacy and safety of vedolizumab for the maintenance of clinical response and remission.* *The 6-week Induction Phase contained 2 cohorts of participants: Cohort 1 participants were randomized and treated with double-blind study drug, and Cohort 2 participants were treated with open-label vedolizumab. The second cohort was enrolled to ensure that the sample size of Induction Phase responders randomized into the Maintenance Study provided sufficient power for the Maintenance Study primary efficacy analysis. These participants did not contribute to the efficacy analyses performed for the Induction Study. Participants in both cohorts were assessed for treatment response at Week 6.* *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.*
Follow-up time	*52 weeks*
Population (inclusion and exclusion criteria)	*Inclusion Criteria:* *Each patient must meet all of the following inclusion criteria to be enrolled in the study:* 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:* a. *Immunomodulators* b. *Tumor necrosis factor-alpha (TNFα) antagonists* c. *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 tuberculosi*
Intervention	*Induction:* • *Placebo*: n=149* • *Vedolizumab* 300 mg iv infusion at week 0 and 2 for cohort 1 (DB): n=225 + cohort 2 (OL): n= 521* *Maintenance:* • *Placebo*: n= 126* • *Vedolizumab* 300 mg iv maintenance every 4 weeks: n=125* • *Vedolizumab* 300 mg iv maintenance every 8 weeks: n= 122* ** (with optional mesalamine and/or immunnosuppressors and background Glucocorticoids to be tapered)*
Baseline characteristics	• *See table A2.4.1*
Primary and secondary endpoints	*The primary endpoint for the induction phase was clinical response at week 6, defined as a reduction in the Mayo score of ≥ 3 points and ≥ 30% from baseline with an accompanying decrease in rectal bleeding subscore of ≥ 1 point or absolute rectal bleeding subscore of ≤ 1 point.* *Secondary endpoints at week 6 were clinical remission (complete Mayo score of ≤ 2 points and no individual subscore > 1 point), and mucosal healing (Mayo endoscopic subscore of ≤ 1 point)* *The primary endpoint for the maintenance phase was clinical remission at week 52. The secondary endpoints for the maintenance phase were durable clinical response (reduction in complete Mayo score of ≥ 3 points and ≥ 30% from Baseline (Week 0) with an accompanying decrease in rectal bleeding subscore of ≥ 1 point or absolute rectal bleeding subscore of ≤ 1 point at both Weeks 6 and 52.), durable clinical remission (complete Mayo score of ≤ 2 points and no individual subscore > 1 point at both Weeks 6 and 52), mucosal healing at week 52, and corticosteroid-free remission (Corticosteroid-free clinical remission is defined as participants using oral corticosteroids at baseline (Week 0) who discontinued corticosteroids and were in clinical remission at Week 52.)*
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 mucosal 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. Page 51 of 108 Application form version 2.0, revision 08-Apr-2019 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.*

Table A2.4.1 Baseline characteristics of GEMINI I induction trial (15).

Characteristics	**Placebo (N=149)**	**Vedolizumab cohort 1 (N=225)**	**Vedolizumab cohort 2 (N=521)**	**Vedolizumab combined (N=746)**	**Total (N=895)**
Age — yr	41.2±12.5	40.1±13.1	40.1±13.3	40.1±13.2	40.3±13.1
Male sex — no. (%)	92 (61.7)	132 (58.7)	301 (57.8)	433 (58.0)	525 (58.7)
White race — no. (%)‡	115 (77.2)	183 (81.3)	436 (83.7)	619 (83.0)	734 (82.0)
Body weight — kg	72.4±17.6	72.4±17.1	74.2±19.3	73.6±18.7	73.4±18.5
Current smoker — no. (%)	11 (7.4)	12 (5.3)	32 (6.1)	44 (5.9)	55 (6.1)
Duration of disease — yr	7.1±7.2	6.1±5.1	7.2±6.6	6.8±6.2	6.9±6.4
Mayo Clinic score§	8.6±1.7	8.5±1.8	8.6±1.8	8.6±1.8	8.6±1.8
Partial Mayo Clinic score¶	6.1±1.5	6.0±1.6	6.0±1.6	6.0±1.6	6.0±1.6
IBDQ score‖	126±34	125±35	121±32	122±33	122±33
Fecal calprotectin — µg/g**					
Median	1006	1112	782	868	899
Interquartile range	333–2943	449–2931	331–1594	344–1915	341–2127
Site of disease — no. (%)					
Rectum and sigmoid colon only	22 (14.8)	25 (11.1)	69 (13.2)	94 (12.6)	116 (13.0)
Left side of colon	59 (39.6)	92 (40.9)	188 (36.1)	280 (37.5)	339 (37.9)
Proximal to the splenic flexure	18 (12.1)	25 (11.1)	66 (12.7)	91 (12.2)	109 (12.2)
All of the colon	50 (33.6)	83 (36.9)	198 (38.0)	281 (37.7)	331 (37.0)
Concomitant medications for ulcerative colitis — no. (%)					
Glucocorticoids only	58 (38.9)	79 (35.1)	195 (37.4)	274 (36.7)	332 (37.1)
Immunosuppressants only††	18 (12.1)	28 (12.4)	113 (21.7)	141 (18.9)	159 (17.8)
Glucocorticoids and immunosuppressants	26 (17.4)	47 (20.9)	76 (14.6)	123 (16.5)	149 (16.6)
No glucocorticoids or immunosuppressants	47 (31.5)	71 (31.6)	137 (26.3)	208 (27.9)	255 (28.5)
Prednisone equivalent dose — mg					
Median	20.0	20.0	20.0	20.0	20.0
Interquartile range	10.0–30.0	10.0–25.0	10.0–30.0	10.0–25.0	10.0–25.0
Prior anti-TNF therapy — no. (%)	73 (49.0)	95 (42.2)	263 (50.5)	358 (48.0)	431 (48.2)
Prior failure of anti-TNF therapy — no. (%)					
≥1 failure	63 (42.3)	82 (36.4)	222 (42.6)	304 (40.8)	367 (41.0)
Inadequate response	29 (46.0)	44 (53.7)	103 (46.4)	147 (48.4)	176 (48.0)
Loss of response‡‡	26 (41.3)	32 (39.0)	83 (37.4)	115 (37.8)	141 (38.4)

Unacceptable adverse events	8 (12.7)	6 (7.3)	36 (16.2)	42 (13.8)	50 (13.6)
Hemoglobin concentration — g/liter	123.7±19.6	125.2±19.6	124.9±119.5	125.0±19.5	124.8±19.5
White-cell count — ×10−9/liter	8.7±3.3	8.2±3.1	8.6±3.2	8.5±3.2	8.5±3.2

* Plus–minus values are means ±SD. TNF denotes tumor necrosis factor.
† P values for the comparison in cohort 1 between the placebo group and the vedolizumab group are all greater than 0.05.
‡ Race was self-reported.
§ Mayo Clinic scores range from 0 to 12, with higher scores indicating more active disease.19,20
¶ The partial Mayo Clinic score consists of the Mayo Clinic score minus the sigmoidoscopy subscore; range, 0 to 9, with higher scores indicating more active disease.
‖ Scores on the Irritable Bowel Disease Questionnaire (IBDQ) range from 0 to 224, with higher scores indicating a better quality of life.
** Data on fecal calprotectin were available for 857 patients: 139 receiving placebo, 213 receiving vedolizumab in cohort 1, 505 receiving vedolizumab in cohort 2, and 718 receiving vedolizumab in the combined cohorts.
†† Immunosuppressants included azathioprine and mercaptopurine.
‡‡ Loss of response indicates that the patient had a response initially but subsequently did not have a response.

7.1.6 Results per study

Table A3 Results of the UNIFI study for the bio-naïve patient population.

Trial name:	*UNIFI*						
NCT number:	*NCT02407236*						
	Data extracted from UNIFI				Estimated relative difference in effect (risk ratio)		Description of methods used for estimation
Outcome	Study arm	N	Result	Significant difference (p-value)	Difference	95% CI	
Clinical remission at week 8	Ustekinumab 6mg/kg	29/156	18.6%	0.002	1.96	1.09-3.51	*Data extracted as stated in the UNIFI study or EPAR with the p-value based on the Cochran-Mantel-Haenszel test (11). Relative difference is provided as unadjusted risk ratio. *Pooled population of bio-naïve and bio-experienced patients.*
	Placebo SC	15/158	9.5%				
Corticosteroid-free clinical remission at week 52	Ustekinumab SC 90mg q12w	49/102	48%	p<0.05	1.55	1.07-2.25	
	Placebo SC	27/87	31%				
*Serious adverse events at week 52**	Ustekinumab SC 90mg q12w	13/172	7.6%	n/a	0.78	0.39-1.55	
	Placebo SC	17/175	9.7%				
Mucosal healing at week 52	Ustekinumab SC 90mg q12w	57/102	55.9%	p<0.05	1.62	1.16-2.27	
	Placebo SC	30/87	34.5%				
IBDQ remission	Ustekinumab	n/a	n/a	n/a	n/a	n/a	
	Placebo	n/a	n/a				
*IBDQ mean change at week 8**	Ustekinumab	n/a	35.0 (CI;31.51-38.49)	n/a	18.9**	13.99-23.81**	*Population of bio-naïve and bio-experienced patients. Difference between means was calculated using following formula (25): 1) Mean difference = Mean1 − Mean2, 2) Standard error of the mean difference (SE) = $\sqrt{(SD_1^2/N_1 + SD_2^2/N_2)}$, 3) 95% CI = mean difference ± 1.96 × SE **No relative difference in effect reported.*
	Placebo	n/a	16.1 (CI;12.64-19.56)				

Table A3a Results of the UNIFI study for the bio-experienced patient population.

Trial name:	*UNIFI*						
NCT number:	*NCT02407236*						
	Data extracted from UNIFI or EPAR				Estimated relative difference in effect (risk ratio)		Description of methods used for estimation
Outcome	Study arm	N	Result	Significant difference (p-value)	Difference	95% CI	
Clinical remission at week 8	Ustekinumab 6mg/kg	21/166	12.7%	P<0.001	10.18	2.43-42.73	*Data extracted as stated in the UNIFI study or EPAR with the p-value based on the Cochran-Mantel-Haenszel test (11). Relative difference is provided as unadjusted risk ratio.* **Pooled population of bio-naïve and bio-experienced patients.*
	Placebo SC	2/161	1.2%				
Corticosteroid-free clinical remission at week 52	Ustekinumab SC 90mg q12w	16/70	22.9%	P<0.05	1.44	0.75-2.74	
	Placebo SC	14/88	15.9%				
*Serious adverse events at week 52**	Ustekinumab SC 90mg q12w	13/172	7.6%	n/a	0.78	0.39-1.55	
	Placebo SC	17/175	9.7%				
Mucosal healing at week 52	Ustekinumab SC 90mg q12w	18/70	25.7%	Not significant	1.13	0.65-1.97	
	Placebo SC	20/88	22.7%				
IBDQ remission	Ustekinumab	n/a	n/a	n/a	n/a	n/a	
	Placebo	n/a	n/a				
*IBDQ mean change at week 8**	Ustekinumab	n/a	35.0 (CI;31.51-38.49)	n/a	18.9**	13.99-23.81**	**Mean change compared to placebo in pooled population of bio-naïve and bio-experienced patients. Difference between means was calculated using following formula (25): 1) Mean difference = Mean1 − Mean2, 2) Standard error of the mean difference (SE) = $\sqrt{(SD_1^2/N_1 + SD_2^2/N_2)}$, 3) 95% CI = mean difference ± 1.96 × SE* ***No relative difference in effect reported.*
	Placebo	n/a	16.1 (CI;12.64-19.56)				

Table A3b Results of the ACT-1 study for the bio-naïve patient population.

Trial name:	*ACT 1*						
NCT number:	*NCT00036439*						
	Data extracted from ACT 1				Estimated relative difference in effect (risk ratio)		Description of methods used for estimation
Outcome	Study arm	n/N	Result	Significant difference (p-value)	Difference	95% CI	
Clinical remission at week 8	Infliximab 5mg/kg	47/121	38.8%	n/a	2.61	1.61-4.23	*Data extracted as stated in the included studies for infliximab and relative difference is provided as unadjusted risk ratio.*
	Placebo IV	18/121	14.9%				
Corticosteroid-free clinical remission at week 54	Infliximab 5mg/kg	18/70	25.7%	n/a	2.90	1.29-6.53	
	Placebo IV	7/79	8.9%				
Serious adverse events at week 54	Infliximab 5mg/kg	26/121	21.5%	n/a	0.84	0.53-1.32	
	Placebo IV	31/121	25.6%				
Mucosal healing at week 54	Infliximab 5mg/kg	55/121	45.5%	n/a	2.5	1.63-3.83	
	Placebo IV	22/121	18.2%				
IBDQ remission week 54	Infliximab 5mg/kg	n/a	n/a	n/a	n/a	n/a	
	Placebo IV	n/a	n/a				
*IBDQ mean change week 8**	Infliximab 5mg/kg	n/a	40 (35.72-44.28)	n/a	19**	13.46-24.54**	*Pooled data from ACT 1 and ACT 2 *Difference between means was calculated using following formula (25): 1) Mean difference = Mean1 − Mean2, 2) Standard error of the mean difference (SE) = $\sqrt{(SD_1^2/N_1 + SD_2^2/N_2)}$, 3) 95% CI = mean difference ± 1.96 × SE* ***No relative difference in effect reported.*
	Placebo IV	n/a	21 (17.49-24.51)				

Table A3c Results of the ACT-2 study for the bio-naïve patient population.

Trial name:	*ACT 2*						
NCT number:	*NCT00096655*						
	Data extracted from ACT 2				Estimated relative difference in effect (risk ratio)		Description of methods used for estimation
Outcome	Study arm	n/N	Result	Significant difference (p-value)	Difference	95% CI	
Clinical remission at week 8	Infliximab 5mg/kg	41/121	33.9%	n/a	5.95	2.78-12.75	*Data extracted as stated in the included studies for infliximab and relative difference is provided as unadjusted risk ratio*
	Placebo IV	7/123	5.7%				
Corticosteroid -free clinical remission at week 30	Infliximab 5mg/kg	11/60	18.3%	n/a	5.50	1.27-23.77	
	Placebo IV	2/60	3.3%				
Serious adverse events at week 30	Infliximab 5mg/kg	13/121	10.7%	n/a	0.55	0.29-1.03	
	Placebo IV	24/123	19.5%				
Mucosal healing at week 30	Infliximab 5mg/kg	56/121	46.3%	n/a	1.54	1.11-2.14	
	Placebo IV	37/123	30.1%				
IBDQ remission week 30	Infliximab 5mg/kg	n/a	n/a	n/a	n/a	n/a	
	Placebo IV	n/a	n/a				
*IBDQ mean change week 8**	Infliximab 5mg/kg	n/a	40 (35.72-44.28)	n/a	19**	13.46-24.54**	*Pooled data from ACT 1 and ACT 2 *Difference between means was calculated using following formula (25): 1) Mean difference = Mean1 − Mean2, 2) Standard error of the mean difference (SE) = √(SD_1^2 /N_1 + SD_2^2 /N_2), 3) 95% CI = mean difference ± 1.96 × SE* ***No relative difference in effect reported.*
	Placebo IV	n/a	21 (17.49-24.51)				

Table A3d Results of the GEMINI I study for the bio-naïve patient population.

Trial name:	*GEMINI I*						
NCT number:	*NCT00783718*						
	Data extracted from GEMINI I				Estimated relative difference in effect (risk ratio)		Description of methods used for estimation
Outcome	Study arm	n/N	Result	Significant difference (p-value)	Difference	95% CI	
Clinical remission at week 6	Vedolizumab 300mg	30/130	23.1%	n/a	3.51	1.42-8.66	*Data extracted as stated in the included studies for vedolizumab and relative difference is provided as unadjusted risk ratio* **Pooled population of bio-naïve and bio-experienced patients being vedolizumab induction responders and receiving vedolizumab every 8 weeks*
	Placebo IV	5/76	6.6%				
Corticosteroid-free clinical remission at week 52	Vedolizumab 300mg	14/39	35.9%	n/a	1.93	0.91-4.10	
	Placebo IV	8/43	18.6%				
Serious adverse events at week 52	Vedolizumab 300mg	28/309	9.1%	n/a	0.57	0.31-1.08	
	Placebo IV	12/76	15.8%				
*Serious adverse events at week 52**	Vedolizumab 300mg	10/122	8%	n/a	0.52	0.25-1.06	
	Placebo IV	20/126	16%				
Mucosal healing at week 52	Vedolizumab 300mg	43/72	59.7%	n/a	2.39	1.55-3.68	
	Placebo IV	19/79	24.1%				
IBDQ remission week 52	Vedolizumab 300mg	n/a	n/a	n/a	n/a	n/a	
	Placebo IV	n/a	n/a				

IBDQ change week 52 for bio-naïve	Vedolizumab 300mg	n/a	n/a	n/a	25.9*	14.6-37.3*	*Mean change in total IBDQ score compared to placebo in bio-naïve patients and no relative difference in effect reported
	Placebo IV	n/a					
*IBDQ change week 52 for bio-naïve and bio-experienced**	Vedolizumab 300mg	n/a	48.4 (CI; 41.7-55.1)	n/a	21.1**	11.8-30.4**	**Pooled population of bio-naïve and bio-experienced patients.* **Mean change in total IBDQ score compared to placebo and no relative difference in effect reported.
	Placebo IV	n/a	27.3 (CI; 20.8-33.8)				

Table A3e Results of the GEMINI I study for the bio-experienced patient population.

Trial name:	*GEMINI I*						
NCT number:	*NCT00783718*						
	Data extracted from GEMINI I				Estimated relative difference in effect (risk ratio)		Description of methods used for estimation
Outcome	Study arm	N	Result	Significant difference (p-value)	Difference	95% CI	
Clinical remission at week 6	Vedolizumab 300mg	8/82	9.8%	n/a	3.07	0.68-13.97	*Data extracted as stated in the included studies for vedolizumab and relative difference is provided as unadjusted risk ratio*
	Placebo IV	2/63	3.2%				
Corticosteroid-free clinical remission at week 52	Vedolizumab 300mg	6/26	23.1%	n/a	5.31	0.69-40.87	
	Placebo IV	1/23	4.3%				
Serious adverse events at week 52	Vedolizumab 300mg	44/266	16.5%	n/a	1.49	0.70-3.15	
	Placebo IV	7/63	11.1%				
Musocal healing at week 52	Vedolizumab 300mg	18/43	41.9%	n/a	5.30	1.69-16.61	
	Placebo IV	3/38	7.9%				
IBDQ remission week 52	Vedolizumab 300mg	n/a	n/a	n/a	n/a	n/a	
	Placebo IV	n/a	n/a				
IBDQ change week 52 for bio-experienced	Vedolizumab 300mg	n/a	n/a	n/a	*14.1	*-2.5-30.7	*Mean change in total IBDQ score compared to placebo in bio-experienced patients and no relative difference in effect reported
	Placebo IV	n/a	n/a				

7.2 Results per PICO

Table A4 Results referring to clinical question 1 comparing ustekinumab to infliximab.

Results per outcome	.							
		Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	Difference	CI	*P* value	Risk ratio	CI	*P* value	
Clinical remission at week 8	UNIFI ACT 1 and ACT 2	-17.30%	-29.31%-15.01%	n/a	0.52	0.19-1.41	n/a	*Meta-analysis was used to combine the results of the ACT 1 and ACT 2 studies of infliximab using random effects models in OpenMetaAnalyst. Indirect comparison between ustekinumab and infliximab has been performed based on Bucher´s methodology using the results from the meta-analyses (27). Absolute difference in effect were calculated using the estimated risk ratio from the meta-analyses and the formula provided in the Handbook of the Medicines Council's process and methodologies version 2.4. The event rate of infliximab based on meta-analysis for clinical remission week 8 of 36.4% and corticosteroid-free clinical remission week 52 of 22.3% was utilized.*
Corticosteroid-free clinical remission at week 52	UNIFI ACT 1 and ACT 2	-12.1%	-17.7%-0.51%		0.46	0.21-1.02	n/a	
Corticosteroid-free clinical remission at week 52	UNIFI ACT 1	-11.99	-20.09%-7.78%	n/a	0.53	0.22-1.30	n/a	*Secondary analysis with indirect comparison between ustekinumab and infliximab using only ACT 1 has been performed based on Bucher´s methodology. Absolute difference in effect were calculated using the estimated risk ratio and infliximab event rate of 25.7%*
*Serious adverse events at week 52**	UNIFI ACT 1 and ACT 2	n/a	n/a	n/a	n/a	n/a	n/a	*Narrative comparison, see section 5.3, as indirect comparison of safety is not appropriate.*
Mucosal healing at week 52	UNIFI ACT 1 and ACT 2	-7.2%	-24.3%-23.3%	n/a	0.84	0.47-1.51	n/a	*Same method as described for clinical remission at week 8 and corticosteroid-free clinical remission at week 52. Infliximab event rate of 45.9%*

Mucosal healing at week 52	UNIFI ACT 1	-16%	-28.4%-5.3%	n/a	0.65	0.38-1.12	n/a	*Secondary analysis with indirect comparison between ustekinumab and infliximab using only ACT 1 has been performed based on Bucher´s methodology. Absolute difference in effect were calculated using the estimated risk ratio and infliximab event rate of 45.5%*
IBDQ remission	UNIFI ACT 1 and ACT 2	n/a	n/a	n/a	n/a	n/a	n/a	
IBDQ mean change at week 8	UNIFI ACT 1 and ACT 2	-5	-10.52-0.52	n/a	n/a	n/a	n/a	*Difference between means was calculated using following formula (25): 1) Mean difference = Mean1 − Mean2, 2) Standard error of the mean difference (SE) = $\sqrt{(SD_1^2/N_1 + SD_2^2/N_2)}$, 3) 95% CI = mean difference ± 1.96 × SE*

Table A4.1 Results referring to clinical question 1 comparing ustekinumab to vedolizumab.

Results per outcome	Studies included in the analysis	Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
		Difference	CI	*P* value	Risk ratio	CI	*P* value	
Clinical remission at week 8	UNIFI GEMINI 1	10.2%	-18.70%-14.99%	n/a	0.56	0.19-1.64	n/a	*Indirect comparison between ustekinumab and vedolizumab has been performed based on Bucher´s methodology (27). Absolute difference in effect were calculated using the estimated risk ratio and the formula provided in the Handbook of the Medicines Council's process and methodologies version 2.4. The event rate of vedolizumab for clinical remission week 8 of 23.1% and corticosteroid-free clinical remission week 52 of 35.9% was utilized.*
Corticosteroid-free clinical remission at week 52	UNIFI GEMINI 1	-7.1%	-23.5%-30.8%	n/a	0.8	0.35-1.86	n/a	
Serious adverse events at week 52	UNIFI GEMINI 1	n/a	n/a	n/a	n/a	n/a	n/a	*Narrative comparison, see section 5.3, as indirect comparison of safety is not appropriate.*
Mucosal healing at week 52	UNIFI GEMINI 1	-19.2%	-36.3%-10.4%	n/a	0.68	0.39-1.17	n/a	*Same method as described for clinical remission at week 8 and corticosteroid-free clinical remission at week 52. Vedolizumab event rate of 59.7%*
IBDQ remission	UNIFI GEMINI 1	n/a	n/a	n/a	n/a	n/a	n/a	
IBDQ mean change at week 52	UNIFI GEMINI 1	n/a	n/a	n/a	n/a	n/a	n/a	*Narrative evaluation in bio-naïve + bio-experienced population as the endpoint is reported for week 52 in GEMINI 1 vs. week 8 for UNIFI*

Table A4.2 Results referring to clinical question 2 comparing ustekinumab to vedolizumab.

Results per outcome	.							
		Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	Difference	CI	*P* value	Risk ratio	CI	*P* value	
Clinical remission at week 8	UNIFI GEMINI 1	22.7%	-5.8-251.6%	n/a	3.31	0.41-26.67	n/a	*Indirect comparison between ustekinumab and vedolizumab has been performed based on Bucher´s methodology (27). Absolute difference in effect were calculated using the estimated risk ratio and the formula provided in the Handbook of the Medicines Council's process and methodologies version 2.4. The event rate of vedolizumab for clinical remission week 8 of 9.8% and corticosteroid-free clinical remission week 52 of 23.1% was utilized.*
Corticosteroid-free clinical remission at week 52	UNIFI GEMINI 1	-16.8%	-22.4%-30.1%	n/a	0.27	0.03-2.30	n/a	
Serious adverse events at week 52	UNIFI GEMINI 1	n/a	n/a	n/a	n/a	n/a	n/a	*Narrative comparison, see section 5.3, as indirect comparison of safety is not appropriate.*
Mucosal healing at week 52	UNIFI GEMINI 1	-33%	-39.4%-(-10.1%)		0.21	0.06-0.76	n/a	*Same method as described for clinical remission at week 8 and corticosteroid-free clinical remission at week 52. Vedolizumab event rate of 41.9%*
IBDQ remission	UNIFI GEMINI 1	n/a	n/a	n/a	n/a	n/a	n/a	
IBDQ mean change at week 8	UNIFI GEMINI 1	n/a	n/a	n/a	n/a	n/a	n/a	*Narrative evaluation in bio-naïve + bio-experienced population as the endpoint is reported for week 52 in GEMINI 1 vs. week 8 for UNIFI*

7.3 Safety comparison

In this appendix, a comparison of safety profiles for the relevant comparator treatments (based on SmPC information) is provided, as requested in the medicine councils protocol for the evaluation of ustekinumab. The information retrieved was related to: warnings and precautions specifically focused on infections, infections and adverse events. If a dash ("-") was included in the table, no relevant information was retrieved from the SmPC. The comparison is for the entire patient population consisting of bio-naïve and bio-experienced patients.

Table A4.3 Adverse events.

	Ustekinumab (1) Published: 2009 Last update: 2019	**Vedolizumab (31)** Published: 2014 Last update: 2019	**Infliximab (Remicade) (32)** Published: 2009 Last update: 2019
Infections and infestations	Common • Upper respiratory tract infection, nasopharyngitis, sinusitis Uncommon • Cellulitis, dental infections, herpes zoster, lower respiratory tract infection, viral upper respiratory tract infection, vulvovaginal mycotic infection	Very common • Nasopharyngitis Common • Bronchitis, gastroenteritis, upper respiratory tract infection, influenza, sinusitis, pharyngitis Uncommon • Respiratory tract infection, vulvovaginal candidiasis, oral candidiasis, herpes zoster Very rare • Pneumonia	Very common • Viral infections (e.g. influenza, herpes virus infection) Common • Bacterial infections (e.g. sepsis, cellulitis, abscess) Uncommon • Tuberculosis, Fungal infections (e.g. candidiasis, onychomycosis) Rare • Meningitis, opportunistic infections (such as invasive fungal infections [pneumocystosis, histoplasmosis, aspergillosis, coccidiodomycosis, cryptoccosis, blastomycosis], Bacterial infections [atypical mycobacterial, listeriosis, salmonellosis], Viral infections [cytomegalovirus], Parasitic infections, Hepatitis B reactivation Not known

			• Vaccine breakthrough infection (after in utero exposure to infliximab)
Neoplasms, benign, malignant and unspecified (including cysts and polyps)	-	-	Rare • Lymphoma, Non-Hodgkin's lymphoma, Hodgkin's disease, Leukaemia, Melanoma, Cervical cancer Not known • Heptaosplenic T-cell lymphoma (primarily in adolescents and young adult males with Crohn's disease or ulcerative colitis), Merkel cell carcinoma
Blood and lymphatic system disorders	-	-	Common • Neutropenia, Leucopenia, Anaemia, Lymphadenopathy Uncommon • Thrombocytopenia, Lymphopenia, Lymphocytosis Rare • Agranulocytosis (including infants exposed in utero to infliximab), Thrombotic thrombocytopenic purpura, Pancytopenia, Haemolytic anaemia, Idiopathic thrombocytopenic purpura
Immune system disorders	Uncommon • Hypersensitivity reactions (including rash, urticaria) Rare	Very Rare • Anaphylactic reaction, Anaphylactic shock	Common • Allergic respiratory system Uncommon • Anaphylactic reaction, Lupus-like syndrome, Serum sickness or serum sickness-like reaction

	• Serious hypersensitivity reactions (including anaphylaxis, angioedema)		Rare • Anaphylactic shock, Vasculitis, Sarcoid-like reaction
Endocrine disorders	-	-	-
Metabolism and nutrition disorders	-	-	-
Psychiatric disorders	Uncommon • Depression	-	Common • Depression, Insomnia Uncommon • Amnesia, Agitation, Confusion, Somnolence, Nervousness Rare • Apathy
Nervous system disorders	Common • Dizziness, headache Uncommon • Facial palsy	Very common • Headache Common • Paraesthesia	Very common • Headache Common • Vertigo, Dizziness, Hypoaesthesia, Paraesthesia Uncommon • Seizure, Neuropathy Rare • Transverse myelitis, Central nervous system demyelinating disorders (multiple sclerosis-like disease and optic neuritis), Peripheral demyelinating disorders (such as Guillain-Barre syndrome, chronic inflammatory demyelinating polyneuropathy and multifocal motor neuropathy)

Eye disorders	-	Very rare • Blurred vision	Common • Conjunctivitis Uncommon • Keratitis, Periorbital oedema, Hordeolum Rare • Endophthalmitis Not known • Transient visual loss occurring during or within 2 hours of infusion
Ear and labyrinth disorders	-	-	-
Cardiac disorders	-	-	Common • Tachycardia, Palpitation Uncommon • Cardiac failure (new onset or worsening), Arrhythmia, Syncope, Bradycardia Rare • Cyanosis, Pericardial effusion Not known • Myocardial ischaemia/ myocardial infarction

Vascular disorders	-	Common • Hypertension	Common • Hypotension, Hypertension, Ecchymosis, Hot flush, Flushing Uncommon • Peripheral ischaemia, Thrombophlebitis, Haemotoma Rare • Circulatory failure, Petechia, Vasospasm
Respiratory, thoracic and mediastinal disorders	Common • Oropharyngeal pain Uncommon • Nasal congestion Rare • Allergic alveolitis, eosinophilic pneumonia	Common • Oropharyngeal pain, nasal congestion, cough	Very common • Upper respiratory tract infection, Sinusitis Common • Lower respiratory tract infection (e.g. bronchitis, pneumonia), Dyspnoea, Epistaxis Uncommon • Pulmonary oedema, Bronchospasm,Pleurisy, Pleural effusion Rare • Interstitial lung disease (including rapidly progressive disease, lung fibrosis and pneumonitis)
Gastrointestinal disorders	Common • Diarrhea, nausea, vomiting	Common • Anal abscess, anal fissure, nausea, dyspepsia, constipation, abdominal distension, flatulence, haemorrhoids	Very common • Abdominal pain, Nausea Common • Gastrointestinal haemorrhage, Diarrhea, Dyspepsia, Gastroesophageal reflux, Constipation Uncommon

			• Intestinal perforation, Intestinal stenosis, Diverticulitis, Pancreatitis, Cheilitis
Hepatobiliary disorders	-	-	Common • Hepatic function abnormal, Transaminases
Skin and subcutaneous tissue disorders	Common • Pruritus Uncommon • Pustular psoriasis, skin exfoliation, acne Rare • Exfoliative dermatitis	Common • Rash, pruritus, eczema, erythema, night sweats, acne	-
Musculoskeletal and connective tissue disorders	Common • Back pain, myalgia, arthralgia	Very common • Arthralgia Common • Muscle spasms, back pain, muscular weakness, fatigue, pain in the extremity	-
Renal and urinary disorders	-	-	-
Reproductive system and breast disorders	-	-	-
General disorders and administration site conditions	Common • Fatigue, injection site erythema, injection site pain Uncommon • Injection site reactions (including haemorrhage,	Common • Pyrexia Uncommon • Infusion site reaction (including: infusion site pain and Infusion site irritation), Infusion related reaction, Chills, Feeling cold)	-

	haematoma, induration, swelling and pruritus), asthenia		
Investigations	-	-	-
Injury, poisoning and procedural complications	-	-	-

Table A4.4 Infections.

	Ustekinumab (1) Published: 2009 Last update: 2019	**Vedolizumab (31)** Published: 2014 Last update: 2019	**Infliximab (Remicade) (32)** Published: 2009 Last update: 2019
Percentage of infections per patient year in pbo controlled studies	1.38 per patient year versus 1.35 with placebo	0.85 per patient year versus 0.70 with placebo	36% of infliximab-treated patients were treated for infections compared with 25% of placebo-treated patients (clinical study specific)
Incidence of serious infections per patient year	0.03 (829 patient years follow-up) versus 0.03 with placebo (385 patient-years of follow-up)	0.07% of patients versus 0.06 for placebo.	-
Additional clinical experience (controlled, uncontrolled and open label)	0.91% infections per patient year and 0.02 % serious infections per patient year (10953 years of follow-up) Serious infections were anal abcess, cellulitis, pneumonia, diverticulitis, gastro-enteritis and viral infections.	Serious infections have been reported which include TB, sepsis (some fatal), salmonella sepsis, listeria meningitis and CMV colitis.	-
TB specific information	In clinical studies, patients with latent TB and concomitant isoniazide treatment did not develop TB.	-	-
Post-marketing spontaneous reporting	-	-	Infections are the most common serious adverse reaction; some with fatal outcomes. Nearly 50% of reported deaths have been associated with infection. Cases of tuberculosis, sometimes fatal, including miliary tuberculosis and tuberculosis with extra-pulmonary location have been reported

Table A4.5 Warnings and precautions with regard to infections.

	Ustekinumab (1) Published: 2009 Last update: 2019	**Vedolizumab (31)** Published: 2014 Last update: 2019	**Infliximab (Remicade) (32)** Published: 2009 Last update: 2019
Not to be initiated	No specific text, but contra-indicated in patients with clinically important active infection (e.g. active TB)	Not to be initiated in patients with active, severe infections.	Not to be initiated in patients with serious infection or sepsis, chronic infection or a history of recurrent infections
Serious infections and risk factors	Serious bacterial, fungal and viral infections reported	Potential increased risk for opportunistic infections or infections for which the gut is a defensive barrier.	Increased risk for infection, and serious infections; tuberculosis, bacterial infections, including sepsis and pneumonia, invasive fungal, viral and other opportunistic infections have been observed; fatal infections observed.
Risk benefit to be considered	-	-	Risk benefit to be considered for patients who have resided in o travelled to regions where invasive fungal infections such as histoplasmosis, coccidioidomycosis, or blastomycosis are endemic r
Cautious use	Cautious use in patients with chronic infection or history of recurring infections	Caution in patients with controlled chronic severe infections or a history of recurring severe infections.	-
TB screening & pretreatment of latent TB before use or a history of latent or active TBC	TB screening; treatment of latent TB before use; monitoring of TB patients	TB screening; treatment of latent TB before use	TB screening; treatment of latent TB before use; monitoring of TB patients
Use in patients with active TB	Contra-indicated	Contra-indicated	Contra-indicated
Other TB related text	-	-	-

Monitoring of patients related to infections	Instructions to patients to recognize symptoms of infections	Closely monitored for infections before, during and after treatment.	Monitor closely; warning for invasive fungal infections
Continuation in patients developing a serious infection	Not to be administered until infection resolves	Consider withholding treatment in patients who develop a severe infection	Discontinue
Other cautions (population-specific)	-	-	Incidence of serious infections in Remicade-treated patients 65 years and older was greater than in those under 65 years of age; some with fatal outcome. Infections also reported in a higher proportion of paediatric patients compared to adult patients
Other cautions (viral reactivation & herpes)	-	-	-
Other cautions (viral hepatitis)	-	-	Reactivation of hepatitis B has occurred, with fatal cases. Screening for hepatitis B.
Other cautions	-	Some integrin antagonists and some systemic immunosuppressive agents have been associated with PML. PML monitoring, although vedolizumab exerts an immunosuppressive effect specific to the gut.	• May mask symptoms of infection such as fever • Patients with fistulising Crohn's disease with acute suppurative fistulas must not initiate treatment

7.4 Forest plots

7.4.1 Clinical remission at week 8 - infliximab (ACT 1 and ACT 2)

Summary:

Binary Random-Effects Model
Metric: Relative Risk

Model Results

Estimate	Lower bound	Upper bound	p-Value
3.732	1.676	8.311	0.001

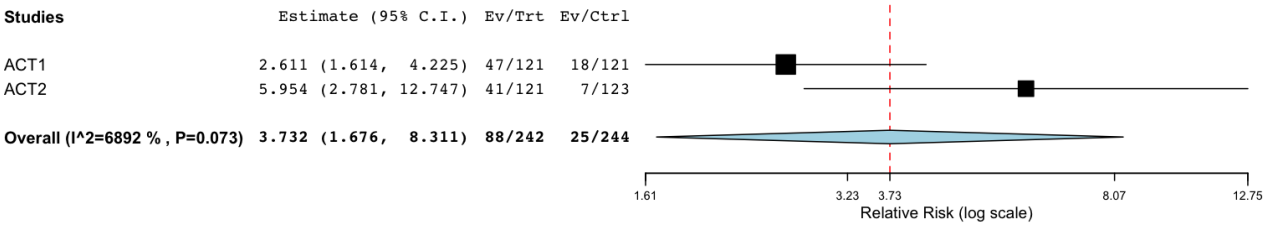
Heterogeneity

tau^2	Q(df=1)	Het.p-Value	I^2
0.234	3.218	0.073	68.922

Results (log scale)

Estimate	Lower bound	Upper bound	Std. error
1.317	0.516	2.118	0.408

Forest plot:



7.4.2 Corticosteroid free clinical remission at week 30-54 - infliximab (ACT 1 and ACT 2)

Summary:
Binary Random-Effects Model
Metric: Relative Risk

Model Results

Estimate	Lower bound	Upper bound	p-Value
3.373	1.659	6.859	< 0.001

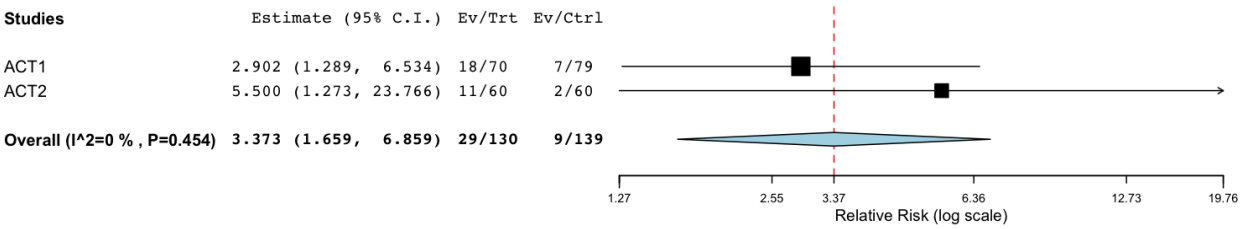
Heterogeneity

tau^2	Q(df=1)	Het.p-Value	I^2
0.000	0.561	0.454	0

Results (log scale)

Estimate	Lower bound	Upper bound	Std. error
1.216	0.506	1.926	0.362

Forest plot:



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

Summary:
Binary Random-Effects Model
Metric: Relative Risk

Model Results

Estimate	Lower bound	Upper bound	p-Value
1.924	1.197	3.091	0.007

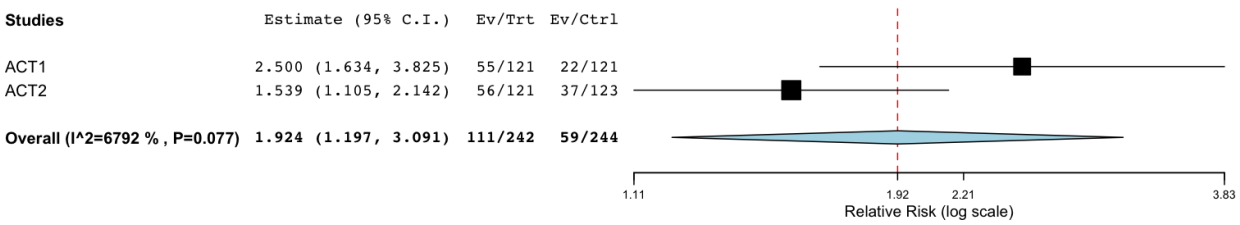
Heterogeneity

tau^2	Q(df=1)	Het.p-Value	I^2
0.080	3.118	0.077	67.923

Results (log scale)

Estimate	Lower bound	Upper bound	Std. error
0.654	0.180	1.129	0.242

Forest plot:



Medicinrådet

Medicinrådets protokol for vurdering af ustekinumab til behandling af moderat til svær colitis ulcerosa

Versionsnr.: 1.0

Medicinrådet

Om Medicinrådet

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

Medicinrådet vurderer, om nye lægemidler og indikationsudvidelser 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 protokollen

Protokollen er grundlaget for Medicinrådets vurdering af et nyt lægemiddel. Den indeholder et eller flere kliniske spørgsmål, som den ansøgende virksomhed skal besvare i den endelige ansøgning, og som Medicinrådet skal basere sin vurdering på.

Lægemidlet vurderes efter Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser – version 2. Se Medicinrådets metodehåndbog for yderligere information.

Dokumentoplysninger	
Godkendelsesdato	5. november 2019
Ikrafttrædelsesdato	5. november 2019
Dokumentnummer	60966
Versionsnummer	1.0

Fremkommer der nye og væsentlige oplysninger i sagen af betydning for protokollens indhold, kan Medicinrådet tage protokollen op til fornyet behandling. Det samme gælder, hvis der er begået væsentlige fejl i forbindelse med sagsbehandlingen vedrørende protokollen. Hvis Medicinrådet foretager ændringer i protokollen, vil ansøgende virksomhed få besked.

Medicinrådet, Dampfærgevej 27-29, 3. th., 2100 København Ø
www.medicinraadet.dk
Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 5. november 2019

Indhold

1 Lægemiddelinformationer

Lægemidlets oplysninger	
Handelsnavn	Stelara
Generisk navn	Ustekinumab
Firma	Janssen-Cilag
ATC-kode	L04AC05
Virkningsmekanisme	Ustekinumab er et humant monoklonalt antistof, som binder sig til cytokinerne IL-12 og IL-23. Ustekinumab forhindrer derved, at IL-12 og IL-23 bidrager til immunaktivering.
Administration/dosis	Induktion: Enkelt i.v. dosis baseret på kropsvægt ~ 6 mg/kg infusion uge 0: 260 mg [≤ 55 kg]; 390 mg [55 kg - 85 kg]; 520 mg [> 85 kg]. Vedligeholdelsesbehandling: Subkutan injektion á 90 mg i uge 8, herefter hver 12. uge.
Forventet EMA-indikation	Behandling af moderat til alvorlig aktiv colitis ulcerosa hos voksne, der har haft et utilstrækkeligt respons, ophørt respons eller har været intolerante over for enten konventionel behandling eller et biologisk lægemiddel eller har en medicinsk kontraindikation til disse behandlinger.

2 Forkortelser

ARR:	Absolut risikoreduktion
BMSL:	Biologiske og målrettede syntetiske lægemidler
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*)
IL:	Interleukin
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

3 Formål

Protokollen har til formål at definere de kliniske spørgsmål, der ønskes belyst i vurderingen af ustekinumab som mulig standardbehandling af patienter med colitis ulcerosa. I protokollen angives en definition af population(er), komparator(er) 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 ustekinumab modtaget den 17. juli 2019.

Protokollen danner grundlag for den endelige ansøgning for vurdering af ustekinumab sammenlignet med dansk standardbehandling[1]. Alle effektmål, der er opgivet i denne protokol, skal besvares med en sammenlignende analyse mellem ustekinumab og hhv. infliximab og vedolizumab. Begge analyser skal indeholde både absolutte og relative værdier for de udspecificerede populationer i de angivne måleenheder (se tabel 1). Litteratursøgning og databehandling udføres som beskrevet i protokollen.

4 Baggrund

Colitis ulcerosa er en kronisk, inflammatorisk tarmsygdom, karakteriseret ved konfluerende inflammation i ende- og tyktarmens slimhinde [1]. Inflammationen fører til sårdannelse i slimhinden og involverer altid endetarmen og oftest den nedre del af tyktarmen men kan involvere hele tyktarmen. De mest almindelige symptomer ved colitis ulcerosa er blodig og pusholdig diarré, mavesmerter (ofte i relation til afføring) og almen sygdomsfornemmelse [2,3]. Colitis ulcerosa kan også medføre symptomer i organer udenfor tarmen, i særdeleshed fra led, lever, øjne og hud (såkaldte ekstraintestinale manifestationer), og kan ledsages af komplikationer som knogleskørhed, nyresten og anæmi [4].

Colitis ulcerosa er en livsvarig sygdom med skiftende perioder af sygdomsaktivitet og remission (hvor sygdommen er i ro) [3]. Sygdommen betegnes som værende i remission ved ophør af symptomer og heling af slimhinden, påvist ved endoskopi [2].

Colitis ulcerosa debuterer hyppigst omkring 20-35-årsalderen men kan debutere i tidlig barnealder og hos ældre. Antallet af patienter med colitis ulcerosa i Danmark blev i 2013 anslået til 35.200, og incidensen var ca. 18,6 pr. 100.000 [1]. Incidensen i Danmark er let stigende og blandt de højeste i verden [1,5]. Hos børn under 15 år var incidensen i 2013 ca. 4,2 pr. 100.000 [1].

En eventuel aktivitet i sygdommen kan klassificeres som mild, moderat eller svær. I beskrivelsen af sygdommen er udbredelsen også af betydning [2,3]. Der anvendes forskellige indices til at beskrive sygdomsaktiviteten i forbindelse med klinisk kontrollerede undersøgelser inkl. Mayo-score (baseret på symptomer og endoskopi) især til voksne og PUCAI (baseret alene på symptomer) til børn/unge [2,3].

4.1 Nuværende behandling

Der findes ikke lægemidler, som helbreder patienterne. Førstevalgs medicinsk behandling ved colitis ulcerosa er 5-aminosalicylsyre, der anvendes både ved aktiv sygdom og som recidivprofylakse. Ved manglende effekt suppleres oftest med kortikosteroider og som vedligeholdelsesterapi med immunsuppressiv behandling (azathioprin eller 6-mercaptopurin). Ved manglende effekt af denne behandling, ved aktiv sygdom eller hvis sygdommen recidiverer trods immunsuppressiv behandling, og hvis kirurgi ikke er at

[1] Ved dansk standardbehandling forstås de(t) generelt anerkendte kliniske alternativ(er) som anvendes i klinisk praksis i Danmark.

foretrække, kan behandling med biologiske og målrettede syntetiske lægemidler (BMSL) iværksættes efter Dansk Selskab for Gastroenterologi og Hepatologis (DSGH) retningslinjer [6].

Målet med behandlingen af colitis ulcerosa er at behandle den akutte sygdom, dvs. inducere klinisk remission og dernæst at fastholde remissionen uden brug af kortikosteroider for dermed at forbedre patientens livskvalitet. Da langvarig behandling med kortikosteroider er forbundet med væsentlige bivirkninger, er det ligeledes et mål at mindske patienternes brug heraf.

Hvis sygdommen er i langvarig remission, kan man forsøge at ophøre behandling med BMSL, følge tilstanden og revurdere behov for at genoptage behandlingen [6]. Hos cirka en tredjedel af patienterne aftager effekten af behandlingen (sekundært tab af respons), og her kan dosis øges, eller intervallerne mellem behandling afkortes. Ved ophør af behandlingseffekt kan patienterne i 25-35 % af tilfældene opnå en effekt ved at skifte behandling til et andet BMSL. Ved manglende respons må behandlingen med et BMSL ophøre, og kirurgi kan anbefales [6].

Rådet for Anvendelse af Dyr Sygehusmedicin (RADS) har i 2016 ligestillet de tre lægemidler golimumab, infliximab og vedolizumab som 1., 2. og 3. linjebehandling af moderat til svær aktiv colitis ulcerosa, mens adalimumab kan overvejes som 3. linjebehandling [7]. Sidenhen har Medicinrådet anbefalet endnu et lægemiddel, tofacitinib, som mulig behandling af bioerfarne patienter, dvs. det kan anvendes, efter at de ovenstående 1. linjepræparater har været prøvet.

Der findes ingen præcise opgørelser over andelen af danske patienter med moderat til svær aktiv colitis ulcerosa, som er i behandling med et BMSL. På baggrund af data fra Region Nordjylland skønnes det på landsplan, at der er ca. 1.600 patienter i behandling, og at ca. 500 patienter pr. år starter ny behandling med et af de lægemidler, som indgår i behandlingsvejledningen. En undersøgelse af børn i perioden fra 1998-2008 viste, at ca. 17-19 % var i behandling med et TNF-hæmmende lægemiddel 5 år efter diagnosen [8].

4.2 Ustekinumab

Ustekinumab er et fuldt humant monoklonalt antistof, der specifikt binder sig til den delte p40-proteinunderenhed af interleukin (IL)-12 og IL-23, som er associerede med immunmedierede sygdomme. Ustekinumab hæmmer derved bioaktiviteten af IL-12 og IL-23 ved at forhindre, at p40 binder sig til receptorproteinet, der er udtrykt på overfladen af immunceller. Herved hæmmes det immunologiske respons, som skal medføre, at den inflammatoriske tilstand mindskes. Ustekinumab gives som induktion de første 8 uger og efterfølgende som vedligeholdelsesbehandling:

- Induktion: ~ 6 mg/kg intravenøs (i.v.) infusion uge 0: 260 mg [≤ 55 kg]; 390 mg [55 kg - 85 kg]; 520 mg [> 85 kg].
- Vedligeholdelsesbehandling: subkutan (s.c.) injektion 90 mg uge 8, herefter hver 12. uge.

5 Kliniske spørgsmål

Patienter, som ikke har modtaget anden behandling end førstevalgs medicinsk behandling, som omfatter behandling med 5-aminosalicylsyre, kortikosteroider, azathioprin eller 6-mercaptopurin, betegnes som BMSL behandlingsnaive patienter. Patienter, som har modtaget behandling med et eller flere biologiske eller målrettede syntetiske lægemidler, betegnes som BMSL behandlingserfarne. Fagudvalget finder det vigtigt at se på både BMSL behandlingsnaive og BMSL behandlingserfarne patienter, da effekten af lægemidler kan være forskellig i de to populationer. Der er derfor opstillet 2 kliniske spørgsmål, som ønskes besvaret.

5.1 Klinisk spørgsmål 1

Hvad er værdien af ustekinumab sammenlignet med hhv. infliximab og vedolizumab til behandling af voksne biologiske og målrettede syntetiske lægemiddel (BMSL) behandlingsnaive patienter med moderat til svær aktiv colitis ulcerosa?

Population
BMSL behandlingsnaive patienter med moderat til svær aktiv colitis ulcerosa, der opfylder kriterierne for behandling med biologiske og målrettede syntetiske lægemidler (jf. afsnit 4.1).

Intervention
Ustekinumab intravenøs (i.v.) infusion 6 mg/kg uge 0: 260 mg hvis patienten vejer ≤ 55 kg, 390 mg hvis patienten vejer 55-85 kg, og 520 mg hvis patienten vejer > 85 kg. Subkutan (s.c.) injektion 90 mg uge 8, herefter hver 12. uge.

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

- 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
Angivet i tabel 1. Begrundelsen for valg af effektmål er uddybet i afsnit 5.3.

5.2 Klinisk spørgsmål 2

Hvad er værdien af ustekinumab sammenlignet med hhv. infliximab og vedolizumab til behandling af voksne biologiske og målrettede syntetiske lægemiddel (BMSL) behandlingserfarne patienter med moderat til svær aktiv colitis ulcerosa?

Population
BMSL behandlingserfarne patienter med moderat til svær aktiv colitis ulcerosa, der opfylder kriterierne for behandling med biologiske og målrettede syntetiske lægemidler (jf. afsnit 4.1).

Intervention
Ustekinumab intravenøs (i.v.) infusion 6 mg/kg uge 0: 260 mg hvis patienten vejer ≤ 55 kg, 390 mg hvis patienten vejer 55-85 kg, og 520 mg hvis patienten vejer > 85 kg. Subkutan (s.c.) injektion 90 mg uge 8, herefter hver 12. uge.

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

- 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
Angivet i tabel 1. Begrundelsen for valg af effektmål er uddybet i afsnit 5.3.

5.3 Valg af effektmål

Tabel 1 summerer de valgte effektmål, deres vigtighed, den retningsgivende mindste klinisk relevante forskel, en justeret mindste klinisk relevant forskel og effektmålsgruppe. I forbindelse med justeringen af Medicinrådets metodehåndbog, som trådte i kraft pr. 1. januar 2019, vil absolutte effektforskelle fremover blive kategoriseret ud fra konfidensintervaller (tabel 3, side 29 i metodehåndbogen). Det er derfor nødvendigt at foretage en justering af den mindste klinisk relevante forskel. Den *retningsgivende* mindste klinisk relevante forskel er den MKRF, som fagudvalget har defineret og finder, er den relevante grænse for, hvor stor forskellen mellem intervention og komparator skal være, for at behandlingen klinisk set anses at have merværdi. Når lægemidlets værdi for det enkelte effektmål skal kategoriseres, vil grænsen for konfidensintervallet blive sammenholdt med den *justerede* mindste klinisk relevante forskel. Den justerede værdi vil være det halve af den retningsgivende værdi i de tilfælde, hvor et konfidensinterval forventes at være tilgængeligt. Rationalet for denne tilgang er at sikre, at alle værdier i konfidensintervallet ligger tættere på den *retningsgivende MKRF* end på 'ingen forskel' (absolut effektforskel på 0). Eller sagt på en anden måde – alle de sandsynlige værdier for effekten er tættere på en klinisk relevant effekt end på 'ingen effekt'.

For alle effektmål ønskes både absolutte og relative værdier, jf. ansøgningsskemaet. Der ønskes både punktestimater og konfidensintervaller (for de absolutte værdier ønskes dog ikke konfidensintervaller, hvor metoderne til beregning af disse ikke er veldefinerede). For de absolutte værdier, hvor der kan beregnes konfidensintervaller efter veldefinerede metoder, vurderes den kliniske relevans (værdi), jf. tabel 3 i Medicinrådets håndbog for vurdering af nye lægemidler. For de relative værdier vurderes den kliniske relevans (værdi), jf. væsentlighedskriterierne beskrevet i Medicinrådets håndbog. De relative effektestimater skal angives i relativ risiko (RR) eller hazard ratio (HR). Hvis studierne resulterer i en odds ratio (OR), skal denne transformeres til relativ risiko, jf. appendiks 2 i Medicinrådets håndbog. 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 og måleenhed. For kritiske og vigtige effektmål er desuden angivet den mindste klinisk relevante forskel (retningsgivende og evt. justeret) samt indplacering i de tre effektmålsgrupper (”dødelighed” ”livskvalitet, alvorlige symptomer og bivirkninger” og ”ikkealvorlige symptomer og bivirkninger”).

Effektmål	Vigtighed	Effektmålsgruppe	Måleenhed	Retningsgivende mindste klinisk relevante forskel	Justeret mindste klinisk relevante forskel
Klinisk remission, efter induktions-behandling, uge 8	Kritisk	Livskvalitet, alvorlige symptomer og bivirkninger	Andel patienter med total Mayo-score ≤ 2, ingen subscore > 1 og rektal blødning score = 0	10 procentpoint	5 procentpoint
Systemisk steroidfri remission, efter vedligeholdelses-behandling, uge 52	Kritisk	Livskvalitet, alvorlige symptomer og bivirkninger	Andel patienter, der ikke er i systemisk steroid-behandling efter 52 uger og har en total Mayo-score ≤ 2, ingen subscore > 1 og rektal blødning-score = 0	10 procentpoint	5 procentpoint
Alvorlige uønskede hændelser*	Kritisk	Livskvalitet, alvorlige symptomer og bivirkninger	Andel patienter, der oplever en alvorlig uønsket hændelse	5 procentpoint	2,5 procentpoint
			Kvalitativ gennemgang af bivirkningsprofil		
Mukosal heling, vedligeholdelses-behandling, uge 52	Vigtig	Livskvalitet, alvorlige symptomer og bivirkninger	Andel patienter med endoskopisk subscore ≤ 1	10 procentpoint	5 procentpoint
Livskvalitet*	Vigtig	Livskvalitet, alvorlige symptomer og bivirkninger	Andel patienter, der opnår score ≥ 170 på Inflammatory Bowel Disease Questionnaire (IBDQ)	10 procentpoint	5 procentpoint
			Forskel i ændring fra baseline på IBDQ	16 point	8 point

* For disse effektmål ønskes data med længst mulig opfølgningstid.

Såfremt der ikke eksisterer data med de angivne 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. Hvis der er forskel på måden, de enkelte effektmål opgøres på tværs af studier, vil fagudvalget vurdere, hvorvidt effektmålene er sammenlignelige.

Kritiske effektmål

Klinisk remission, efter induktionsbehandling (uge 8)

Fagudvalget finder, at klinisk remission efter induktionsbehandlingen, i uge 6-8, er et kritisk effektmål, da tidlig remission er afgørende for patienter med colitis ulcerosa. Ved ufuldstændigt, manglende respons eller

forværring efter induktionsbehandling ophører behandlingen, og den videre behandlingsstrategi afgøres i samråd med patienten [6].

Klinisk remission er defineret ved en total Mayo-score ≤ 2, ingen subscore > 1 og blod i afføringen-score = 0. Mayo-score er det mest anvendte scoringssystem i kliniske studier til at vurdere sygdomsaktivitet hos patienter med colitis ulcerosa [9].

Mayo-score indeholder en samlet vurdering af følgende fire subscores: afføringshyppighed, blod i afføringen, endoskopiske fund og en samlet vurdering af sygdomsaktiviteten (global assessment) 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 højere score indikerer sværere sygdomsaktivitet [9,10].

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 ved colitis ulcerosa er 10 procentpoint ved sammenligning af to lægemidler [11]. Fagudvalget er enige i denne vurdering og finder, at en forskel på 10 procentpoint er klinisk relevant, og har lagt dette til grund i vurderingen.

Systemisk steroidfri remission, vedligeholdelsesbehandling (uge 52)
Langvarig behandling med systemiske kortikosteroider kan være forbundet med væsentlige bivirkninger. Fagudvalget finder derfor, at systemisk steroidfri remission efter 52 uger er et kritisk effektmål.

Systemisk steroidfri remission er defineret ved, at patienterne ikke er i systemisk kortikosteroidbehandling og har en total Mayo-score ≤ 2, ingen subscore > 1 og blødning fra endetarmen-score = 0 i uge 52.

Fagudvalget vurderer, at hvis mere end 10 procent flere opnår systemisk steroidfri remission ved behandling med et af lægemidlerne i forhold til et andet, er der en klinisk relevant forskel mellem lægemidlerne.

Bivirkninger
Bivirkninger belyser de negative konsekvenser, patienten kan opleve ved behandling med lægemidler. Da colitis ulcerosa er en livslang sygdom, da der ikke findes kurative lægemidler, og hvor kun kirurgi kan fjerne sygdommen, anser fagudvalget bivirkninger som et kritisk effektmål. Fagudvalget ønsker at se på bivirkninger ud fra et kvantitativt mål, alvorlige uønskede hændelser og et kvalitativt mål, i form af en narrativ beskrivelse af bivirkningsprofilerne for lægemidlerne.

Alvorlige uønskede hændelser: Fagudvalget finder, at andelen af patienter, som oplever en eller flere alvorlige uønskede hændelser, er særligt relevant for vurderingen, da ustekinumab 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. Ved indirekte sammenligninger af ustekinumab med komparatorerne, bør ansøger lave en vurdering af, om sammenligningen af hændelsesfrekvenser kan foretages på forsvarlig vis på baggrund af studiedesign, opfølgningstid, dataindsamling, og hvordan de alvorlige uønskede hændelser er opgjort og rapporteret. Overvejelser omkring dette skal fremgå i den endelige ansøgning.

Bivirkninger: Fagudvalget ønsker derudover at foretage en kvalitativ gennemgang af bivirkningsprofilerne for de enkelte lægemidler med henblik på at vurdere bivirkningernes alvorlighed, type, hyppighed og håndterbarhed. Fagudvalget ønsker særligt en belysning af, hvor ustekinumab adskiller sig fra hhv. infliximab og vedolizumab. Ansøger bedes derfor bidrage med en opgørelse og narrativ beskrivelse af bivirkningsprofilerne baseret på studierne, produktresuméet og EPAR'en.

Vigtige effektmål

Mukosal heling, vedligeholdelsesbehandling (uge 52)
Mukosal heling er defineret ved en endoskopisk subscore ≤ 1 (subscoren indgår i den samlede Mayo-score). Subscoren afspejler inflammationens sværhedsgrad i slimhinden, og scoren går fra 0-3, hvor en højere score indikerer mere udtalt inflammation i slimhinden [10]. Mukosal heling er et vigtigt klinisk behandlingsmål, da det er indikator for behandlingseffekt og en prognostisk markør for langtidseffekt af behandlingen [12,13].

Fagudvalget finder, at mukosal heling i uge 52 er et vigtigt effektmål, da langtidseffekten af behandlingen er betydningsfuld. Fagudvalget vurderer, at hvis 10 procent flere opnår mukosal heling i uge 52 ved behandling med ét eller flere lægemidler i indbyrdes sammenligning, er det klinisk relevant.

Livskvalitet
Livskvalitet er et vigtigt effektmål, da patienternes livskvalitet påvirkes betragteligt ved moderat til svær aktiv colitis ulcerosa. Til at måle livskvalitet blandt patienter med inflammatoriske tarmsygdomme anvendes Inflammatory Bowel Disease Questionnaire (IBDQ), som er et velvalideret, sygdomsspecifikt livskvalitetsinstrument, der vægter symptomer og problemer, der er særlige for patienter med inflammatoriske tarmsygdomme [14]. 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, som er i remission, typisk har en score på IBDQ-skalaen, som ligger mellem 170-190 [15]. Fagudvalget vurderer, at en forskel på 10 procentpoint i andelen af patienter, som opnår en samlet score på minimum 170, er klinisk relevant.

Det er ligeledes angivet i litteraturen, at en forskel i ændring fra baseline på ≥ 16 point er klinisk relevant og indikerer behandlingsrespons [15,16]. Fagudvalget ønsker derfor data også for gennemsnitlig ændring fra baseline og vurderer, at den mindste klinisk relevante forskel er en ændring på ≥ 16 point.

Da data på livskvalitet kan være opgjort forskelligt i studierne, ønsker fagudvalget at anvende begge mål for livskvalitet i vurderingen.

6 Litteratursøgning

Vurderingen af klinisk værdi baseres som udgangspunkt på data fra peer-reviewede publicerede fuldtekstartikler og data fra EMAs EPAR – public assessment report(s). Data skal derudover stemme overens med protokollens beskrivelser.

Sekretariatet har på baggrund af den foreløbige ansøgning undersøgt, om der findes et eller flere peer-reviewede publicerede fuldtekstartikler, hvor ustekinumab er sammenlignet direkte med hhv. infliximab og vedolizumab.

Sekretariatet har ikke fundet artikler, som kan anvendes til en direkte sammenligning af ustekinumab og hhv. infliximab og vedolizumab.

Virksomheden skal derfor søge efter studier, der kan anvendes til en indirekte sammenligning af ustekinumab med hhv. infliximab og vedolizumab. Det betyder, at der både skal søges efter primærstudier af ustekinumabs effekt og efter primærstudier af effekten af infliximab og vedolizumab. Til det formål har sekretariatet udarbejdet søgestrenge, som skal anvendes i MEDLINE (via PubMed) og CENTRAL (via Cochrane Library). Søgestrengene kan findes i bilag 1. Derudover skal EMAs European public assessment

reports (EPAR) konsulteres for både det aktuelle lægemiddel og dets komparatorer.

Kriterier for udvælgelse af litteratur
Virksomheden skal først ekskludere artikler 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: de inkluderede studier skal være randomiserede kontrollerede forsøg, og opfølgningstiden skal være minimum 8 uger. Derudover skal studierne stemme overens med de kliniske spørgsmål og vedrøre de beskrevne populationer, de valgte komparatorer og indeholde minimum ét relevant effektmål. Andre studiedesigns end randomiserede kontrollerede studier ekskluderes, fase I- og fase IIa-studier ekskluderes.

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

For effektmål (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).

Hvis der er mere end ét 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. Det skal desuden

vurderes, om studierne er homogene nok til en sammenligning. Medicinrådet forbeholder sig retten til at foretage sensitivitets- og subgruppeanalyser på baggrund af studiernes validitet og relevans.

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

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

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

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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

Formand	**Indstillet af**
Jens Kjeldsen Professor, overlæge, ph.d.	Lægevidenskabelige Selskaber
Medlemmer	**Udpeget af**
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Charlotte Nielsen Patient/patientrepræsentant	Danske Patienter
Anders Pærregaard Overlæge, dr.med.	Inviteret af formanden

Medicinrådets sekretariat

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10 Versionslog

Version	Dato	Ændring
1.0	5. november 2019	Godkendt af Medicinrådet.

11 Bilag 1

Søgestrategi PubMed https://www.ncbi.nlm.nih.gov/pubmed/advanced

Søgelinje	Søgetermer	Kommentar
1	"Colitis, Ulcerative"[mh]	Termer for indikation
2	(ulcerative[tiab] OR ulcerosa[tiab]) AND colitis[tiab]	
3	#1 OR #2	
4	Ustekinumab[mh]	Termer for lægemidler
5	ustekinumab[tiab] OR Stelara*[tiab] OR CNTO1275[tiab] OR CNTO-1275[tiab]	
6	Infliximab[mh]	
7	SB2 infliximab[nm]	
8	infliximab[tiab] OR PF-06438179[tiab] OR Remicade*[tiab] OR Inflectra*[tiab] OR Remsima*[tiab] OR CT-P13[tiab] OR Renflexis*[tiab] OR Flixabi*[tiab]	
9	vedolizumab[nm]	
10	vedolizumab[tiab] OR Entyvio*[tiab] OR MLN0002[tiab]	
11	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10	
12	#3 AND #11	Indikation og lægemidler kombineres
13	("Randomized Controlled Trial"[pt] OR "Controlled Clinical Trial"[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR "Clinical Trials as Topic"[mh:noexp] OR randomly[tiab] OR trial[ti]) NOT ("Animals"[mh] NOT "Humans"[mh])	RCT-filter
14	#12 AND #13	
15	Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Guideline[pt] OR Letter[pt] OR News[pt] OR Observational Study[pt] OR Practice Guideline[pt] OR Review[pt] OR Systematic Review[pt]	Eksklusion af irrelevante publikationstyper
16	#14 NOT #15	
17	English[la] OR Danish[la] OR Norwegian[la] OR Swedish[la]	Afgrænsning på sprog
18	**#16 AND #17**	**Endeligt resultat**

Feltkoder:

mh = MeSH Term

nm = Supplementary Concept/Substance

tiab = title/abstract, inkl. forfatterkeywords

pt = publication type

Søgestrategi, CENTRAL via Cochrane Library https://www.cochranelibrary.com/advanced-search/search-manager

Søgelinje	Søgetermer	Kommentar
#1	[mh "Colitis, Ulcerative"]	Termer for indikation
#2	ulcerative colitis:kw	
#3	((ulcerative OR ulcerosa) NEAR/2 colitis):ti,ab	
#4	#1 OR #2 OR #3	
#5	[mh Ustekinumab]	Termer for lægemidler
#6	(ustekinumab OR Stelara* OR CNTO1275 OR "CNTO 1275"):ti,ab,kw	
#7	[mh Infliximab]	
#8	(infliximab OR "PF 06438179" OR Remicade* OR Inflectra* OR Remsima* OR "CT P13" OR Renflexis* OR Flixabi*):ti,ab,kw	
#9	(vedolizumab OR Entyvio* OR MLN0002):ti,ab,kw	
#10	#5 OR #6 OR #7 OR #8 OR #9	
#11	#4 AND #10	
#12	("conference abstract" OR review):pt	Eksklusion af irrelevante publikationstyper og poster fra forsøgsregistre
#13	NCT*:au	
#14	("clinicaltrials gov" OR trialsearch):so	
#15	#12 OR #13 OR #14	
#16	**#11 NOT #15 in Trials**	**Endeligt resultat**

Feltkoder:

ti: title

ab: abstract

so: source

[mh]: specifik syntaks for Medlines indekserede termer (MeSH)

kw: keywords, her kontrollerede/indekserede termer fra databaserne Medline og/eller Embase.

pt = publication type