Medicinrådet

Baggrund for Medicinrådets anbefaling vedrørende tildrakizumab som mulig standardbehandling til moderat til svær plaque psoriasis

Versionsnr.: 1.0

Medicinrådet

Om Medicinrådet

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

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

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

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

Om anbefalingen

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

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

Dokumentoplysninger	
Godkendelsesdato	10. april 2019
Ikrafttrædelsesdato	10. april 2019
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Versionsnummer	1.0

Medicinrådet, Dampfærgevej 27-29, 3. th., 2100 København Ø
www.medicinraadet.dk
Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 10. april 2019

Indhold

1 Lægemiddelinformationer

Lægemidlets oplysninger	
Handelsnavn	Ilumetri
Generisk navn	tildrakizumab
Firma	Almirall
ATC-kode	L04AC17
Virkningsmekanisme	Humaniseret monoklonalt antistof rettet mod interleukin (IL)-23.
Administration/dosis	Subkutan injektion 100 mg i uge 0, 4 og hver 12. uge herefter.
EMA-indikation	Behandling af moderat til svær plaque psoriasis hos voksne (≥ 18 år), som er kandidater til systemisk behandling.

2 Medicinrådets anbefaling

Medicinrådet **anbefaler** tildrakizumab som mulig standardbehandling til behandling af moderat til svær plaque psoriasis hos voksne, som er kandidater til 2. generations immunmodulerende behandling.

Medicinrådet finder, at der er et rimeligt forhold mellem lægemidlets kliniske merværdi og omkostningerne ved behandling med tildrakizumab sammenlignet med dansk standardbehandling.

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

Hvad er den kliniske merværdi af tildrakizumab til voksne patienter med moderat til svær plaque psoriasis, som er kandidater til 2. generations immunmodulerende behandling og ikke har psoriasisartropati?

3 Formål

Formålet med Baggrund for Medicinrådets anbefaling vedrørende tildrakizumab som mulig standardbehandling til moderat til svær plaque psoriasis er at skabe gennemsigtighed om det materiale, der ligger til grund for Medicinrådets anbefaling.

4 Baggrund

I Danmark, som i øvrige dele af verden, får ca. 2-3 % af befolkningen psoriasis i løbet af livet. Psoriasis er en autoimmun, kronisk, inflammatorisk sygdom, hvor plaque psoriasis, også kaldet psoriasis vulgaris, er den mest almindelige (ca. 80 %).

Ved udgangen af 2017 var der registreret 2710 patienter, der havde modtaget behandling med 2. generations immunmodulerende lægemidler. Det forventede antal patienter på landsplan er pr. år ca. 100 nye patienter, som er kandidater til 2. generations immunmodulerende behandling. Det drejer sig om psoriasispatienter, der opfylder kriterierne for biologisk behandling, og som ikke har ledgener. Derudover forventes det, at ca. 100 patienter pr. år fejler på et 2. generations immunmodulerende lægemiddel og skal skifte til et andet lægemiddel.

4.1 Sagsbehandlingstid og proces for Medicinrådets vurdering

Medicinrådet modtog den foreløbige ansøgning den 18. september 2018, og protokollen blev sendt til ansøger den 26. oktober 2018.

Den endelige ansøgning blev modtaget den 19. december 2018. Medicinrådet har derfor gennemført vurderingen af tildrakizumab på 16 uger. Den forlængede sagsbehandlingstid skyldes ændringer i sammensætningen af fagudvalget.

5 Medicinrådets vurdering af samlet klinisk merværdi

Medicinrådet vurderer, at tildrakizumab til voksne (≥18 år) patienter med moderat til svær plaque psoriasis, som er kandidater til 2. generations immunmodulerende behandling og ikke har psoriasisartropati, giver:

- **Ingen klinisk merværdi** til patienter med moderat til svær plaque psoriasis sammenlignet med guselkumab. Evidensens kvalitet vurderes at være lav.
- **Den kliniske merværdi kan ikke vurderes** for subpopulationen af patienter med tidligere behandlingssvigt på biologiske lægemidler generelt.
- **Den kliniske merværdi kan ikke vurderes** for subpopulationen af patienter med tidligere behandlingssvigt på biologiske lægemidler med samme target.

6 Høring

Ansøger har indsendt høringssvar den 18. marts 2019. Ansøger havde ikke bemærkninger til kategoriseringen af klinisk merværdi (bilag 3).

7 Resumé af økonomisk beslutningsgrundlag

Amgros har sammenlignet omkostningerne ved tildrakizumab med alle de behandlinger, der har været betragtet som ligestillede 1. linjebehandlinger (adalimumab, certolizumab pegol, secukinumab, ustekinumab, guselkumab, ixekizumab og brodalumab). Omkostningerne er større ved behandling med tildrakizumab end med det billigste alternativ (adalimumab). På denne baggrund vurderer Amgros, at der ikke er et rimeligt forhold mellem omkostninger og klinisk merværdi.

Amgros har vurderet, at ansøgers budgetkonsekvensanalyse er rimelig, og denne estimerer budgetkonsekvenserne til at være ca. -200.000 kr. årligt (AIP-priser). Budgetkonsekvensanalysen antager, at tildrakizumab erstatter lægemidler med samme virkningsmekanisme i behandlingsalgoritmen.

Amgros vurderer dog, at det vil være hensigtsmæssigt, at tildrakizumab anbefales som mulig standardbehandling og indplaceres i lægemiddelrekommandationen, så lægemidlet i fremtiden kan konkurrenceudsættes på lige fod med de øvrige 1. linjebehandlinger.

Amgros' beslutningsgrundlag er baseret på den sundhedsøkonomiske analyse indsendt af ansøger, den indgåede aftale med Almirall om pris for tildrakizumab, samt gældende aftalepris på komparatorer, herunder priser på biosimilære alternativer (se bilag 1 og 2).

8 Overvejelser omkring alvorlighed/forsigtighed

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

9 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende psoriasis og psoriasis med ledgener

Forvaltningslovens § 4, stk. 2, har været anvendt i forbindelse med udpegning af medlemmer til dette fagudvalg.

Formand	**Indstillet af**
Diljit Kaur Knudsen Speciallæge	Lægevidenskabelige Selskaber
Medlemmer	**Udpeget af**
Trine Høgsberg Afdelingslæge	Region Midtjylland
Dermatologi ikke repræsenteret	Region Nordjylland
Sumangali Chandra Prasad Speciallæge	Region Syddanmark
Kan ikke udpege en kandidat, der opfylder Medicinrådets habilitetskrav	Region Sjælland
Lone Skov Klinisk professor, overlæge, dr.med.	Region Hovedstaden
Thomas Loof Hedegård Farmaceut	Dansk Selskab for Sygehusapoteksledelse
Maija Bruun Haastrup Klinisk farmakolog	Dansk Selskab for Klinisk Farmakologi
Eli Glückstadt Patient/patientrepræsentant	Danske Patienter
Andreas H.M. Jensen Patient/patientrepræsentant	Danske Patienter

Tidligere medlemmer, som har taget del i processen: Lars Erik Bryld, overlæge, ph.d. og Lars Iversen, professor.

Medicinrådets sekretariat

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

Version	Dato	Ændring
1.0	10.04.2019	Godkendt af Medicinrådet.

11 Bilag

Bilagsliste:

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

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Beslutningsgrundlag til Medicinrådet

Dette dokument er Amgros' vurdering af tildrakizumab (Ilumetri) indiceret til behandling af moderat til svær plaque psoriasis hos voksne (≥ 18 år), som er kandidater til 2. generations immunmodulerende behandling og ikke har psoriasisartropati (PsA). Vurderingen er baseret på lægemidlets gennemsnitlige inkrementelle omkostninger, baseret på SAIP (sygehusapotekets indkøbspris) sammenholdt med Medicinrådets vurdering af den kliniske merværdi.

Dato for Medicinrådsbeslutning	10-04-2019
Firma	Almirall (ansøger)
Lægemiddel	Tildrakizumab (Ilumetri)
Indikation	Behandling af moderat til svær plaque psoriasis hos voksne (≥ 18 år), som er kandidater til 2. generations immunmodulerende behandling og ikke har psoriasisartropati.

Amgros' vurdering

- Amgros vurderer, at der **ikke** er et rimeligt forholdet mellem meromkostningerne og den kliniske merværdi for tildrakizumab (Ilumetri) som mulig standardbehandling til voksne (≥ 18 år) med moderat til svære plaque psoriasis, som er kandidater til 2. generations immun-modulerende behandling og ikke har psoriasisatropati. Herunder subpopulationen der omfatter patienter, som har haft behandlingssvigt på biologiske lægemidler generelt samt specifikt på lægemidler IL-23 og IL-12/23 target.

Overordnet konklusion

Medicinrådet har vurderet, at tildrakizumab (Ilumetri) sammenlignet med de mulige komparatorer giver **ingen klinisk merværdi.**

Behandling med tildrakizumab (Ilumetri) er forbundet med meromkostninger sammenlignet med den billigste 1. linjebehandling til nævnte indikation. Amgros vurderer, at der **ikke** er rimeligt forhold mellem den kliniske merværdi for tildrakizumab (Ilumetri), sammenlignet med behandling med den billigste komparator i 1. linjebehandling. Meromkostninger drives af prisen på tildrakizumab (Ilumetri) og komparator. Behandling med tildrakizumab (Ilumetri) er forbundet med besparelser hvis der sammenlignes med flere andre komparatorer end den billigste til nævnte indikation.

Andre overvejelser

Amgros har indgået en aftale med Almirall om indkøb af tildrakizumab (Ilumetri) til en aftalepris, som er lavere end AIP. Amgros vurdering af tildrakizumab (Ilumetri) resulterer i både meromkostninger og besparelser afhængig af valgte komparator. Amgros vurderer forholdet til den kliniske merværdi sammenlignet med billigste mulige komparator (adalimumab) i behandlingslinjen.

Tildrakizumab (Ilumetri) kan ifølge SPC'et gives i dosis 200 mg til patienter der vejer ≥ 90 kg. Anvendes tildrakizumab (Ilumetri) i en dosis på 200 mg, er tildrakizumab (Ilumetri) forbundet med meromkostninger sammenlignet med behandling med alle komparatorer i 1. linjebehandlingen.

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

Amgros har en kontrakt med Almirall indtil 31-12-2019.

Konklusion for populationen

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

Population	Komparator	Merværdi	Usikkerhed for klinisk merværdi	Amgros' konklusion om forholdet mellem meromkostninger og merværdi
Voksne (≥ 18 år) med moderat til svære plaque psoriasis, som er kandidater til 2. generations immun-modulerende behandling og ikke har psoriasisatropati. Herunder subpopulationen der omfatter patienter, som har haft behandlingssvigt ved anvendelse af en 1. linje IL-23 og IL-12/23 target.	Adalimumab	Ingen klinisk merværdi	Lav evidenskvalitet	Ikke rimeligt

Supplerende informationer (resumé af resultaterne fra afrapporteringen)

Konklusion på omkostnings- og budgetkonsekvensanalyserne

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

Amgros' afrapportering - Inkrementelle omkostninger per patient

Behandling med tildrakizumab (Ilumetri) er forbundet med meromkostninger sammenlignet med behandling med billigste 1. linjebehandling til indikationen.

I tabel 2 ses de inkrementelle omkostninger for tildrakizumab (Ilumetri) og komparatorerne.

Amgros' hovedanalyse resulterer i gennemsnitlige meromkostninger per patient for tildrakizumab (Ilumetri) sammenlignet med billigste komparator i 1. linjebehandling på ca. [redacted] DKK og ca. [redacted] DKK for lægemidlet med samme target (guselkumab) som tildrakizumab (Ilumetri). I tabellen ses alle inkrementelle omkostninger for tildrakizumab (Ilumetri) og komparatorerne i SAIP.

Tabel 2: 18 mdr. behandling sammenlignet med andre 1. linjebehandlinger, DKK, SAIP

	18 måneder	
	Lægemiddelomkostninger (SAIP)	Inkrementelle omkostninger (SAIP)
Tildrakizumab (Ilumetri)	[redacted]	-
Adalimumab (Imraldi)	[redacted]	[redacted]
Certolizumab pegol (Cimzia)	[redacted]	[redacted]
Secukinumab (Cosentyx)	[redacted]	[redacted]
Ustekinumab (Stelara)	[redacted]	[redacted]
Guselkumab (Tremfya)	[redacted]	[redacted]
Ixekizumab (Taltz)	[redacted]	[redacted]
Brodalumab (Kyntheum)	[redacted]	[redacted]

Hvis analysen udføres på baggrund af AIP, bliver de inkrementelle omkostninger for tildrakizumab (Ilumetri) sammenlignet med den billigste komparator i 1. linjebehandling ca. 60.000 DKK. I tabel 3 ses de inkrementelle meromkostninger og lægemiddelomkostninger for alle komparatorer i AIP-priser.

Tabel 3: 18 mdr. behandling sammenlignet med andre 1. linjebehandlinger, DKK, AIP

	18 måneder	
	Lægemiddelomkostninger (AIP)	Inkrementelle omkostninger (AIP)
Tildrakizumab (Ilumetri)	166.445	-
Adalimumab (Imraldi)	108.062	58.583
Certolizumab pegol (Cimzia)	151.719	14.926
Secukinumab (Cosentyx)	164.547	2.098
Ustekinumab (Stelara)	169.893	- 3.248
Guselkumab (Tremfya)	174.651	- 8.007
Ixekizumab (Taltz)	190.092	- 23.448
Brodalumab (Kyntheum)	181.220	- 14.575

Amgros' afrapportering – Budgetkonsekvenser

Amgros vurderer at anbefaling af tildrakizumab (Ilumetri) som mulig standardbehandling, vil resultere i budgetkonsekvenser på ca. [redacted] DKK per år. Udføres analysen i AIP er budgetkonsekvenserne på ca. -200.000 DKK, hvis tildrakizumab (Ilumetri) anbefales.

Budgetkonsekvenser er beregnet ud fra et markedsperspektiv, og der ses derfor på hvilket lægemiddel tildrakizumab (Ilumetri) vil erstatte i gruppen for 1. linjebehandling til svær plaque psoriasis, og ikke hvilket lægemiddel i gruppen for 1. linjebehandling der er det billigste. Budgetkonsekvenserne kan være forbundet med større besparelser, da tildrakizumab (Ilumetri) er forbundet med besparelser sammenlignet med alle andre komparatorer end adalimumab i behandlingslinjen. Tildrakizumab (Ilumetri) vil derfor erstatte flere lægemidler inden for behandlingslinjen, for patienter der skifter behandling. Der er store usikkerheder forbundet med den potentielle besparelse ved anbefaling af tildrakizumab (Ilumetri).

TILDRAKIZUMAB (ILUMETRI)

MODERAT TIL SVÆR PLAQUE PSORIASIS HOS VOKSNE

AMGROS 26. marts 2019

AMGROS

OPSUMMERING

Baggrund

Tildrakizumab (Ilumetri) er en systemisk biologisk antistofbehandling indiceret til behandling af moderat til svær plaque psoriasis hos voksne, som er kandidater til 2. generations immunmodulerende behandling. Der forventes at ca. 100 nye patienter per år kandiderer til 2. generations immunmodulerende behandling, derudover forventes det, at ca. 100 patienter per år fejler på et 2. generations immunmodulerende lægemiddel og skal skifte til et andet. Amgros' vurdering tager udgangspunkt i dokumentationen indsendt af Almirall.

Analyse

I analysen estimeres de inkrementelleomkostninger forbundet med behandling med tildrakizumab (Ilumetri) sammenlignet med behandling med guselkumab, adalimumab, secukinumab, ixekizumab, ustekinumab, brodalumab og certolizumab pegol til voksne (≥ 18 år), herunder subpopulationen af patienter med tidligere behandlingssvigt ved anvendelse af en 1. linje med IL-23 og IL-12/23 target.

Inkrementelle omkostninger og budgetkonsekvenser

Amgros har vurderet de gennemsnitlige inkrementelleomkostninger per patient ved brug af tildrakizumab (Ilumetri) sammenlignet med komparator. De inkrementelle omkostninger er angivet i SAIP.

I analysen, som Amgros mener er mest sandsynlig, er de inkrementelle omkostninger for tildrakizumab (Ilumetri) ca. [redacted] DKK sammenlignet med den billigste komparator i 1. linjebehandling til ca. [redacted] DKK for den dyreste komparator i 1. linjebehandling for 18 måneder, for den generelle patientpopulation herunder subpopulationen af patienter med tidligere behandlingssvigt ved anvendelse af en 1. linje med IL-23 og IL-12/23 target.

Anvendes lægemiddelpriserne i AIP er de inkrementelle omkostninger for tildrakizumab (Ilumetri) ca. 60.000 DKK sammenlignet med den billigste komparator i 1. linjebehandling til ca. -23.000 DKK for den dyreste komparator i 1. linjebehandling.

Amgros vurderer at budgetkonsekvenserne for regionerne per år ved anbefaling af tildrakizumab (Ilumetri) som standardbehandling vil være ca. [redacted] DKK. Hvis analysen udføres med AIP, er budgetkonsekvenserne ca. -200.000 DKK om året.

Konklusion

Amgros kan konkludere, at behandling med tildrakizumab (Ilumetri) er forbundet med meromkostninger sammenlignet med den billigste komparator i 1. linjebehandling, men besparelser sammenlignet med andre komparatorer i 1. linjebehandling. Meromkostningerne eller besparelserne for tildrakizumab (Ilumetri) er i denne analyse udelukkende drevet af lægemiddelomkostninger for tildrakizumab (Ilumetri) og komparator.

Liste over forkortelser

AIP	Apotekernes indkøbspris
DKK	Danske kroner
DRG	Diagnose Relaterede Grupper
IL	Interleukin
mAb	Monoklonalt antistof
PsA	Psoriasisartropati
SPC	Summary of Product Characteristics

INDHOLD

LOG

Ansøgning	
Lægemiddelfirma:	Almirall
Handelsnavn:	Ilumetri
Generisk navn:	Tildrakizumab
Indikation:	Behandling af moderat til svær plaque psoriasis hos voksne (≥ 18 år), som er kandidater til 2. generations immunmodulerende behandling og ikke har psoriasisartropati.
ATC-kode:	L04AC17

Proces	
Ansøgning modtaget hos Amgros:	19-12-2018
Endelig rapport færdig:	26-03-2019
Sagsbehandlingstid fra endelig ansøgning:	98 dage
Arbejdsgruppe:	**Louise Greve Dal** Line Brøns Jensen Lianna Christensen Mark Friborg Pernille Winther Johansen

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

1 BAGGRUND

Tildrakizumab (Ilumetri) er som enkeltstofbehandling indiceret til behandling af moderat til svær plaque psoriasis hos voksne (≥ 18 år), som er kandidater til 2. generations immunmodulerende behandling og ikke har psoriasisartropati(PsA)(1). Almirall (herefter omtalt som ansøger) er markedsføringstilladelsesindehaver af tildrakizumab (Ilumetri) og har den 19.12.2018 indsendt en ansøgning til Medicinrådet om anbefaling af tildrakizumab (Ilumetri) som standardbehandling på danske sygehuse af den nævnte indikation. Som et led i denne ansøgning vurderer Amgros, på vegne af Medicinrådet de økonomiske analyser, ansøger har sendt som en del af den samlede ansøgning til Medicinrådet. Denne rapport er Amgros' vurdering af de fremsendte økonomiske analyser (herefter omtalt som analysen).

1.1 Problemstilling

Formålet med analysen er at estimere de inkrementelle omkostninger forbundet med behandling af moderat til svær plaque psoriasis hos voksne (≥ 18 år), som er kandidater til 2. generations immunmodulerende behandling og ikke har PsA, i form af de gennemsnitlige inkrementelle omkostninger per patient og de samlede budgetkonsekvenser for regionerne ved anbefaling af tildrakizumab (Ilumetri) som standardbehandling på danske sygehuse af den nævnte indikation. I analyserne sammenlignes behandling med tildrakizumab (Ilumetri) med behandling med guselkumab, adalimumab, secukinumab, ixekizumab, ustekinumab, brodalumab og certolizumab pegol, der er defineret i Medicinrådets protokol som nuværende standardbehandling(1).

1.2 Patientpopulation

Psoriasis er en autoimmun, kronisk, inflammatorisk sygdom, hvor plaque psoriasis er den mest almindelige (ca. 80%). Det forventede antal patienter på landsplan er per år ca. 100 nye patienter, som er kandidater til 2. generations immunmodulerende behandling. Det drejer sig om psoriasispatienter, der opfylder kriterierne for biologisk behandling, og som ikke har psoriasisartropati (PsA). Derudover forventes det, at ca. 100 patienter per år fejler på et 2. generations immunmodulerende lægemiddel og skal skifte til et andet lægemiddel(1). Adalimumab, secukinumab, ixekizumab og ustekinumab anbefales aktuelt alle som 1. linjebehandlinger til psoriasis begrundet i samme effekt på hudsymptomer og sammenlignelig bivirkningsprofil(1). Lægemidlerne brodalumab og guselkumab er af Medicinrådet (15. marts 2018) vurderet til at gøre et klinisk ligestillet alternativ 1. linjebehandling(2,3). Lægemidlet certolizumab pegol er af medicinrådet (12. december 2018) vurderet til at gøre et klinisk ligestillet alternativ til 1. linjebehandling(4).

1.3 Behandling med tildrakizumab (Ilumetri)

Indikation

Tildrakizumab (Ilumetri) er indiceret til behandling af Voksne (≥ 18 år) med moderat til svær plaque psoriasis, som er kandidater til 2. generations immunmodulerende behandling og ikke har psoriasisartropati. Herunder subpopulationen der omfatter patienter, som har haft behandlingssvigt på biologiske lægemidler generelt samt specifikt på lægemidler med IL-23 og IL-12/23 target(1).

Virkningsmekanisme

Tildrakizumab (Ilumetri) er et humant monoklonalt antistof (mAb), som binder selektivt til interleukin (IL)-23(1).

Dosering

Enkeltstofbehandlingen administreres således(1):

- Tildrakizumab (Ilumetri), subkutan injektion á 100 mg i uge 0, 4 og herefter hver 12. uge

1.3.1 Komparator

Medicinrådet har defineret komparator som de lægemidler, der aktuelt anbefales som 1. linjebehandling, til den generelle patientpopulation med moderat til svær plaque psorasis. Heraf er ustekinumab og guselkumab henholdsvis et anti-interleukin(IL)-12/23 og anti-IL-23, der derfor deler samme target som tildrakizumab (Ilumetri)(1).

Tabel 1: Definerede populationer og komparatorer

Population	Komparator
Voksne (≥ 18 år) med moderat til svær plaque psoriasis, som er kandidater til 2. generations immunmodulerende behandling og ikke har psoriasisartropati. (Herunder subpopulation som har haft behandlingssvigt ved anvendelse af en 1. linje IL-23 og IL-12/23 targit)	Adalimumab Secukinumab Ixekizumab Ustekinumab Brodalumab Guselkumab Certolizumab pegol

1.4 Medicinrådets kliniske spørgsmål

Medicinrådet har vurderet den kliniske merværdi af behandling med tildrakizumab (Ilumetri) sammenlignet med komparator for voksne (≥18 år) med moderat til svær plaque psoriasis, som er kandidater til 2. generations immunmodulerende behandling og ikke har psoriasisartropati(1).

2 VURDERING AF INDSENDT ØKONOMISK ANALYSE

I analysen af gennemsnitlige behandlingsomkostninger per patient sammenlignes behandling med tildrakizumab (Ilumetri) med behandling med guselkumab (Tremfya) til voksne (≥ 18 år) med moderat til svær plaque psoriasis uden PsA, som er kandidater til 2. generations immunmodulerende behandling, herunder subpopulationen af patienter med tidligere behandlingssvigt ved anvendelse af en 1. linje IL-23 og IL-12/23 target.

2.1 Model, metode og forudsætninger

2.1.1 Modelbeskrivelse

Ansøger har indsendt en simpel omkostningsmodel for behandling af patienter i den nævnte population. Ansøger antager at behandlingsforløbene for tildrakizumab (Ilumetri) og guselkumab (Tremfya) er identiske og at effekt- og bivirkningsprofil er helt ens. Frafald inkluderes således ikke i analysen
I modellen antages, at der behandles i 18 måneder. Behandling vil have færre omkostninger efterfølgende år. Ansøger har ikke indsendt nogen følsomhedsanalyser.

Amgros' vurdering

Amgros accepterer ansøgers antagelser om ens patientforløb for tildrakizumab (Ilumetri) og guselkumab (Tremfya), da der ikke er forskelle i udredning, diagnostik, behandlingsmåde eller opfølgning mellem tildrakizumab (Ilumetri) og komparator.

Udfaldet efter 12 måneder er at forsætte i behandling eller at seponere behandling. Amgros mener at ansøgers hovedanalyse på 18 måneder inkluderer alle relevante omkostninger for behandlingerne.

Der er i Medicinrådets protokol defineret flere mulige komparatorer til tildrakizumab (Ilumetri) for populationen(1). Amgros mener derfor, at det i hovedanalysen er relevant at estimere de inkrementelle omkostninger for alle mulige komparatorer jf. tabel. Amgros udarbejder i sin hovedanalyse behandlingssammenligning med tildrakizumab (Ilumetri) med komparativerne defineret i protokollen.

Amgros vurderer, at det er rimeligt ikke at inkludere frafald i modellen, da der ikke findes data der understøtter, at der vil være forskel i frafaldsraten mellem de sammenlignende lægemidler.

Amgros udarbejder en ny hovedanalyse hvor de inkrementelle omkostninger for tildrakizumab (Ilumetri) sammenlignet med alle relevante komparatorer hvor omkostninger estimeres for 18 måneder.

2.1.2 Analyseperspektiv

Analysen inkluderer udelukkende lægemiddelomkostninger. Tidshorisonten i analysen er fra første dosis og 18 måneder frem. Ansøger har diskonteret omkostninger efter 12 måneder med en diskonteringsfaktor på 4%.

Amgros' vurdering

Analysens perspektiv er i tråd med Amgros' retningslinjer, Jf. Amgros Metodevejledning om, hvad der må inkluderes i en økonomisk analyse.

Amgros vurderer, at tidshorisonten er tilstrækkeligt lang til at opfange betydelige relevante forskelle mellem de sammenlignede interventioner i analysen for den angivne population, da patienterne får behandling i 12 måneder eller potentielt får behandling i mange år, og hvor antallet af administrationer differentiere fra år 1 og efterfølgende år, hvormed det er relevant at estimere omkostninger for 12 måneder og derefter for efterfølgende måneder.

Amgros godtager analysens perspektiv og tidshorisonten.

2.1.3 Omkostninger

Lægemiddelomkostninger

Ansøger har for tildrakizumab (Ilumetri) og guselkumab (Tremfya) anvendt SPC'erne for lægemidlerne(5,6). Alle anvendte lægemiddelpriser er i SAIP.
Tabel 2 illustrerer de lægemiddelpriser, som anvendes i analysen.

Tabel 2: Anvendte lægemiddelpriser, SAIP (april 2019)

Lægemiddel	Styrke	Pakningsstørrelse	Pris pr pakning (DKK)	Kilde
Tildrakizumab (Ilumetri)	100 mg, s.c	1 stk.	[redacted]	Ansøger
Guselkumab (Tremfya)	100 mg, s.c	1 stk.	[redacted]	Amgros

Tildrakizumab (Ilumetri) administreres med 100 mg i uge 0, 4 og derefter hver 12. uge, tilsvarende 5 administrationer over år 1 og 7,17 over 18 måneder.
Guselkumab (Tremfya) administreres med 100 mg i uge 0, 4 og derefter hver 8. uge, tilsvarende 7 administrationer i år 1 og 10,25 administrationer over 18 måneder.
Tabel 3 illustrerer doseringen af lægemidlerne, som anvendes i analysen og prisen per patient for hver population.

Tabel 3: Gennemsnitlig dosis og lægemiddelomkostninger pr. patient over 18 måneder, DKK

Behandlingsregime	Styrke	Administrationer	Pris pr. enhed	I alt 18 måneder
Tildrakizumab (Ilumetri)	100 mg, s,c	7,17	[redacted]	[redacted]
Guselkumab (Tremfya)	100 mg, s.c	10,25	[redacted]	[redacted]

Amgros' vurdering

Doseringen af lægemidlerne er i tråd med lægemidlernes SPC'er(5,6).

Amgros accepterer den valgte dosering.

3 RESULTATER

3.1 Ansøgers hovedanalyse

3.1.1 Antagelser i ansøgers hovedanalyse

- *Tidshorisonten er 18 måneder i analysen for tildrakizumab (Ilumetri) og guselkumab (Tremfya)*
- *Der inkluderes udelukkende lægemiddelomkostninger i analysen*
- *Det antages, at subpopulationen med patienter, som har haft behandlingssvigt ved anvendelse af en 1. linje med IL-23 eller IL-12/23 target, også dækkes af hovedpopulationen*

3.1.2 Resultat af ansøgers hovedanalyse

Resultaterne fra ansøgers hovedanalyse præsenteres i tabel 4.

Tabel 4: Resultat af ansøgers hovedanalyse, gns. omkostninger per patient, 18 måneder, DKK, SAIP

Tildrakizumab (Ilumetri)	Guselkumab (Tremfya)	Inkrementelle omkostninger (DKK)
[redacted] DKK	[redacted] DKK	[redacted]

3.2 Amgros' hovedanalyse

3.2.1 Antagelser i Amgros hovedanalyse

- *Amgros inkluderer alle relevante komparatorer i analysen*

3.2.2 Resultat af Amgros hovedanalyse

Resultaterne fra Amgros hovedanalyse præsenteres nedenfor.

Tabel 5: Anvendte lægemiddelpriser, SAIP (april 2019)

Lægemiddel	Styrke	Pakningsstørrelse	Pris pr pakning (DKK)	Kilde
Tildrakizumab (Ilumetri)	100 mg, s.c	1 stk.	[redacted]	Ansøger
Guselkumab (Tremfya)	100 mg, s.c	1 stk.	[redacted]	Amgros
Adalimumab (Imraldi)	40 mg, s.c	2 stk.	[redacted]	Amgros
Secukinumab (Cosentyx)	300 mg, s.c	2 stk.	[redacted]	Amgros
Ustekinumab (Stelara)	≤100 kg: 45 mg, s.c >100 kg: 90 mg, s.c	1 stk.	[redacted]	Amgros
Certolizumab pegol	200 mg, s.c	1 stk.	[redacted]	Amgros
Ixekizumab (Taltz)	80 mg, s.c	1 stk	[redacted]	Amgros
Brodalumab (Kyntheum)	210 mg, s.c	2 stk.	[redacted]	Amgros

I tabel 6 ses resultatet af Amgros hovedanalyse.

Tabel 6: 18 mdr. behandling sammenlignet med andre 1. linjebehandlinger, DKK, SAIP

	18 måneder	
	Lægemiddelomkostninger (SAIP)	Inkrementelleomkostninger (SAIP)
Tildrakizumab (Ilumetri)	[redacted]	-
Adalimumab (Imraldi)	[redacted]	[redacted]
Certolizumab pegol (Cimzia)	[redacted]	[redacted]
Secukinumab (Cosentyx)	[redacted]	[redacted]
Ustekinumab (Stelara)	[redacted]	[redacted]
Guselkumab (Tremfya)	[redacted]	[redacted]
Ixekizumab (Taltz)	[redacted]	[redacted]
Brodalumab (Kyntheum)	[redacted]	[redacted]

De inkrementelle omkostninger for tildrakizumab (Ilumetri) er ca. [redacted] DKK per patient for lægemidler med target IL-23 (guselkumab). De inkrementelle omkostninger for tildrakizumab (Ilumetri) sammenlignet med behandling med billigste komparator i 1. linjebehandling (adalimumab) er på ca. [redacted] DKK.

Hvis analysen udføres med AIP, er de inkrementelle omkostninger for tildrakizumab (Ilumetri) sammenlignet med guselkumab ca. -8.000 DKK og ca. 60.000 DKK sammenlignet med behandling med billigste komparator i 1. linjebehandling (adalimumab).

4 BUDGETKONSEKVENSER

Anbefaling af tildrakizumab (Ilumetri) som standardbehandling til indikationen omhandlet af denne analyse, vil ikke udvide brugen af immunsupprimerende lægemidler til behandling af moderat til svær plaque psoriasis hos voksne (≥ 18 år), som er kandidater til 2. generations immunmodulerende behandling, men i stedet øge konkurrencen om det eksisterende marked. Ansøger antager at tildrakizumab (Ilumetri) kun vil blive anvendt til skifte-patienter hvis tildrakizumab (Ilumetri) anbefales. Dette betyder at 0% vil blive behandlet med tildrakizumab (Ilumetri) for bionaïve patienter. Ansøger antager at 27% af de 100 skifte-patienter vil blive behandlet med tildrakizumab (Ilumetri) såfremt tildrakizumab (Ilumetri) anbefales. Ansøger antager at skifte-patienterne der behandles såfremt tildrakizumab (Ilumetri) anbefales erstatter lægemidlet guselkumab (Tremfya) der har samme target som tildrakizumab (Ilumetri). Med de nuværende priser på lægemidlerne vil tildrakizumab (Ilumetri) således være resulterende i budgetkonsekvenser på ca. [redacted] DKK per budget år. Amgros mener tildrakizumab (Ilumetri) vil anvendes til flere af de 100 skifte-patienter, og dermed også tage markedsandele fra andre komparatorer end guselkumab (Tremfya). Amgros mener derfor at budgetkonsekvenserne fører til en større besparelse af budgetkonsekvenserne end ansøgers estimat. Den potentielle besparelse kendes ikke.

Angives lægemidlerne i AIP vil budgetkonsekvenserne resultere i ca. – 200.000 DKK per budget år.

5 DISKUSSION

Ansøger har kun inkluderet lægemiddelomkostninger, eftersom det er accepteret, at behandlingerne er ligeværdige med hensyn til effekt og bivirkningsprofil. Alle lægemidler administreres subkutant, og derfor antages ens administrationsomkostninger. Der vil dog være forskel i antal doser år 1 og efterfølgende år.

Amgros vurderer, at de inkrementelle omkostninger med behandling med tildrakizumab (Ilumetri) er ca. [redacted] DKK for 18 måneder sammenlignet med den billigste komparator i 1. linjebehandling. Amgros vurderer, at anbefalingen af tildrakizumab (Ilumetri) vil resultere i budgetkonsekvenser på ca. [redacted] DKK per budget år.Budgetkonsekvenserne er beregnet på hvilket lægemiddel tildrakizumab (Ilumetri) vil erstatte i gruppen for 1. linjebehandling til svær plaque psoriasis. Da tildrakizumab (Ilumetri) forventes at tage markedsandel fra flere dyrere alternativer, vil budgetkonsekvenserne være yderligere forbundet med besparelser

Angives lægemidlerne i AIP, vil de inkrementelle omkostninger med behandling med tildrakizumab (Ilumetri) være ca. 60.000 DKK for 18 måneder sammenlignet med billigste komparator i 1. linjebehandling (adalimumab) og budgetkonsekvenser på ca. – 200.000 DKK per budget år.

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AMGROS

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Hellerup, 18. Marts 2019

Høringssvar vedr. vurdering af klinisk merværdi for tildrakizumab til behandling af moderat til svær plaque psoriasis

Almirall takker for modtagelse af udkast til Medicinrådets vurdering af klinisk merværdi for tildrakizumab til behandling af moderat til svær plaque psoriasis.

Vi har noteret, at Fagudvalget har bemærket, at den valgte komparator er blandt de mest effektive psoriasis præparater på markedet. Endvidere anderkender vi, at Medicinrådet overordnet vurderer, at tildrakizumab til patienter med moderat til svær plaque psoriasis giver ingen klinisk merværdi sammenlignet med guselkumab. Dette gælder også for effektmålene PASI75, PASI90, alvorlige uønskede hændelser og behandlingsophør.

Endelig noterer vi os, at Medicinrådet vurderer en negativ klinisk merværdi for DLQI 0/1, men samtidigt bemærker at DLQI ikke er et optimalt redskab til måling af livskvalitet for psoriasispatienter, og at der derfor tages konservativt forbehold for dette. Almirall mener det er vigtigt at tilføje, at forskellen er forårsaget af et unormalt stort placebo respons i reSURFACE 2 studiet (8 % mod 3 % i VOYAGE 2 studiet), og at konfidensintervallet associeret med estimatet for den absolutte forskel mellem de to behandlinger inkluderer den klinisk mindst relevante forskel på 15 %. Desuden synes det relevant at pointerer, at DLQI 0/1 respons rater i modsætning til de øvrige effektmål kun undersøger den ene "hale" af hele DLQI data fordelingen og derfor sandsynligvis ikke opfanger hele relationen mellem behandlingerne. Som alternativ har Almirall i ansøgningen indsendt en indirekte sammenligning på DLQI ændring fra baseline efter samme metode som angivet i Medicinrådets protokol. Denne analyse viser ingen forskel mellem de to behandlinger (gennemsnitlige forskel på 0,70 DLQI point med et 95 % konfidensinterval på -1.46 til 2.86), men vi anderkender at analysen for nuværende beror på upublicerede data.

Almirall ser frem til, at tildrakizumab bliver inkluderet i patientbehandlingen og at vi får mulighed for at deltage i fremtidige udbud med tildrakizumab i gruppen af 1. linjebehandlinger til psoriasis uden ledgener.

Med venlig hilsen
Almirall Nordic

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Medicinrådet

Medicinrådets vurdering af klinisk merværdi for tildrakizumab til behandling af moderat til svær plaque psoriasis

Versionsnr. 1.0

Medicinrådet

Om Medicinrådet

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

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

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

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

Om vurderingen af klinisk merværdi

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

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

Se Medicinrådets metodehåndbog for yderligere information.

Dokumentoplysninger	
Godkendelsesdato	13. marts 2019
Ikrafttrædelsesdato	13. marts 2019
Dokumentnummer	42448
Versionsnummer	1.0

Medicinrådet, Dampfærgevej 27-29, 3. th., 2100 København Ø
www.medicinraadet.dk
Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 13. marts 2019

Indhold

1 Lægemiddelinformationer

Lægemidlets oplysninger	
Handelsnavn	Ilumetri
Generisk navn	tildrakizumab
Firma	Almirall
ATC-kode	L04AC17
Virkningsmekanisme	Humaniseret monoklonalt antistof rettet mod interleukin (IL)-23.
Administration/dosis	Subkutan injektion 100 mg i uge 0, 4 og hver 12. uge herefter.
EMA-indikation	Behandling af moderat til svær plaque psoriasis hos voksne (≥ 18 år), som er kandidater til systemisk behandling.

2 Medicinrådets konklusion vedrørende klinisk merværdi

Medicinrådet vurderer, at tildrakizumab til voksne (≥18 år) patienter med moderat til svær plaque psoriasis, som er kandidater til 2. generations immunmodulerende behandling (behandling med biologiske lægemidler) og ikke har psoriasisartropati giver:

- **Ingen klinisk merværdi** til patienter med moderat til svær plaque psoriasis sammenlignet med guselkumab. Evidensens kvalitet vurderes at være lav.
- **Den kliniske merværdi kan ikke vurderes** for subpopulationen af patienter med tidligere behandlingssvigt på biologiske lægemidler generelt.
- **Den kliniske merværdi kan ikke vurderes** for subpopulationen af patienter med tidligere behandlingssvigt på biologiske lægemidler med samme target.

Medicinrådet kategoriserer lægemidlers kliniske merværdi i en af følgende kategorier:

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

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

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

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

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

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

3 Forkortelser

BSA:	*Body Surface Area*
CI:	Konfidensinterval
DDS:	Dansk Dermatologisk Selskab
Dermbio:	National database for psoriasispatienter i biologisk behandling
DLQI:	*Dermatology life quality index*
EMA:	*European Medicines Agency*
GRADE:	System til vurdering af evidens (*Grading of Recommendations Assessment, Development and Evaluation*)
HR:	*Hazard ratio*
IL:	Interleukin
mAb:	Monoklonalt antistof
OR:	*Odds ratio*
PASI:	*Psoriasis area and severity index*
PGA:	*Physician's Global Assessment*
RR:	Relativ risiko
SAE:	Alvorlig uønsket hændelse (*serious adverse effect*)
TNF:	*Tumor necrosis factor*

4 Formål

Formålet med Medicinrådets vurdering af klinisk merværdi af tildrakizumab til moderat til svær plaque psoriasis er at vurdere den kliniske merværdi i forhold til et eller flere lægemidler til samme patientgruppe (komparator(er)). Den kliniske merværdi af tildrakizumab vurderes i den generelle population af voksne (≥ 18 år) med moderat til svær plaque psoriasis uden ledgener (psoriasisartropati), som er kandidater til 2. generations immunmodulerende behandling. Derudover vurderes den kliniske merværdi i subpopulationerne af patienter, som har haft behandlingssvigt på biologiske lægemidler generelt samt specifikt på lægemidler med IL-23 og IL-12/23 target.

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

5 Baggrund

Moderat til svær plaque psoriasis

I Danmark, som i øvrige dele af verden, får ca. 2-3 % af befolkningen psoriasis i løbet af livet. Psoriasis er en autoimmun, kronisk, inflammatorisk sygdom, hvor plaque psoriasis, også kaldet psoriasis vulgaris, er den mest almindelige (ca. 80 %) [1,2].

Der findes ikke et definitivt mål for sværhedsgraden af psoriasis. Dog anses sygdommen som moderat til svær, hvis enten psoriasis area and severity index (PASI) er over 10, eller det påvirkede overfladeareal (body surface area, BSA) er over 10, eller hvis patientens vurdering af livskvalitet, sædvanligvis vurderet ved dermatology life quality index (DLQI), er over 10. Samlet betegnes dette "10-reglen" [3,4].

Bedømt på Dermbios seneste årsrapport fra 2017 er antallet af patienter, der er i biologisk behandling i Danmark, fortsat stigende. Ved udgangen af 2017 var der registreret 2710 patienter, der havde modtaget behandling med 2. generations immunmodulerende lægemidler [5]. Det forventede antal patienter på landsplan er pr. år ca. 100 nye patienter, som er kandidater til 2. generations immunmodulerende behandling. Det drejer sig om psoriasispatienter, der opfylder kriterierne for biologisk behandling, og som ikke har ledgener. Derudover forventes det, at ca. 100 patienter pr. år fejler på et 2. generations immunmodulerende lægemiddel og skal skifte til et andet lægemiddel [6].

I 2014 blev psoriasis anerkendt af World Health Organisation (WHO) som en alvorlig kronisk sygdom, der ofte er yderst smertefuld og invaliderende. Dette skyldes blandt andet den stigmatisering, som ofte er forbundet med sygdommen [7]. Livskvalitetsundersøgelser viser, at mænd og kvinder er ligeligt påvirket af psoriasis og at psoriasis kan påvirke patienten på linje med diabetes og hjertekarsygdomme [7].

Nuværende behandling

2. generations immunmodulerende behandling igangsættes efter kriterier defineret i RADS-behandlingsvejledningen [6] og retningslinjer fra Dansk Dermatologisk Selskab [8]. Disse omfatter bl.a., at patienten skal have psoriasis med svære hudmanifestationer, defineret som PASI ≥ 10, BSA ≥ 10 % eller DLQI ≥ 10.

Til behandling af moderat til svær psoriasis anvendes ti biologiske lægemidler med forskellige virkningsmekanismer: fire Tumor Nekrose Faktor-alfa (TNF-alfa) hæmmere (infliximab, certolizumab pegol, eternacept og adalimumab), et anti-interleukin (IL)-12/23 (ustekinumab), to anti-IL-17 (secukinumab og ixekizumab), et anti-IL-17RA (brodalumab), et anti-IL-23 (guselkumab) og en PDE4-inhibitor (apremilast). De fleste af disse behandlinger virker dæmpende på immunsystemet.

Adalimumab, certolizumab pegol, secukinumab, ixekizumab, brodalumab, guselkumab og ustekinumab anbefales alle som 1. linjebehandlinger til psoriasis, da de er vurderet til at have sammenlignelige effekter på hudsymptomer og sammenlignelige bivirkningsprofiler [9].

Patienterne vurderes før opstart, efter 12 ugers behandling og derefter mindst to gange årligt. Der er i DDS-guidelines samt RADS' vejledning opstillet kriterier for den forventede effekt på PASI, og hvornår behandlingsskift er nødvendigt. Alle patienter med psoriasis, som sættes i 2. generations immunmodulerende behandling, skal registreres i Dermbio-databasen. For patienter med moderat til svær psoriasis har de biologiske præparater medført en betydelig bedring i behandlingsrespons.

Anvendelse af det nye lægemiddel

Ilumetri er en systemisk, biologisk antistofbehandling, som administreres som injektion (subkutan á 100 mg i uge 0, 4 og herefter hver 12. uge). Indholdsstoffet tildrakizumab er et monoklonalt humaniseret antistof (mAb), der specifikt binder sig til det ekstracellulære humane interleukin (IL)-23. Herved forhindres, at IL-23 bidrager til immunaktivering, og samtidig begrænses den inflammatoriske reaktion i huden, der spiller en central rolle i udviklingen af psoriasis. Ilumetri har ikke indikation til patienter med ledgener. Hos patienter med specifikke karakteristika (bl.a. høj sygdomsbyrde, kropsvægt ≥ 90 kg) kan dosering med 200 mg overvejes [10].

6 Metode

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

Ansøger har anvendt og fulgt den præspecificerede metode, jf. "Medicinrådets protokol for vurdering af klinisk merværdi for tildrakizumab til behandling af moderat til svær plaque psoriasis - 1.0", som blev godkendt i Medicinrådet den 22.oktober 2018.

Ansøger har valgt guselkumab som komparator og har udarbejdet en indirekte sammenligning med placebo som fælles komparator. De indirekte sammenlignende analyser (udarbejdet efter Buchers metode) er gennemført for effektmålene PASI 75, PASI 90, alvorlige uønskede hændelser (SAEs), DLQI og behandlingsophør, alle ved uge 12-16 og 24-28. Fagudvalget har anført i protokollen, at den samlede kliniske merværdi af tildrakizumab baseres på en tidshorisont på 1 år, og at der ønskes data med længst mulig opfølgningstid. Ansøger er derfor blevet bedt om at supplere uge 12-16 og 24-28-analyser med narrative sammenligninger af data for tildrakizumab og guselkumab af alle effektmål ved 1-års behandling. Tidshorisonten på 1 år er valgt som tidsenhed for alle effektmål for at kunne vurdere langtidseffekten og derved vedligeholdelsen af den kliniske effekt.

Ansøger har tilkendegivet, at der ikke foreligger publicerede data for subpopulationerne, som omfatter patienter, der enten har haft behandlingssvigt ved anvendelse af et biologisk lægemiddel generelt eller ved et lægemiddel med samme target.

Ansøger har desuden belyst forhold vedr. mulighed for behandlingspause, dosisreduktion/behandlingsintervalforlængelse, herunder muligheden for behandling med 200 mg, forhold mellem initialdosis og vedligeholdelsesdosis samt vedligeholdelse af effekt mellem doseringer hver 12. uge, som efterspurgt af fagudvalget i protokollen.

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

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

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

7 Litteratursøgning

Ansøger har gennemført en systematisk litteratursøgning for det kliniske spørgsmål, som beskrevet i protokollen, og ansøgers litteratursøgning har resulteret i inklusion af nedenstående hovedstudier:

- reSURFACE 1 og 2 publiceret af Reich et al., 2017 (tildrakizumab) [11].
- VOYAGE 1 publiceret af Blauvelt et al., 2017 (guselkumab) [12].
- VOYAGE 2 publiceret af Reich et al., 2017 (guselkumab) [13].
- Othsuki et al., 2018 (guselkumab) [14].

Medicinrådet har, udover ovenstående studier, inddraget studieregistreringerne på clinicaltrials.gov, produktresuméer samt data i EPAR for både tildrakizumab og guselkumab.

8 Databehandling

Ansøger har præsenteret sammenlignende analyser mellem tildrakizumab og komparator ved uge 12-16 og 24-28 på alle effektmål, hvor det var muligt. For tildrakizumab er uge 12-data for placebobehandlingen i reSURFACE-studierne fremskrevet til uge 28, mens uge 16-data for placebobehandlingen i VOYAGE-studierne er fremskrevet til uge 24. Denne fremskrivning er foretaget, da fagudvalget ønsker længst mulig opfølgningstid og samtidig vurderer, at der fra uge 12 til 28 ikke sker en ændring i respons for placeboarmen ift. de præspecificerede effektmål. Fagudvalget vurderer endvidere, at data for uge 24 og 28 er sammenligneligt, og vurderingen af det kliniske spørgsmål vil derfor blive baseret på data for uge 24-28.

De forhåndsdefinerede mindste klinisk relevante forskelle til grundlag for vurderingen var, jf. protokollen, baseret på behandlingseffekter ved 1 år og ikke ved uge 12-16 eller 24-28. For tildrakizumab findes der kun

publicerede studier, som rapporterer data frem til uge 28 (reSURFACE 1 og 2), mens der for guselkumab er publiceret data frem til uge 48 (VOYAGE 1 og 2). Ansøger har indsendt upublicerede data til besvarelse af det kliniske spørgsmål ved ~1 år, så disse er ikke indgået i fagudvalgets vurdering af tildrakizumab. På denne baggrund vurderer fagudvalget, at det tilgængelige datagrundlag ikke tillader vurdering af langtidseffekten af tildrakizumab.

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

9 Klinisk merværdi

9.1 Konklusion klinisk spørgsmål

Hvad er den kliniske merværdi af tildrakizumab til voksne patienter med moderat til svær plaque psoriasis, som er kandidater til 2. generations immunmodulerende behandling og ikke har psoriasisartropati?

- Fagudvalget vurderer, at tildrakizumab til patienter med moderat til svær plaque psoriasis giver **ingen klinisk merværdi** sammenlignet med guselkumab. Evidensens kvalitet er lav.
- Fagudvalget vurderer, at den kliniske merværdi af tildrakizumab **ikke kan vurderes** til subpopulationen af patienter med tidligere behandlingssvigt på biologiske lægemidler generelt.
- Fagudvalget vurderer, at den kliniske merværdi af tildrakizumab **ikke kan vurderes** til subpopulationen af patienter med tidligere behandlingssvigt på biologiske lægemidler med samme target.

9.1.1 Gennemgang af studier

Karakteristika

reSURFACE 1 og reSURFACE 2 (tildrakizumab) [11]

reSURFACE 1 og reSURFACE 2 er to randomiserede, multicenter, dobbelt-blindede, kontrollerede fase 3-studier. I reSURFACE 1 blev patienter (n = 772) randomiseret 2:2:1 til subkutan behandling med enten tildrakizumab 200 mg, tildrakizumab 100 mg eller placebo ved uge 0 og 4 (del 1). I reSURFACE 2 blev patienter (n = 1090) randomiseret 2:2:1:2 til behandling med tildrakizumab 200 mg, tildrakizumab 100 mg, placebo eller etanercept. Ved afslutning af del 1 i både reSURFACE 1 og 2 (dvs. ved uge 12) blev patienter, som frem til uge 12 havde modtaget placebo-behandling, re-randomiseret til at modtage enten tildrakizumab 200 mg eller 100 mg ved uge 12 og 16 og hver 12. uge derefter.

I begge studier blev patienter, som ved uge 28 havde opnået PASI ≥ 50, re-randomiseret til behandling med enten tildrakizumab 100 mg, tildrakizumab 200 mg eller placebo. Patienter, som ved uge 28 ikke havde responderet på tildrakizumab (< PASI 50), blev ekskluderet. Behandlingen fortsatte derefter frem til hhv. uge 64 (reSURFACE 1) og uge 52 (reSURFACE 2). Re-randomisering ved uge 12 og 28 blev udført ift. region og stratificeret ift. kropsvægt (≤ 90 kg eller > 90 kg). Bivirkningsprofilen blev vurderet blandt alle randomiserede patienter, som enten i del 1 eller 2, og modtog mindst én dosis tildrakizumab.

De primære endepunkter var andelen af patienter, som ved uge 12 havde opnået PASI 75 eller PGA-score på 'clear' eller 'minimal' med minimum en to-punkts reduktion fra baseline. Sekundære endepunkter inkluderede andelen af patienter, som havde opnået PASI 90 eller PASI 100 (uge 12), PASI 75 (uge 28),

DLQI-score på 0 eller 1 (uge 12 og 28) samt PGA-respons (uge 28). De primære endepunkter (PASI 75, PGA 0/1 samt sikkerhedsprofilen ved uge 12) og de vigtigste sekundære endepunkter (reSURFACE 1 og 2: PASI 90 ved uge 12 og DLQI ved uge 12 og 28; reSURFACE 2: PASI 75 og PGA ved uge 28) blev analyseret i det fulde datasæt (full analysis set). Det fulde datasæt var i del 1 defineret som alle randomiserede patienter, som modtog mindt én dosis af lægemidlet, mens det i del 2 var defineret som alle patienter, som fuldførte del 1 og påbegyndte del 2, og som modtog mindst én dosis af lægemidlet. Patienter med manglende data blev angivet til at være non-responders (non-responder imputering). I andre sekundære endepunkter, herunder DLQI, blev det fulde sæt af observerede data anvendt, dvs. der blev ikke foretaget imputering af manglende data.

VOYAGE 1 (guselkumab) [12]

VOYAGE 1 er et randomiseret, dobbeltblindet, placebo- og aktiv komparatorkontrolleret fase 3-studie. 837 patienter med moderat til svær plaque psoriasis, som kandiderede til biologisk behandling, blev randomiseret 2:1:2 til hhv. guselkumab 100 mg (329 patienter), placebo med skift til guselkumab efter 16 uger (174 patienter) og adalimumab doseret iht. produktresuméet (334 patienter). Studiet varede i 48 uger. Studiets primære endepunkter var andelen af patienter, som ved uge 16 opnåede IGA-score 0/1 samt andelen af patienter, som ved uge 16 opnåede PASI 90. Studiets sekundære endepunkter inkluderede PASI 90 efter 48 uger samt andelen af patienter, som ved uge 24 eller 48 opnåede en DLQI-score på 0 eller 1 (ud af de patienter, der havde DLQI > 1 ved baseline). Desuden var andelen af patienter, som opnåede PASI 75 efter 16 uger et sekundært effektmål. Alle randomiserede patienter (intention-to-treat (ITT)-populationen) blev inkluderet ved analyse af de primære (PASI 90 og IGA 0/1 ved uge 16) og nogle af de sekundære endepunkter. Patienter med manglende data blev anset som non-respondere. Bivirkningsprofilen blev analyseret i alle patienter, som modtog mindst én dosis af interventionen.

VOYAGE 2 (guselkumab) [13]

VOYAGE 2 er et randomiseret, dobbeltblindet, placebo- og aktiv komparatorkontrolleret fase 3-studie. 1279 patienter indgik i studiet. Patienterne blev randomiseret 2:1:1 til guselkumab 100 mg (n = 496), placebo med skift til guselkumab efter uge 16 (n = 248) eller adalimumab doseret iht. produktresuméet (n = 248). I uge 28 blev patienter i guselkumab-behandling, som havde opnået PASI 90, re-randomiseret 1:1 til behandling med guselkumab eller placebo frem til uge 48. PASI 90 nonrespondere fra adalimumab-gruppen fik guselkumab i uge 28, 32 og hver 8. uge derefter. PASI 90 respondere fra adalimumab-gruppen overgik til placebo i uge 28. Alle patienter blev fulgt i sammenlagt 48 uger. Studiets primære endepunkter var andelen af patienter, som ved uge 16 opnåede IGA-score 0/1 samt andelen af patienter, som ved uge 16 opnåede PASI 90. Studiets sekundære endepunkter inkluderede PASI 90 efter 48 uger samt andelen af patienter, som ved uge 24 eller 48 opnåede en DLQI-score på 0 eller 1 (ud af de patienter, der havde DLQI > 1 ved baseline). Desuden var andelen af patienter, som opnåede PASI 75 efter 16 uger et sekundært effektmål. Analysen af de primære endepunkter (PASI 90 og IGA 0/1 ved uge 16) blev foretaget på alle randomiserede patienter (ITT-populationen). Patienter, som oplevede behandlingssvigt før uge 16, blev anset som non-respondere ved analyse af uge 16 endepunkter. Bivirkningsprofilen blev analyseret i alle patienter, som modtog mindst én dosis af interventionen.

Tabel 1: Studiekarakteristika for inkluderede studier til besvarelse af det kliniske spørgsmål

Studie [reference]	Intervention	Komparator	NCT-nummer	Design	Studielande	Placebo-kontrolleret periode (uger)[a]	Samlet behandlings-periode (uger)
reSURFACE 1 [11]	Tildrakizumab	Placebo og etanercept	NCT01722331	Kontrolleret	Australien, Canada, Japan, Storbritannien og USA	12	64[b]
reSURFACE 2 [11]	Tildrakizumab	Placebo og etanercept	NCT01729754	Kontrolleret	Østrig, Belgien, Canada, Tjekkiet, Danmark, Frankrig, Tyskland, Ungarn, Italien, Israel, Holland, Polen og USA	12	52[b]
VOYAGE 1 [12]	Guselkumab	Placebo og ADA	NCT02207231	Kontrolleret	Australien, Canada, Tyskland, Ungarn, Korea, Polen, Rusland, Spanien, Taiwan og USA[c]	16	48[d]
VOYAGE 2 [13]	Guselkumab	Placebo og ADA	NCT02207244	Kontrolleret	Australien, Canada, Tjekkiet, Tyskland, Korea, Polen, Rusland, Spanien og USA[c]	16	48[e]

[a] Dette er den initiale placebo-kontrollerede periode.
[b] Publikationen rapporterer kun effekt frem til uge 28. Ved uge 12 blev patienter i placebobehandling randomiseret 1:1 til behandling med tildrakizumab 100 mg eller tildrakizumab 200 mg. Ved uge 28 blev patienter, der havde opnået PASI ≥ 50, re-randomiseret til enten samme behandling, anden dosis af tildrakizumab eller placebo.
[c] Studielande jf. "Listed Location Countries" i studieprotokol på clinicaltrials.gov.
[d] Ved uge 16 kunne patienter overgå til et 32-ugers extension-studie (uge 16-48) med behandling alene med guselkumab.
[e] Ved uge 16 overgik patienter i placebobehandling til behandling med guselkumab. Ved uge 28 blev patienter, der havde opnået PASI 90, re-randomiseret 1:1 til behandling med guselkumab eller placebo frem til uge 48.

Population

reSURFACE 1 og reSURFACE 2 (tildrakizumab) [11]

Inkluderede patienter var voksne (≥ 18 år) med moderat til svær plaque psoriasis defineret ved baseline BSA ≥ 10 %, PASI ≥ 12 samt Physician's Global Assessment (PGA) ≥ 3. Alle patienter var kandidater til fototerapi eller systemisk behandling. Kvindelige patienter skulle være seksuelt afholdende eller anvende prævention. Eksklusionskriterierne inkluderede graviditet, aktiv eller latent ubehandlet tuberkulose, tidligere behandling med tildrakizumab eller andre IL-23 antagonister samt en række konkurrerende lidelser/sygdomme, herunder infektioner og ukontrollerede systemiske tilstande. I reSURFACE 2 var et yderligere eksklusionskriterie tidligere behandling med etanercept.

VOYAGE 1 (guselkumab) [12]

Patienter var voksne (≥ 18 år) med moderat til svær plaque psoriasis i mindst 6 mdr., og som kandiderede til lysbehandling eller systemisk terapi. Patienterne havde ved baseline IGA ≥ 3, PASI ≥ 12 og BSA ≥ 10 %. Eksklusionskriterier inkluderede: andre psoriasisformer end plaque psoriasis; lægemiddelinduceret psoriasis; tidligere behandling med guselkumab eller adalimumab; anti-TNF-hæmmer-behandling de seneste 3 mdr.; anden biologisk behandling de seneste 6 mdr.; systemisk behandling eller lysbehandling de seneste 4 uger; tidligere eller nuværende symptomer på alvorlig, progredierende eller ukontrolleret sygdom (undtaget nonmelanoma hudkræft) i det renale, hepatiske, kardiovaskulære, pulmonale, gastrointestinale, endokrine, neurologiske, hæmatologiske, reumatologiske, psykiatriske eller metaboliske system, der jf. investigator kunne forhindre patienten i at deltage i studiet; graviditet og amning, herunder planlægning af graviditet hos begge køn inden for 5 mdr. efter sidste dosis i studiet; historie af aktiv tuberkulose eller symptomer på tuberkulose.

VOYAGE 2 (guselkumab) [13]

Patienter var voksne (≥ 18 år) med moderat til svær plaque-psoriasis med eller uden psoriasis artritis etableret mindst 6 mdr. før første dosering af studiemedicinen. Patienterne havde PASI ≥ 12, IGA ≥ 3 samt BSA ≥ 10 % ved screening og baselinebesøget. Patienterne, som indgik i studiet, var kandidater til lysbehandling eller systemisk behandling. Eksklusionskriterier inkluderede: andre psoriasisformer end plaque psoriasis; lægemiddelinduceret psoriasis; tidligere behandling med guselkumab eller adalimumab; tidligere eller nuværende symptomer på alvorlig, progredierende eller ukontrolleret sygdom (undtaget nonmelanoma hudkræft) i det renale, hepatiske, kardiovaskulære, pulmonale, gastrointestinale, endokrine, neurologiske, hæmatologiske, reumatologiske, psykiatriske eller metaboliske system, der jf. investigator kunne forhindre patienten i at deltage i studiet; graviditet og amning, herunder planlægning af graviditet hos begge køn inden for 5 mdr. efter sidste dosis i studiet; historie af aktiv tuberkulose eller symptomer herpå.

Ingen af de fire studier angiver andelen af patienter, der tidligere har oplevet svigt på biologisk behandling generelt eller på biologisk behandling med samme target (IL-23 og IL-12/23).

Fagudvalget vurderer, at populationerne i de fire studier er sammenlignelige med den danske patientpopulation ift. bl.a. kropsvægt, sygdomsvarighed og -alvorlighed.

Tabel 2: Populationskarakteristika for vurderede studier til klinisk spørgsmål 1

Studie [reference]	reSURFACE 1 [11]		reSURFACE 2 [11]		VOYAGE 1 [12]		VOYAGE 2 [13]		Othsuki [14]	
Behandlingsarm	Placebo	Tildrakizumab	Placebo	Tildrakizumab	Placebo	Guselkumab	Placebo	Guselkumab	Placebo	Guselkumab
Patienter, n	155	309	156	307	174	329	248	496	64	63
Alder, år Middelværdi ± SD Range	47,9 ± 13,5 19–76	46,4 ± 13,1 18–82	46,4 ± 12,2 20–76	44,6 ± 13,6 19–80	44,9 ± 12,9	43,9 ± 12,74	43,3 ± 12,4	43,7 ± 12,2	48,3 ± 10,56	47,8 ± 11,07
Mænd, n (%)	100 (65)	207 (67)	112 (72)	220 (72)	119 (68,4)	240 (72,9)	173 (69,8)	349 (70,4)	54 (84,4)	47 (74,6)
Vægt, kg (middelværdi ± SD)	87,50 ± 26,04	88,53 ± 23,87	88,74 ± 22,73	89,35 ± 22,12	NA	NA	NA	NA	71,56 ± 14,01†	74,27 ± 16,04
BMI (middelværdi ± SD)	NA	NA	NA	NA	28,9 ± 6,9	29,7 ± 6,22	29,6 ± 6,6	29,6 ± 6,5	25,42 ± 4,79†	26,33 ± 5,03
Sygdomsvarighed, år (middelværdi ± SD)	NA	NA	NA	NA	17,6 ± 12,4	17,9 ± 12,27	17,9 ± 11,9	17,9 ± 12,0	13,66 ± 10,29	14,39 ± 9,23
BSA, %-involvering af kroppen (middelværdi ± SD)	29,6 ± 17,28	29,7 ± 17,44	31,3 ± 14,75	34,2 ± 18,44	25,8 ± 15,9	28,3 ± 17,10	28,0 ± 16,5	28,5 ± 16,4	33,6 ± 18,39	37,9 ± 21,48
PASI-score (middelværdi ± SD)	19,3 ± 7,07	20,0 ± 7,85	20 ± 7,57	20,5 ± 7,63	20,4 ± 8,7	22,1 ± 9,49	21,5 ± 8,0	21,9 ± 8,8	25,92 ± 12,34	26,73 ± 12,20
DLQI-score (middelværdi ± SD)	13,2 ± 7,25	13,9 ± 6,68	13,7 ± 6,98	14,8 ± 7,24	13,3 ± 7,1	14,0 ± 7,48	15,1 ± 7,2	14,7 ± 6,9	10,6 ± 7,74	10,3 ± 7,27
Psoriasis-artritis, n (%)	NA	NA	NA	NA	30 (17,2)	64 (19,5)	46 (18,5)	89 (17,9)	10 (15,6) §	10 (15,9) §
Tidl. systemisk behandling, n (%)	NA	NA	NA	NA	92 (52,9)	210 (63,8)	149 (60,1)	331 (66,7)	38 (59,4)	37 (58,7)
Tidl. biologisk behandling, n (%)	35 (23)	71 (23)	20 (13)	39 (13)	34 (19,5)	71 (21,6)	54 (21,8)	101 (20,4)	10 (15,6)	11 (17,5)

BMI: Body mass index; BSA: Body surface area; DLQI: Dermatology Life Quality Index; PASI: Psoriasis Area and Severity Index.
† n = 63. § Diagnosis based on Classification Criteria for Psoriatic Arthritis.

9.1.2 Resultater og vurdering

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

PASI 75 (kritisk)

PASI er et valideret mål for sværhedsgraden af kronisk plaque psoriasis, der kombinerer areal og læsionernes sværhedsgrad. PASI 75 er reduktion i PASI-værdi med 75 % i forhold til baseline.

Tabel 3. Vurdering af klinisk merværdi: PASI 75 ved uge 24-28

	Forhåndsdefineret grundlag for vurdering		Resultater
Absolutte forskelle	15 procentpoint forskel i respons		0,0 [-38,8; 67,8] procentpoint
Relative forskelle	Stor merværdi	Nedre konfidensgrænse > 1,33 og risiko ≥ 5 %	
	Vigtig merværdi	Nedre konfidensgrænse > 1,11	
	Lille merværdi	Nedre konfidensgrænse > 1,00 og < 1,11	
	Ingen merværdi	Nedre konfidensgrænse < 1,00 og øvre konfidensgrænse > 1	1,00 [0,57; 1,75]
	Negativ merværdi	Øvre konfidensgrænse < 1	
Evidensens kvalitet	Moderat		

I reSURFACE 1 opnåede 74 % (229/309) og 6 % (9/155) af patienterne i behandling med hhv. tildrakizumab og placebo PASI 75 ved uge 28. I reSURFACE 2 var andelen af patienter 70 % (216/307) og 6 % (9/156) for hhv. tildrakizumab og placebo [11].

I VOYAGE 1 opnåede 91 % (300/329) og 6 % (10/174) af patienterne i behandling med hhv. guselkumab og placebo PASI 75 ved uge 24 [12], mens det samme var tilfældet for hhv. 89 % (442/496) og 8 % (20/248) i VOYAGE 2 [13].

Baseret på den indirekte statistiske sammenligning ved uge 24-28 er der beregnet en absolut forskel mellem tildrakizumab og guselkumab på 0,0 procentpoint. Den mindste klinisk relevante forskel på 15 procentpoint er dermed ikke opnået.

Den relative forskel er på 1,00 (0,57; 1,75), hvilket svarer til ingen merværdi ud fra de forhåndsdefinerede væsentlighedskriterier, idet den nedre grænse for konfidensintervallet er < 1, og den øvre grænse er > 1.

Fagudvalget bemærker, at en større andel af de patienter, der får guselkumab i VOYAGE-studierne, opnår PASI 75, sammenlignet med andelen af patienter, som opnår PASI 75 i reSURFACE-studierne. I VOYAGE 2-studiet er der dog også flere af patienterne i placebo-armen, som opnår PASI 75. Den meta-analyserede relative risiko for henholdsvis guselkumab vs. placebo (12,5, 95 % CI: [9,09; 16,67]) og tildrakizumab vs. placebo (12,5, 95 % CI: [7,69; 20,0]) er ens. Sammenlagt bliver der derfor ingen forskel mellem lægemidlerne i den indirekte analyse.

Samlet vurderer fagudvalget, at tildrakizumab har ingen **klinisk merværdi** vedr. PASI 75 sammenlignet med guselkumab (moderat evidenskvalitet).

PASI 90 (vigtig)

PASI 90 er reduktion i PASI-værdi med 90 %. Det ideelle langsigtede behandlingsmål for patienter med hudpsoriasis er en fuldstændig eller næsten fuldstændig afglatning af huden, hvorfor det er relevant også at lægge data for PASI 90 til grund for vurdering af klinisk effekt.

Tabel 4. Vurdering af klinisk merværdi: PASI 90 ved uge 24-28

	Forhåndsdefineret grundlag for vurdering		Medicinrådets vurdering
Absolutte forskelle	15 procentpoint forskel i respons		-14,4 procentpoint [-53.9; 90,6]
Relative forskelle	Stor merværdi	Nedre konfidensgrænse > 1,33 og risiko ≥ 5 %	
	Vigtig merværdi	Nedre konfidensgrænse > 1,11	
	Lille merværdi	Nedre konfidensgrænse > 1,00 og <1,11	
	Ingen merværdi	Nedre konfidensgrænse < 1,00 og Øvre konfidensgrænse > 1	0,81 [0,30; 2,17]
	Negativ merværdi	Øvre konfidensgrænse < 1	
Evidensens kvalitet	Moderat		

I reSURFACE 1 opnåede 48 % (147/309) og 3 % (4/155) af patienterne i behandling med hhv. tildrakizumab og placebo PASI 90 ved uge 28. I reSURFACE 2 var andelen af patienter 52 % (161/307) og 1 % (2/156) for hhv. tildrakizumab og placebo [11].

I VOYAGE 1 opnåede 80 % (264/329) og 3 % (5/174) af patienterne i behandling med hhv. guselkumab og placebo PASI 90 ved uge 24 [12], mens det samme var tilfældet for hhv. 75 % (373/496) og 2 % (6/248) i VOYAGE 2 [13].

Baseret på den indirekte statistiske sammenligning ved uge 24-28 er der beregnet en absolut forskel mellem tildrakizumab og guselkumab på -14,4 procentpoint til fordel for guselkumab. Den mindste klinisk relevante forskel på 15 procentpoint er dermed ikke opnået.

Den relative forskel er på 0,81 (0,30; 2,17), hvilket svarer til ingen merværdi ud fra de forhåndsdefinerede væsentlighedskriterier, idet den nedre grænse for konfidensintervallet er < 1, og den øvre grænse er > 1.

Samlet vurderer fagudvalget, at tildrakizumab har **ingen klinisk merværdi** vedr. PASI 90 sammenlignet med guselkumab (moderat evidenskvalitet).

Livskvalitet målt ved DLQI (vigtig)

For både tildrakizumab og guselkumab blev livskvalitet målt ved DLQI-spørgeskemaet. Fagudvalget havde i protokollen defineret den mindste klinisk relevante forskel som 15 procentpoint forskel i respons på andelen af patienter, som opnåede en DLQI-score på 0-1.

Tabel 5. Vurdering af klinisk merværdi: Livskvalitet målt ved DLQI 0-1 ved uge 24-28

	Forhåndsdefineret grundlag for vurdering	Medicinrådets vurdering
Absolutte forskelle	15 procentpoint forskel i respons	-30,6 procentpoint [-43,8; -4,8]
Evidensens kvalitet	Moderat	

I reSURFACE 1 opnåede 49 % (152/309) og 5 % (8/155) af patienterne i behandling med hhv. tildrakizumab og placebo DLQI 0-1 ved uge 28. I reSURFACE 2 var dette tilfældet for 51 % (157/307) og 8 % (12/156) af patienterne i behandling med hhv. tildrakizumab og placebo [11].

I VOYAGE 1 opnåede 59 % (195/329) og 4 % (7/174) af patienterne i behandling ved hhv. guselkumab og placebo DLQI 0-1 ved uge 24 [12], mens det samme var tilfældet for hhv. 57 % (283/496) og 3 % (8/248) i VOYAGE 2 [13].

Baseret på den indirekte statistiske sammenligning ved uge 24-28 er der beregnet en absolut forskel mellem tildrakizumab og guselkumab på -30,6 % til fordel for guselkumab. Den mindste klinisk relevante forskel på 15 % er dermed opnået. Fagudvalget bemærker dog, at i VOYAGE-studierne ekskluderes patienter med baseline DLQI = 0-1 i analysen af uge 24 data, mens dette ikke er tilfældet i reSURFACE-studierne. Denne eksklusion stiller guselkumab dårligere ved sammenligningen med tildrakizumab ved uge 24-28. Ydermere betoner fagudvalget, at DLQI ikke er et optimalt redskab til måling af livskvalitet for psoriasispatienter, og at der derfor tages konservativt forbehold for dette.

Fagudvalget vurderer på denne baggrund, at tildrakizumab har en **negativ klinisk merværdi** vedr. livskvalitet sammenlignet med guselkumab (moderat evidenskvalitet).

Alvorlige uønskede hændelser (SAEs) (kritisk)

SAEs omfatter enhver alvorlig hændelse eller bivirkning opstået i de kliniske studier ved behandling med lægemidlet.

Tabel 6. Vurdering af klinisk merværdi: Alvorlige uønskede hændelser (SAEs) ved uge 24-28

	Forhåndsdefineret grundlag for vurdering		Medicinrådets vurdering
Absolutte forskelle	5 procentpoint forskel		-1,0 procentpoint [-3,0;8,8]
Relative forskelle	Stor merværdi	Øvre konfidensgrænse < 0,75 og risiko ≥ 5 %	
	Vigtig merværdi	Øvre konfidensgrænse < 0,90	
	Lille merværdi	Øvre konfidensgrænse < 1,00	
	Ingen merværdi	Øvre konfidensgrænse > 1	0,72 [0,15;3,45]
	Negativ merværdi	Nedre konfidensgrænse > 1	
Evidensens kvalitet	Lav		

ANM: Første kolonne indeholder de i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen. Anden kolonne indeholder data fra ansøgningen, som indgår i Medicinrådets vurdering.

I reSURFACE 1 blev der ved uge 28 registreret SAEs for 4 % (11/309) og 1% (1/155) af patienterne i behandling med hhv. tildrakizumab og placebo. Det samme gjorde sig gældende for hhv. 4 % (13/307) og 3 % (4/156) af patienterne i reSURFACE 2 [11].

I VOYAGE 2 havde 4 % (18/496) og 1 % (3/248) af patienterne i behandling med hhv. guselkumab og placebo oplevet SAEs ved uge 28 [13]. SAEs blev ikke rapporteret i VOYAGE 1.

Baseret på den indirekte statistiske sammenligning ved uge 24-28 er der beregnet en absolut forskel mellem tildrakizumab og guselkumab på -1,0 procentpoint. Dermed oplevede 1,0 procentpoint færre patienter i behandling med tildrakizumab alvorlige uønskede hændelser sammenlignet med patienter i behandling med guselkumab. Den mindste klinisk relevante forskel på 5 procentpoint er dog ikke opnået.

Den relative forskel er på 0,72 (0,15; 3,45), hvilket svarer til ingen merværdi ud fra de forhåndsdefinerede væsentlighedskriterier, idet den nedre grænse for konfidensintervallet er < 1, og den øvre grænse er > 1.

Fagudvalget bemærker, at SAEer i reSURFACE 1 og 2 er opgjort som antallet af patienter med mindst én SAE i to tidsintervaller (uge 0-16 og uge 17-28) [11]. Patienter, som oplevede mindst én SAE i hvert af de to tidsintervaller, bliver derfor talt dobbelt i den samlede opgørelse af SAEs, hvilket stiller tildrakizumab dårligere i den statistiske sammenligning.

Samlet vurderer fagudvalget, at tildrakizumab har **ingen klinisk merværdi** vedr. alvorlige uønskede hændelser sammenlignet med guselkumab (lav evidenskvalitet).

Behandlingsophør (vigtig)

Behandlingsophør reflekterer, hvor mange patienter som afbryder behandlingen i de kliniske studier uanset årsag, herunder bivirkninger og manglende effekt. Effektmålet er medtaget som indikator for behandlingskvalitet og tolerancen ved langtidsbehandling.

I den endelige ansøgning ses der en betydelig heterogenitet (84,5 %) ift. graden af behandlingsophør mellem placebo-armene i reSURFACE 1 (0,13 %) og reSURFACE 2 (0,06 %) ved uge 28. Ansøger har indsendt analyser baseret på to forskellige statistiske modeller, *fixed effects* modellen der anvendes hvis der ikke er tegn på heterogenitet, og *random effects* modellen der anvendes hvis der er heterogenitet. Dermed anvendes analysen der er baseret på *random effects* modellen i vurderingen af dette effektmål.

Tabel 7. Vurdering af klinisk merværdi: Behandlingsophør ved uge 24-28

	Forhåndsdefineret grundlag for vurdering		Medicinrådets vurdering
Absolutte forskelle	15 procentpoint forskel		1,2 procentpoint [-1,9;13,2]
Relative forskelle	Stor merværdi	Øvre konfidensgrænse < 0,75 og risiko ≥ 5 %	
	Vigtig merværdi	Øvre konfidensgrænse < 0,90	
	Lille merværdi	Øvre konfidensgrænse < 1,00	
	Ingen merværdi	Øvre konfidensgrænse > 1	1,41 [0,36;5,56]
	Negativ merværdi	Nedre konfidensgrænse > 1	
Evidensens kvalitet	Meget lav		

I reSURFACE 1 blev der ved uge 28 registreret behandlingsophør for 13 % (41/309) og 6 % (9/155) af patienterne i behandling med hhv. tildrakizumab og placebo. I reSURFACE 2 var dette tilfældet for hhv. 6 % (18/307) og 9 % (14/156) af patienterne [11].

I VOYAGE 2 blev der ved uge 28 registreret behandlingsophør for 5 % (26/496) og 6 % (15/248) af patienterne i behandling med hhv. guselkumab og placebo [13]. Behandlingsophør blev ikke registreret i VOYAGE 1.

Baseret på den indirekte statistiske sammenligning ved uge 24-28 er der beregnet en absolut forskel mellem tildrakizumab og guselkumab på 1,2 % til fordel for guselkumab. Den mindste klinisk relevante forskel på 15 % er dermed ikke opnået.

Den relative forskel er 1,41 (0,36; 5,56), hvilket svarer til ingen merværdi ud fra de forhåndsdefinerede væsentlighedskriterier, idet den nedre grænse for konfidensintervallet er < 1, og den øvre grænse er > 1.

Samlet vurderer fagudvalget, at tildrakizumab har **ingen klinisk merværdi** vedr. behandlingsophør sammenlignet med guselkumab (meget lav evidenskvalitet).

PASI 90 i subpopulationer (vigtig)

For subpopulationerne af patienter med tidligere behandlingssvigt på biologiske lægemidler generelt samt specifikt på lægemidler med hhv. IL-23 og IL-12/23-target, ønsker fagudvalget at vurdere, om behandling med tildrakizumab har den ønskede effekt. En effekt af tildrakizumab i disse populationer vil potentielt betyde flere behandlingsmuligheder for patienterne.

Ansøger angiver dog, at der ikke foreligger publicerede data for de to subpopulationer. På denne baggrund vurderer fagudvalget, at den tilgængelige evidens ikke tillader en vurdering af den kliniske merværdi af tildrakizumab for subpopulationerne af patienter med behandlingssvigt på et biologisk lægemiddel generelt eller på et biologisk lægemiddel med samme target.

9.1.3 Evidensens kvalitet

Evidensens kvalitet for voksne (≥ 18 år) med moderat til svær plaque psoriasis er samlet set vurderet som værende **lav,** da evidensens kvalitet for det laveste vurderede kritiske effektmål, er **lav**. Overvejelser vedrørende evidensens kvalitet kan ses i bilag 1.

Indledningsvist blev lægemidlernes direkte sammenligninger med placebo vurderet. Overordnet var alle studier af høj kvalitet, og der blev ikke nedgraderet for risiko for bias (se bilag 1).

For alvorlige uønskede hændelser (SAEs) blev evidensens kvalitet nedjusteret for "*Imprecision"*, da konfidensintervallet er bredt og inkluderer både negativ og positiv merværdi. For effektmålet behandlingsophør er der nedjusteret både for "*Inconsistency"* (heterogeniteten i meta-analysen var høj) og for "*Imprecision"* (konfidensintervallet er bredt og inkluderer både negativ og positiv merværdi).

Da merværdien af tildrakizumab sammenlignet med guselkumab er vurderet via indirekte sammenligninger med placebo som fælles komparator, er der for alle effektmål nedjusteret for "*Indirectness*".

9.1.4 Konklusion for voksne (≥ 18 år) med moderat til svær plaque psoriasis

Fagudvalget vurderer, at tildrakizumab giver en **ingen klinisk merværdi** for **voksne (≥ 18 år) med moderat til svær plaque psoriasis** (lav evidenskvalitet).

Effektmål	**Vigtighed**	**Aggregeret kategori**	**Evidenskvalitet**
PASI 75	Kritisk	Ingen klinisk merværdi	Moderat
PASI 90	Vigtig	Ingen klinisk merværdi	Moderat
Livskvalitet	Vigtig	Negativ klinisk merværdi	Moderat
Alvorlige uønskede hændelser	Kritisk	Ingen klinisk merværdi	Lav
Behandlingsophør	Vigtig	Ingen klinisk merværdi	Meget lav
PASI 90 *Svigt på biologisk lægemiddel generelt*	Vigtig	Kan ikke vurderes	Kan ikke vurderes

PASI 90 *Svigt på biologisk lægemiddel med samme target*	Vigtig	Kan ikke vurderes	Kan ikke vurderes
Samlet kategori		**Ingen klinisk merværdi**	**Lav**

I den samlede vurdering vægter fagudvalget, at der ikke er fundet klinisk relevante forskelle mellem tildrakizumab og guselkumab for de kritiske effektmål PASI 75 og SAEs samt for de vigtige effektmål PASI 90 og behandlingsophør.

Fagudvalget bemærker, at ansøger som komparator har valgt guselkumab, som er en anden IL-23-hæmmer og er blandt de mest effektive psoriasis-præparater på markedet.

For det vigtige effektmål livskvalitet vurderer fagudvalget, at tildrakizumab giver en negativ klinisk merværdi sammenlignet med guselkumab. Fagudvalget bemærker dog, at DLQI er et generelt dermatologisk redskab, som ikke er optimalt til måling af psoriasis-specifikke gener. Vurderingen af dette effektmål er derfor forbundet med en vis usikkerhed.

Fagudvalget vurderer samlet set, at tildrakizumab og guselkumab har sammenlignelig effekt, og at tildrakizumab har ingen klinisk merværdi sammenlignet med guselkumab.

Evidenskvaliteten er lav for det kritiske effektmål ”alvorlige uønskede hændelser”, dermed er den samlede evidenskvalitet ligeledes vurderet at være lav.

10 Andre overvejelser

Ansøger har leveret oplysninger om de lægemiddelhåndteringsmæssige forhold, som specificeret i protokollen for tildrakizumab:

- Mulighed for behandlingspause.
- Mulighed for dosisreduktion/behandlingsintervalforlængelse. Fagudvalget ønsker specifikt en uddybning af 200 mg doseringsgruppen (”patienter med specifikke karakteristika bl.a. høj sygdomsbyrde og kropsvægt ≥ 90 kg”), herunder om der er forskelle i behandlingseffekt i forhold til 100 mg doseringen, og hvad der forstås ved ”høj sygdomsbyrde”. Derudover ønsker fagudvalget en estimering af andelen af patientpopulationen, som forventes at tilhøre gruppen med behov for 200 mg dosering.
- Forhold mellem initialdosis og vedligeholdelsesdosis.
- Vedligeholdelse af effekt mellem doseringer hver 12. uge.

Samlet set vurderer fagudvalget, at oplysninger om disse forhold ikke påvirker kategoriseringen af den kliniske merværdi af tildrakizumab.

Vurderingen af de enkelte forhold er belyst nedenfor:

Mulighed for behandlingspause

Der er ikke publiceret specifikke undersøgelser af mulighed for behandlingspause. Ansøger har indsendt upublicerede data til at besvare dette forhold, så disse er ikke indgået i fagudvalgets vurdering af tildrakizumab. Fagudvalget kan derfor ikke forholde sig til muligheden for behandlingspause ved behandling med tildrakizumab.

Mulighed for dosisreduktion/behandlingsintervalforlængelse

Der foreligger ikke publicerede data fra reSURFACE-studierne for dosisreduktion eller behandlingsintervalforlængelse ift. indikationen for tildrakizumab på 100 mg. Ansøger henviser dog til et fase 2b-studie (NCT01225731 [15]), hvor PASI 75 respondere ved uge 16 blev re-randomiseret til behandling med tildrakizumab 100 mg hver 12. uge eller tildrakizumab 25 mg hver 12. uge. Andelen af patienter, som ved uge 52 havde bibeholdt PASI 75 var 97 % og 70 % for hhv. tildrakizumab 100 mg og 25 mg, og forskellen i effekt mellem de to doser var statistisk signifikant ($p < 0{,}005$). Fagudvalget bemærker, at der er en stor del af patienterne, der har effekt på den lave dosis, og fagudvalget kunne have ønsket at se data for en dosis på 50 eller 75 mg. hver 12. uge

Ift. administration af 200 mg til patienter med specifikke karakteristika (høj sygdomsbyrde eller kropsvægt > 90 kg) angiver ansøger, at der i den generelle patientpopulation i fase 3-studierne ikke er påvist signifikante forskelle i hverken behandlingseffekt eller bivirkningsprofil ved behandling med tildrakizumab 100 mg sammenlignet med tildrakizumab 200 mg.

Definitionen af høj sygdomsbyrde er ikke klart angivet i hverken produktinformationen eller EPAR'en for tildrakizumab [10,16]. I EPAR'en angives det, at der ud fra farmakokinetiske studier ikke sås en sammenhæng mellem øget dosering af tildrakizumab og forbedret klinisk respons [16]. Ansøger har desuden indsendt upublicerede data til besvarelse af dette forhold, så disse er ikke indgået i fagudvalgets vurdering af tildrakizumab.

I forhold til dosisreduktion/behandlingsintervalforlængelse anbefaler fagudvalget at følge indikation for tildrakizumab, da der ikke er tilstrækkelige data for andre doseringsregimer.

Forhold mellem initialdosis og vedligeholdelsesdosis

Ansøger angiver, at den anbefalede dosis for tildrakizumab (100 mg ved uge 0, 4 og hver 12. uge derefter) blev fastlagt på baggrund af fase 2 og 3-studier [11,15], som viste den mest optimale behandlingseffekt ved behandling ved disse tidsintervaller. Data fra fase 2-studiet [15] såvel som halveringstiden for tildrakizumab (23,4 dage [16]) viste, at en hyppig dosering resulterede i hurtig behandlingseffekt. På denne baggrund blev en *loading* dosis ved uge 4 fastlagt. De to fase 3-studier [11] har fundet den anbefalede dosering både optimal, effektiv og sikker, og ansøger angiver, at lignende data ikke er tilgængeligt for en lavere doseringshyppighed inden for de første 12 uger af behandlingen.

Ansøger angiver endvidere, at med en halveringstid på 23,4 dage er en vedligeholdelsesdosis på tildrakizumab 100 mg nok til at holde serumkoncentrationer på det terapeutiske niveau. Dog er længere tids behandling nødvendig for at opnå det terapeutiske niveau, hvis der udelukkende gives en vedligeholdelsesdosis. Dosering i uge 4 resulterer i en fordobling af plasmaniveauer og dalværdier, hvilket svarer til niveauerne i *steady state* (defineret ved, at udskillelsen af lægemidlet er lig med indtagelsen).

I forhold til forholdet mellem initialdosis og vedligeholdelsesdosis angiver ansøger, at den anbefalede dosering ved uge 4 og 12 resulterer i den mest optimale effekt i hhv. initial- og vedligeholdelsesfasen. Fagudvalget er enige i dette, da der ikke er tilstrækkelige data på andre doseringsregimer.

Vedligeholdelse af effekt mellem doseringer hver 12. uge

Der er ikke publiceret data, der beskriver vedligeholdelsen af effekt mellem doseringer hver 12. uge. Fagudvalget kan derfor ikke forholde sig til vedligeholdelse af effekt mellem doseringer hver 12. uge ved behandling med tildrakizumab.

11 Fagudvalgets vurdering af samlet klinisk merværdi og samlet evidensniveau

Fagudvalget vurderer, at tildrakizumab til voksne (≥18 år) patienter med moderat til svær plaque psoriasis, som er kandidater til 2. generations immunmodulerende behandling (behandling med biologiske lægemidler) og ikke har psoriasisartropati giver:

- **Ingen klinisk merværdi** til patienter med moderat til svær plaque psoriasis sammenlignet med guselkumab. Evidensens kvalitet vurderes at være lav.
- **Den kliniske merværdi kan ikke vurderes** for subpopulationen af patienter med tidligere behandlingssvigt på biologiske lægemidler generelt.
- **Den kliniske merværdi kan ikke vurderes** for subpopulationen af patienter med tidligere behandlingssvigt på biologiske lægemidler med samme target.

12 Rådets vurdering af samlet klinisk merværdi og samlet evidensniveau

Medicinrådet vurderer, at tildrakizumab til voksne (≥18 år) patienter med moderat til svær plaque psoriasis, som er kandidater til 2. generations immunmodulerende behandling (behandling med biologiske lægemidler) og ikke har psoriasisartropati giver:

- **Ingen klinisk merværdi** til patienter med moderat til svær plaque psoriasis sammenlignet med guselkumab. Evidensens kvalitet vurderes at være lav.
- **Den kliniske merværdi kan ikke vurderes** for subpopulationen af patienter med tidligere behandlingssvigt på biologiske lægemidler generelt.
- **Den kliniske merværdi kan ikke vurderes** for subpopulationen af patienter med tidligere behandlingssvigt på biologiske lægemidler med samme target.

13 Relation til eksisterende behandlingsvejledning

Der foreligger en behandlingsvejledning fra RADS fra 2016 for dette terapiområde [6]. Medicinrådet har endnu ingen terapivejledning på området.

Den eksisterende RADS-behandlingsvejledning hviler på en netværksmetaanalyse, som ikke inkluderer tildrakizumab. Indtil en fornyet metaanalyse er udarbejdet, må tildrakizumab med baggrund i vurderingen i forhold til komparatoren guselkumab anses for at udgøre et klinisk ligestillet alternativ til adalimumab, secukinumab, ixekizumab og ustekinumab, som aktuelt alle anbefales som 1. linjebehandlinger til psoriasis uden ledgener samt guselkumab, brodalumab og certolizumab pegol, som er anbefalet af Medicinrådet. Dette er begrundet med samme effekt på hudsymptomer og sammenlignelig bivirkningsprofil.

14 Referencer

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15 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende psoriasis og psoriasis med ledgener

Forvaltningslovens § 4, stk. 2, har været anvendt i forbindelse med udpegning af medlemmer til dette fagudvalg.

Formand	**Indstillet af**
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Medlemmer	**Udpeget af**
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Tidligere medlemmer, som har taget del i processen: Lars Erik Bryld, overlæge, ph.d. og Lars Iversen, professor.

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Versionslog

Version	Dato	Ændring
1.0	13.03.2019	Godkendt af Medicinrådet.

16 Bilag 1: GRADE-evidensprofiler

16.1 Cochrane Risk of Bias

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

16.1.1 reSURFACE 1

Risiko for bias for studie: reSURFACE 1 (NCT01722331) Reich et al., 2017 [11]

Bias	Risk of bias	Elaboration
Selection bias		
Random sequence generation	**Low**	**Up to week 28 (part 1 and 2):** In part 1, patients were randomized in a 2:2:1 ratio to receive one of the three treatments: tildrakizumab 200 mg, tildrakizumab 100 mg or placebo. In part 2, the patients receiving active substances in part 1 continued with their treatment, while the patients receiving placebo were re-randomized to either tildrakizumab 200 mg or tildrakizumab 100 mg.
Allocation concealment	**Low**	The contract research organization (Parexel) generated computer-generated randomization sequences, and an interactive voice-response system and interactive web-response system was used by Parexel to allocate participants to groups. Investigators, participants, and study personnel were blinded to group allocation and remained blinded until completion of the studies.
Performance bias: blinding of participants and personnel. Assessment made for class of outcomes.		
Patient-reported outcomes: PASI, DLQI	**Low**	A double-masking technique was used, in which tildrakizumab and its matching placebo were identical in appearance and packaging. Additional placebo doses were administered to maintain masking.
Objective outcomes: Adverse events, Withdrawal irrespective of reason	**Low**	Ibid.
Detection bias: blinding of outcome assessment. Assessment made for class of outcomes.		
Patient-reported outcomes: PASI, DLQI	**Low**	The team doing the analysis was blinded until the database was locked (while no interim analyses were done).
Objective outcomes Adverse events, Withdrawal irrespective of reason	**Low**	Ibid.
Attrition bias: incomplete outcome data. Assessment made for class of outcomes.	**Low**	772 patients underwent randomization, while over 96 % (744 patients) completed the part 1 and 88 % (676 patients) completed the part 2.
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	**Low**	Overall risk of bias judged low.

16.1.2 reSURFACE 2

Risiko for bias for studie: reSURFACE 2 (NCT01729754) Reich et al., 2017 [11]

Bias	Risk of bias	Elaboration
Selection bias		
Random sequence generation	**Low**	**Up to week 28 (part 1 and 2):** In part 1, patients were randomized in a 2:2:1:2 ratio to receive one of the four treatments: tildrakizumab 200 mg, tildrakizumab 100 mg, placebo, or etanercept 50 mg. In part 2, the placebo group was re-randomised (1:1) to tildrakizumab 200 mg or 100 mg, while the patients receiving active substances in part 1 continued with their treatment.
Allocation concealment	**Low**	The contract research organization (Parexel) generated computer-generated randomization sequences, and an interactive voice-response system and interactive web-response system was used by Parexel to allocate participants to groups. Investigators, participants, and study personnel were blinded to group allocation and remained blinded until completion of the studies.
Performance bias: blinding of participants and personnel. Assessment made for class of outcomes.		
Patient-reported outcomes: PASI, DLQI	**Low**	A double-masking technique was used, in which tildrakizumab and its matching placebo or etanercept and its matching placebo were identical in appearance and packaging. Additional placebo doses were administered to maintain masking.
Objective outcomes: Adverse events, Withdrawal irrespective of reason	**Low**	Ibid.
Detection bias: blinding of outcome assessment. Assessment made for class of outcomes.		
Patient-reported outcomes: PASI, DLQI	**Low**	The team doing the analysis was blinded until the database was locked (while no interim analyses were done).
Objective outcomes Adverse events, Withdrawal irrespective of reason	**Low**	Ibid.
Attrition bias: incomplete outcome data. Assessment made for class of outcomes.	**Low**	1090 patients underwent randomization, while over 98 % (1076 patients) completed the part 1 and 91 % (995 patients) completed the part 2.
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	**Low**	Overall risk of bias judged low.

16.1.3 VOYAGE 1

Risiko for bias for studie: VOYAGE 1 (NCT02207231) Blauvelt et al., 2017 [12]

Bias	Risk of bias	Elaboration
Selection bias		
Random sequence generation	**Low**	Patients were randomly assigned in a 2:1:2 ratio to receive guselkumab, placebo followed by guselkumab or adalimumab.
Allocation concealment	**Low**	Randomization generated via permuted block method. Central randomization was implemented using an interactive www response system.
Performance bias: blinding of participants and personnel. Assessment made for class of outcomes.		
Patient-reported outcomes: PASI, DLQI	**Low**	To maintain the blind, matching placebos were used.
Objective outcomes: Adverse events, Withdrawal irrespective of reason	**Low**	Ibid.
Detection bias: blinding of outcome assessment. Assessment made for class of outcomes.		
Patient-reported outcomes: PASI, DLQI	**Low**	Nothing suggest blinding was unveiled during study.
Objective outcomes Adverse events, Withdrawal irrespective of reason	**Low**	Ibid.
Attrition bias: incomplete outcome data. Assessment made for class of outcomes.	**Unclear**	All randomized patients were included in the primary and secondary efficacy analyses; data analyzed by randomized treatment group. Safety analyses included all patients who received ≥ 1 dose of guselkumab. Patients who discontinued study agent due to lack of efficacy or an AE worsening or who started a protocol-prohibited psoriasis treatment were considered nonresponders (binary endpoints) or had baseline values carried over (continuous endpoints). Other patients with missing data were considered nonresponders for binary endpoints (non-responder imputation). Because of insufficient information on procedure and multiple imputation not used, risk of bias is judged unclear. DLQI response was specifically analyzed for patients with DLQI > 1 at baseline (n = 320 for guselkumab, n = 319 for adalimumab), as pre-specified in study protocol (clinicaltrials.gov). We consider this to be a deviation from standard good practice, however due to only few patients being excluded from these analyses (3-4,5 %) we do not consider that it has affected the results substantially.
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	**Low**	Overall risk of bias judged low.

16.1.4 VOYAGE 2

Risiko for bias for studie: VOYAGE 2 NCT02207244 Reich et al., 2017 [13]

Bias	Risk of bias	Elaboration
Selection bias		
Random sequence generation	**Low**	Patients were randomized 2:1:1 to guselkumab; placebo followed by guselkumab; or adalimumab. At week 28, guselkumab-treated patients achieving PASI 90 (responders) were rerandomized in a 1:1 ratio to guselkumab or placebo. Patients were randomized using a permuted block method at baseline.
Allocation concealment	**Low**	Central randomization occurred using an interactive web-based response system.
Performance bias: blinding of participants and personnel. Assessment made for class of outcomes.		
Patient-reported outcomes: PASI, DLQI	**Low**	To maintain the blind, both guselkumab and adalimumab placebos were administered as necessary. Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) (ClinicalTrials.gov).
Objective outcomes: Adverse events, Withdrawal irrespective of reason	**Low**	Ibid.
Detection bias: blinding of outcome assessment. Assessment made for class of outcomes.		
Patient-reported outcomes: PASI, DLQI	**Low**	Adequate blinding. Nothing suggests that masking/blinding was unveiled during the study.
Objective outcomes Adverse events, Withdrawal irrespective of reason	**Low**	Ibid.
Attrition bias: incomplete outcome data. Assessment made for class of outcomes.	**Unclear**	All randomized patients were included in the primary analysis and some secondary efficacy analyses according to their assigned treatment group. Safety analyses included all patients receiving at least 1 study agent administration (≥ 1 dose of guselkumab). Patients who discontinued treatment due to lack of efficacy or an adverse event [AE] of worsening of psoriasis, or started a protocol-prohibited medication/therapy to improve psoriasis were considered treatment failures. Patients meeting treatment failure criteria before week 16 and patients not returning for week-16 evaluation were considered nonresponders for the week-16 primary end points. Statistical handling of missing data/nonresponders is not clarified. When assessing DLQI response, the percentage of participants who achieved a DLQI score = 0 or 1 was analyzed for patients with baseline DLQI > 1 only (n = 491 for guselkumab; n = 246 at week 16), as specified in the study protocol (Clinical Trials.gov). We consider this to be a deviation from good clinical practice, however, as only a few patients were excluded from these analyses (0.8-1 %), we do not consider this to have substantially affected the results.

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	**Low**	Overall risk of bias judged low.

16.2 GRADE-evaluering af evidenskvaliteten til vurdering af den kliniske merværdi af tildrakizumab

Hvad er den kliniske merværdi af tildrakizumab til voksne patienter med moderat til svær plaque psoriasis, som er kandidater til 2. generations immunmodulerende behandling og ikke har psoriasisartropati?

16.2.1 GRADE evidensprofil, tildrakizumab vs. placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**tildrakizumab**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
PASI75												
2	randomised trials	not serious	not serious	not serious	not serious	none	445/616 (72.2%)	18/311 (5.8%)	**RR 12.50** (7.69 to 20.00)	**666 more per 1.000** (from 387 more to 1.000 more)	⊕⊕⊕⊕ HIGH	CRITICAL
PASI90												
2	randomised trials	not serious	not serious	not serious	not serious	none	308/616 (50.0%)	6/311 (1.9%)	**RR 25.00** (11.11 to 50.00)	**463 more per 1.000** (from 195 more to 945 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
DLQI												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**tildrakizumab**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
2	randomised trials	not serious	not serious	not serious	not serious	none	309/616 (50.2%)	20/311 (6.4%)	**RR 7.69** (5.00 to 12.50)	**430 more per 1.000** (from 257 more to 740 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Alvorlige uønskede hændelser												
2	randomised trials	not serious	not serious	not serious	serious [a]	none	24/616 (3.9%)	5/311 (1.6%)	**RR 2.17** (0.82 to 5.88)	**19 more per 1.000** (from 3 fewer to 78 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Behandlingsophør												
2	randomised trials	not serious	serious [b]	not serious	serious [a]	none	59/616 (9.6%)	23/311 (7.4%)	**RR 1.22** (0.36 to 4.17)	**16 more per 1.000** (from 47 fewer to 234 more)	⊕⊕◯◯ LOW	IMPORTANT

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

Explanations

a. Konfidensintervallet inkluderer både negativ og positiv merværdi.

b. Heterogeniteten i metanalysen var høj (I^2 = 84,5 %).

16.2.2 GRADE evidensprofil, guselkumab vs. placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**guselkumab**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
PASI75												
2	randomised trials	not serious	not serious	not serious	not serious	none	742/825 (89.9%)	30/422 (7.1%)	**RR 12.50** (9.09 to 16.67)	**818 more per 1.000** (from 575 more to 1.000 more)	⊕⊕⊕⊕ HIGH	CRITICAL
PASI90												
2	randomised trials	not serious	not serious	not serious	not serious	none	637/825 (77.2%)	11/422 (2.6%)	**RR 33.33** (16.67 to 50.00)	**843 more per 1.000** (from 408 more to 1.000 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
DLQI												
2	randomised trials	not serious	not serious	not serious	not serious	none	478/825 (57.9%)	15/422 (3.6%)	**RR 16.67** (10.00 to 50.00)	**557 more per 1.000** (from 320 more to 1.000 more)	⊕⊕⊕⊕ HIGH	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**guselkumab**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Alvorlige uønskede hændelser												
2	randomised trials	not serious	not serious	not serious	serious [a]	none	18/496 (3.6%)	3/248 (1.2%)	**RR 3.03** (0.89 to 10.00)	**25 more per 1.000** (from 1 fewer to 109 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Behandlingsophør												
2	randomised trials	not serious	not serious	not serious	serious [a]	none	26/496 (5.2%)	15/248 (6.0%)	**RR 1.19** (0.74 to 1.96)	**11 more per 1.000** (from 16 fewer to 58 more)	⊕⊕⊕◯ MODERATE	IMPORTANT

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

Explanations
a. Konfidensintervallet indeholder både negativ og positiv merværdi.

Application for the assessment of clinically added value of Ilumetri for treatment of moderate to severe plaque psoriasis

Version 1.1 2018-12-17

Version log

1.0	*2018-12-10*	*Original application*
1.1	*2018-12-17*	*Friday December 14, 2018 The Medicines Council requested an update:* *-RR estimates inverted and ARR added for all outcomes* *-Appendix F added showing results of the indirect analysis of DLQI 0/1 responder rate based on alternative definition of population*

Contents

1 Basic information

TABLE 1 CONTACT INFORMATION

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TABLE 2 OVERVIEW OF THE PHARMACEUTICAL

Proprietary name	Ilumetri
Generic name	Tildrakizumab
Marketing authorization holder in Denmark	Almirall, S.A. Ronda General Mitre, 151 08022 Barcelona Spanien
ATC code	L04AC17
Pharmacotherapeutic group	Immunosuppressants, interleukin inhibitors
Active substance(s)	Each pre-filled syringe contains 100 mg of tildrakizumab in 1 mL.
Pharmaceutical form(s)	Ilumetri 100 mg solution for injection in pre-filled syringe
Mechanism of action	Tildrakizumab is a humanized IgG1/k monoclonal antibody that specifically binds to the p19 protein subunit of the interleukin-23 (IL-23) cytokine without binding to IL-12 and inhibits its interaction with the IL-23 receptor.

	IL-23 is a naturally occurring cytokine that is involved in inflammatory and immune responses. Tildrakizumab inhibits the release of proinflammatory cytokines and chemokines.
Dosage regimen	The recommended dose of Ilumetri is 100 mg by subcutaneous injection at week 0, and 4 and every 12th week thereafter. In patients with certain characteristics (e.g. high disease burden, body weight ≥ 90 kg) 200 mg may provide greater efficacy Consideration should be given to discontinuing treatment in patients who have shown no response after 28 weeks of treatment. Some patients with initial partial response may subsequently improve with continued treatment beyond 28 weeks.
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Ilumetri is indicated for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy.
Other approved therapeutic indications	Not applicable
Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	Not applicable
Packaging – types, sizes/number of units, and concentrations	100 mg pre-filled syringe. Pack of 1
Orphan drug designation	Not applicable

2 Abbreviations

ADA	Adalimumab
AE	Adverse Event
ARR	Absolute risk reduction
BIW	Twice a week
BMI	Body mass index
BSA	Body surface area
CASPAR	Classification Criteria for Psoriatic Arthritis
CI	Confidence interval
DLQI	Dermatology Life Quality Index
FE	Fixed effects
Gus	Guselkumab
IGA	Investigators global assessment
IL	Interleukin
Inf	Infinite
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IV	Intravenous

kg	Kilogram
NA	Not applicable / Not available
NAPSI	Nail psoriasis severity index
NR	Non-responders/ not reported
NRI	Non-responder imputation
p.p.	Percentage points
PASI	Psoriasis Area Sensitivity Index
PBO	Placebo
PGA	Physicians' global assessment
PR	Partial responders
PsA	Psoriatic arthritis.
PSSD	Psoriasis signs and symptoms diary
Q12W	Every 12 weeks
Q8W	Every 8 weeks
qow	Every other week
R	Responders
RE	Responders
RE	Random effects
s.c.	Subcutaneous
SAE	Serious Adverse Event
SD	Standard deviation
TNF-a	Tumor necrosis factor-alpha
USA	United States of America

3 Summary

Introduction: This application serves as the basis for the assessment of added clinical value of tildrakizumab (Ilumetri®) for adult patients with moderate to severe plaque psoriasis (without psoriasis arthropathy), who are candidates for second generation immunomodulating therapy. The application form at hand focuses on the clinical aspects of tildrakizumab, and is supported by a separate health economic analysis.

Tildrakizumab is a humanized IgG1/k monoclonal antibody with high affinity for the p19 of interleukin (IL) 23 [1]. By binding to IL-23, tildrakizumab blocks the interaction between this cytokine and the IL-23 receptor [1]. Recent evidence has established a pivotal role of the T-helper cell 17 inflammation pathway in psoriasis, and by blocking IL-23, tildrakizumab provides upstream inhibition of this cascade [2]. A European marketing authorization for Ilumetri was granted by the European Commission on 17th of September, 2018.

Method: Almirall chose guselkumab (Tremfya) as comparator for this application because the two products have identical mechanism of action, almost similar dosing regimen as well as comparable time period for clinical development. The literature search identified five relevant phase III trials (including one trial in a Japanese population) that evaluated the safety and efficacy of either tildrakizumab 100 mg Q12W or guselkumab 100 mg Q8W. A Bucher indirect comparison was undertaken using placebo as common comparator at week 24-28 and week 12-16. The Japanese study was only included in a sensitivity analysis since it was deemed incomparable to the other trials due to differences in baseline characteristics. The treatments were narratively compared at ~1 year of therapy. Finally, a subgroup PASI 90 analysis based on previous treatment experience was conducted.

Results: At week 24-28, the analysis did not reveal any statistically significant difference between guselkumab and tildrakizumab for PASI 75, PASI 90, SAE and rate of discontinuations. For DLQI 0/1 the risk ratio was statistically significant in favor of guselkumab, however the clinical relevance of this finding is uncertain. A sensitivity analysis of the comparative treatment effects on DLQI was performed comparing DLQI change from baseline as the outcome measure. This analysis showed no statistically significant differences in treatment effect on patient quality of life. The week 12-16 analysis as well as further sensitivity analysis yielded identical findings.

The PASI 90 response to tildrakizumab was equal between patients with previous exposure to biologics and biologic naïve patients. No data exists for patients who have previously failed on a biologic including treatments that target IL-23.

Comparison beyond week 28 was obscured by major differences in trial design. However, the two treatments appeared to display similar high maintenance of response throughout ~1 year of therapy, and the risk of serious adverse events was very low and equal for both treatments over this time period.

Conclusion: For all critical endpoints (PASI 75 and SAEs) as well as all but one important endpoint, no difference was detected between tildrakizumab and guselkumab. Findings in favour of guselkumab in terms of DLQI responders were not supported in sensitivity analyses using change in DLQI scores as treatment effect, thereby questioning the clinical relevance of the former result. Long term efficacy and safety also appeared equal between the two treatments. These strong clinical evidence as well as convenient dosing regimen position tildrakizumab as an ideal first-line treatment option for adult psoriasis patients, who are candidates for second generation immunomodulating therapy.

Finally, Almirall has addressed a number of relevant questions posed by the Medical Council pertaining to the clinical use of tildrakizumab in a Danish setting using all relevant published and unpublished data.

4 Literature search

Databases and search strategy

In the protocol from the Expert Committee for psoriasis, Almirall was given the freedom to choose a comparator for this assessment among the group of current first-line 2nd generation immunomodulatory therapies. Due the identical mechanism of action, similar dosing regimen as well as comparable time period for clinical development, Almirall chose guselkumab (Tremfya) as comparator.

Searches were undertaken on the 20th November 2018. Details on the search terms and selection process is available in Appendix A. 95 records were retrieved from MEDLINE and 89 records from CENTRAL. Following de-duplication, 154 unique records were assessed for relevance. Records where scanned to identify phase III, randomized controlled trials reporting on outcomes of relevance to the scientific questions using guselkumab as the comparator. Details on the eligibility criteria applied is available in Appendix A.

A PRISMA study flow diagram (Appendix A, Figure A.2) shows the number of records identified by the search and the numbers excluded at various selection stages. Full texts of potentially relevant studies were obtained and assessed in detail for relevance to the review's eligibility criteria. This produced a list of eligible and ineligible studies. Where results for one study were reported in more than one paper, all related papers were identified and grouped together to ensure that participants in individual studies were only included once. Documents excluded following full-text review are listed in Appendix A (table A.3) along with the reason for exclusion.

4.1 Relevant studies

Five studies (reported in ten documents) met the eligibility criteria for the systematic review and indirect treatment comparison:

- 2 trials of tildrakizumab (Re-SURFACE 1 and 2 [3])
- 3 trials of guselkumab (VOYAGE 1 and 2 [4, 5], and Ohtsuki 2018 [6])

The Ohtsuki trial only included Japanese patients and will only be considered in the sensitivity analysis (appendix D). The rationale to exclude the Japanese trial from the main analysis is given in 5.1.1.

TABLE 4.1: RELEVANT STUDIES INCLUDED IN THE ASSESSMENT

References (title, author, journal, year)	**Trial name**	**NCT number**	**Dates of study**
Tildrakizumab versus placebo or etanercept for chronic plaque psoriasis (reSURFACE 1 and reSURFACE 2): results from two randomised controlled, phase 3 trials **Reich K, Papp KA, Blauvelt A, Tyring SK, Sinclair R, Thaci D, et al.** *Lancet. 2017;390(10091):276-88*.*	reSURFACE 1	NCT01722331	**Start:** 2012-12-06 **1˚ completion:** 2014-06-20 **Est. completion:** 2019-10-04
	reSURFACE 2	NCT01729754	**Start:** 2013-02-05 **1˚ completion:** 2014-12-20 **Est. completion:** 2020-12-04
Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment	VOYAGE 1	NCT02207231	Start 2014-11-26 **1˚ completion:** 2015-09-29

References (title, author, journal, year)	**Trial name**	**NCT number**	**Dates of study**
of patients with moderate to severe psoriasis: Results from the phase III, double-blinded, placebo- and active comparator-controlled VOYAGE 1 trial. **Blauvelt A, Papp KA, Griffiths CEM, Randazzo B, Wasfi Y, Shen Y-K, et al.** *J Am Acad Dermatol. 2017;76(3):405-17.* Long-Term Efficacy of Guselkumab for the Treatment of Moderate-to-Severe Psoriasis: Results from the phase 3 VOYAGE 1 Trial Through Two Years. **Griffiths CEM, Papp KA, Kimball AB, Randazzo B, Song M, Li S, et al.** *J Drugs Dermatol. 2018;17(8):826-32.* Patient-reported symptoms and signs of moderate-to-severe psoriasis treated with guselkumab or adalimumab: results from the randomized VOYAGE 1 trial. **Papp KA, Blauvelt A, Kimball AB, Han C, Randazzo B, Wasfi Y, et al.** *J Eur Acad Dermatol Venereol. 2018;32(9):1515-22.* Efficacy of Guselkumab Compared With Adalimumab and Placebo for Psoriasis in Specific Body Regions: A Secondary Analysis of 2 Randomized Clinical Trials. **Foley P, Gordon K, Griffiths CEM, Wasfi Y, Randazzo B, Song M, et al.** *JAMA Dermatol. 2018;154(6):676-83.* Efficacy of guselkumab in subpopulations of patients with moderate-to-severe plaque psoriasis: a pooled analysis of the phase III VOYAGE 1 and VOYAGE 2 studies. **Gordon KB, Blauvelt A, Foley P, Song M, Wasfi Y, Randazzo B, et al.** *Br J Dermatol. 2018;178(1):132-39.* Improvement in Patient-Reported Outcomes (Dermatology Life Quality Index and the Psoriasis Symptoms and Signs Diary) with Guselkumab in Moderate-to-Severe Plaque Psoriasis: Results from the phase III VOYAGE 1 and VOYAGE 2 Studies. **Armstrong AW, Reich K, Foley P, Han C, Song M, Shen Y-K, et al.** *Am J Clin Dermatol. 2018;12:12.*			**Est. completion:** 2020-07-20
Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the treatment of patients with moderate to severe psoriasis with randomized withdrawal and retreatment: Results from the phase III, double-blind, placebo- and active comparator-controlled VOYAGE 2 trial. **Reich K, Armstrong AW, Foley**	VOYAGE 2	NCT02207244	**Start:** 2014-11-03 **1˚ completion:** 2015-10-01 **Est. completion:** 2020-07-15

References (title, author, journal, year)	**Trial name**	**NCT number**	**Dates of study**
P, Song M, Wasfi Y, Randazzo B, et al. *J Am Acad Dermatol. 2017;76(3):418-31.* Anxiety and depression in patients with moderate-to-severe psoriasis and comparison of change from baseline after treatment with guselkumab vs. adalimumab: results from the Phase 3 VOYAGE 2 study. **Gordon KB, Armstrong AW, Han C, Foley P, Song M, Wasfi Y, et al.** J Eur Acad Dermatol Venereol. 2018;32(11):1940-49. Efficacy of Guselkumab Compared With Adalimumab and Placebo for Psoriasis in Specific Body Regions: A Secondary Analysis of 2 Randomized Clinical Trials. **Foley P, Gordon K, Griffiths CEM, Wasfi Y, Randazzo B, Song M, et al.** *JAMA Dermatol. 2018;154(6):676-83.* Efficacy of guselkumab in subpopulations of patients with moderate-to-severe plaque psoriasis: a pooled analysis of the phase III VOYAGE 1 and VOYAGE 2 studies. **Gordon KB, Blauvelt A, Foley P, Song M, Wasfi Y, Randazzo B, et al.** *Br J Dermatol. 2018;178(1):132-39.* Improvement in Patient-Reported Outcomes (Dermatology Life Quality Index and the Psoriasis Symptoms and Signs Diary) with Guselkumab in Moderate-to-Severe Plaque Psoriasis: Results from the phase III VOYAGE 1 and VOYAGE 2 Studies. **Armstrong AW, Reich K, Foley P, Han C, Song M, Shen Y-K, et al.** *Am J Clin Dermatol. 2018;12:12.*			
Guselkumab, an anti-interleukin-23 monoclonal antibody, for the treatment of moderate to severe plaque-type psoriasis in Japanese patients: Efficacy and safety results from a phase 3, randomized, double-blind, placebo-controlled study. **Ohtsuki M, Kubo H, Morishima H, Goto R, Zheng R, Nakagawa H.** *J Dermatol. 2018;45(9):1053-62.*	Ohtsuki 2018	NCT02325219	**Start:** 2014-12-19 **1˚ completion:** 2016-03-02 **Est. completion:** 2019-02-28

*.Erratum appears in Lancet. 2017 Jul 15;390(10091):230

4.2 Main characteristics of included studies

Characteristics of included studies are presented in section 5.1.1

5 Clinical questions

5.1 What is the clinical added value of tildrakizumab in adult patients with moderate to severe plaque psoriasis, who are candidates for second generation immunomodulating treatment and who do not have psoriasis arthropathy?

5.1.1 Presentation of relevant studies

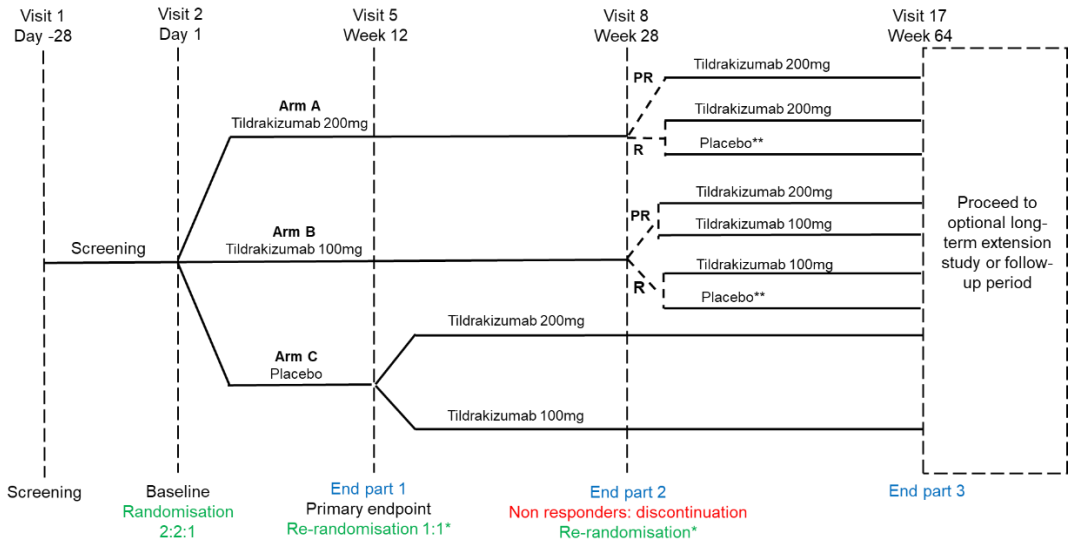
The study designs, methods, outcomes, patient populations are summarised in Table 5.1 to Table 5.3.

reSURFACE 1 and reSURFACE 2

reSURFACE 1 was a 64-week, phase III, randomized, placebo-controlled, parallel design study to evaluate the efficacy and safety/tolerability of subcutaneous (s.c.) tildrakizumab, followed by an optional Long-Term Safety Extension Study, in patients with moderate-to-severe chronic plaque psoriasis.

The study consisted of a 4-week screening period, a 12-week Part 1 period (Week 0 to Week 12), a 16-week Part 2 period (Week 12 to Week 28), a 36-week Part 3 period (Week 28 to Week 64), an optional 4 year long term extension, and a 20-week follow-up period (Figure 5.1).

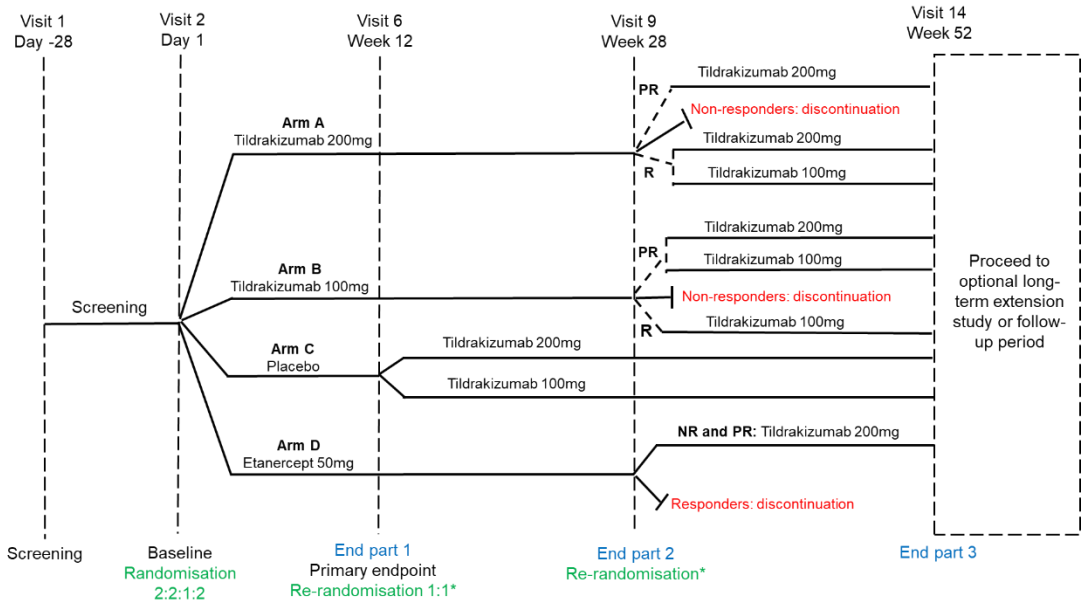
FIGURE 5.1 RESURFACE 1 DESIGN



Non-responders (NR: who achieved <50% improvement in PASI response from baseline) were discontinued at Week 28. Partial responders (PR) were subjects who achieved ≥50% but <75% improvement in PASI response from baseline. Responders (R) were subjects who achieved ≥75% improvement in PASI response from baseline. * Participants in the placebo group (Arm C) were re-randomized (1:1) at Week 12 to receive either tildrakizumab 200 mg or 100 mg; participants in the tildrakizumab 100 mg and 200 mg groups were re-randomized at Week 28 depending on whether they had a response or partial response to treatment. ** Participants in Arms A and B who relapsed on placebo between Week 28 and Week 64 were re-initiated on their initial treatment with tildrakizumab (100 mg or 200 mg). Adapted from Reich et al 2017, supplementary appendix. [3]

reSURFACE 2 was a phase III, randomized, double-blind, active-comparator and placebo-controlled, parallel-group trial to evaluate the efficacy and safety/tolerability of tildrakizumab s.c., followed by an optional long-term safety extension study, in patients with moderate-to-severe chronic plaque psoriasis.

FIGURE 5.2 RESURFACE 2 DESIGN



NRs were subjects who achieved <50% improvement in PASI response from baseline. PR were subjects who achieved ≥50% but <75% improvement in PASI response from baseline. R were subjects who achieved ≥75% improvement in PASI response from baseline. In Arms A and B, NRs were discontinued at Week 28, whereas in Arm D, Rs were discontinued at Week 28 *Participants in the placebo group (Arm C) were re-randomized (1:1) at Week 12 to receive either tildrakizumab 200 mg or 100 mg; participants in the tildrakizumab 200 mg group (Arm A) and 100 mg group (Arm B) were re-randomized at Week 28 depending on whether they had a response or partial response to treatment. In Arm D, there was a 4-week washout period in NR and PR patients on etanercept before they started tildrakizumab 200 mg. Abbreviations: NR: non-responders; R: responders. Adapted from Reich et al 2017, supplementary appendix [3]

Table 5.2 shows the list of primary, secondary endpoints and planned subgroup analyses. The co-primary endpoints in both reSURFACE 1 and reSURFACE were proportions of patients with PASI 75 response and PGA score of “clear” or “minimal”, with at least a 2 grade reduction from baseline at Week 12. The secondary endpoints included PASI 75, 90, 100 and PGA at different time points as well as patient reported outcomes e.g. DLQI at different timepoints. One of the key secondary endpoints in reSURFACE 2 was to assess the efficacy of tildrakizumab compared to etanercept.

Table 5.1 lists the inclusion and exclusion criteria for the trials and Table 5.3 shows the baseline characteristics of patients included in the two trials. Baseline DLQI score appear equal to Danish patients initiating second-generation immunomodulatory anti-psoriasis treatment[7], whereas the initial PASI score seems similar to recent phase III trials for other biologics[5, 8]. Of note, 23 % of participants had previously attempted biological treatment in reSURFACE 1, and 12-13 % in reSURFACE 2.

Consort diagrams for both trials can be found in [3].

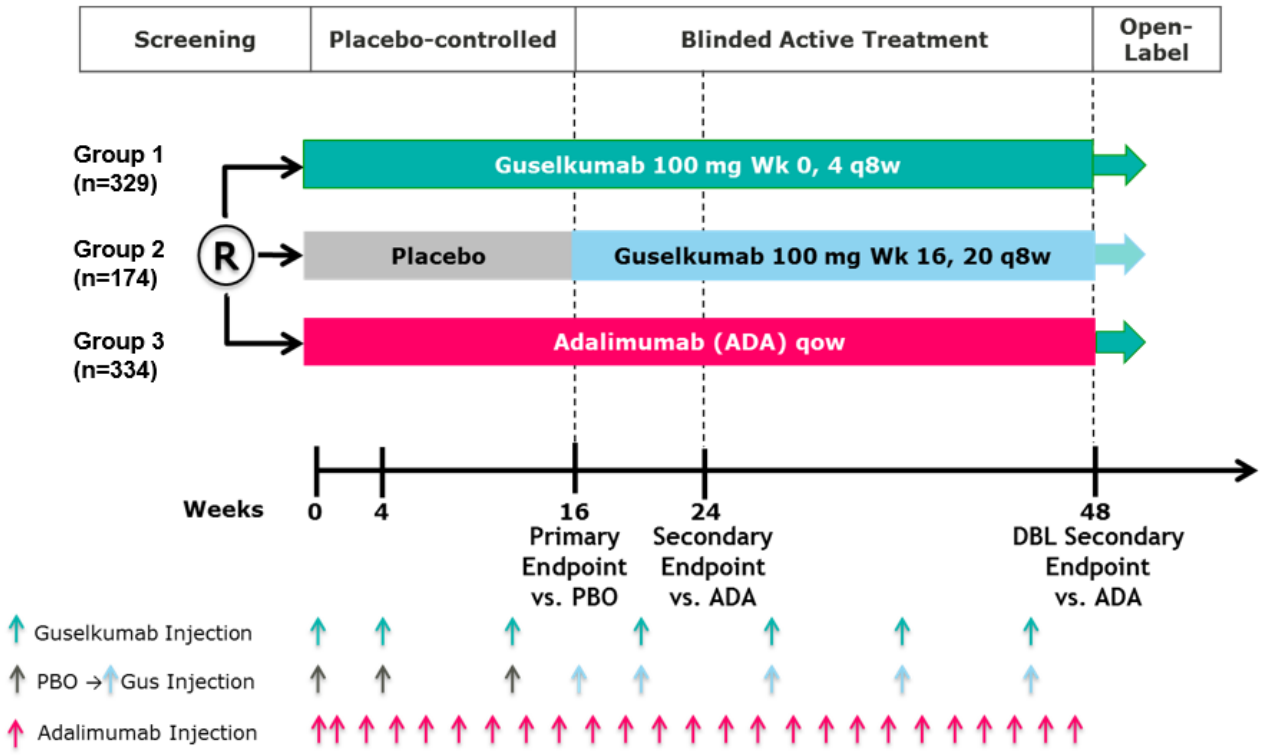
VOYAGE 1 and VOYAGE 2

VOYAGE 1 and VOYAGE 2 are placebo- and active-comparator controlled studies with identical study designs through Week 24, to assess the efficacy, safety, pharmacokinetics, and immunogenicity of guselkumab in subjects with moderate to severe plaque psoriasis who are candidate for phototherapy or systemic therapy (Figure 5.3 and Figure 5.4). The designs diverge beyond Week 24, with each study addressing a distinct aspect of psoriasis treatment between Week 24 and 48. In the VOAYGE 1 study, treatment of subjects randomized to guselkumab and adalimumab continued through Week 48 to allow for an evaluation of the durability of response and comparative efficacy and safety during one year of

continuous treatment. VOYAGE 2 incorporated randomized withdrawal and retreatment design elements from Week 28 and beyond, to assess the efficacy and safety of guselkumab maintenance dosing relative to withdrawal of treatment in PASI 90 responders.

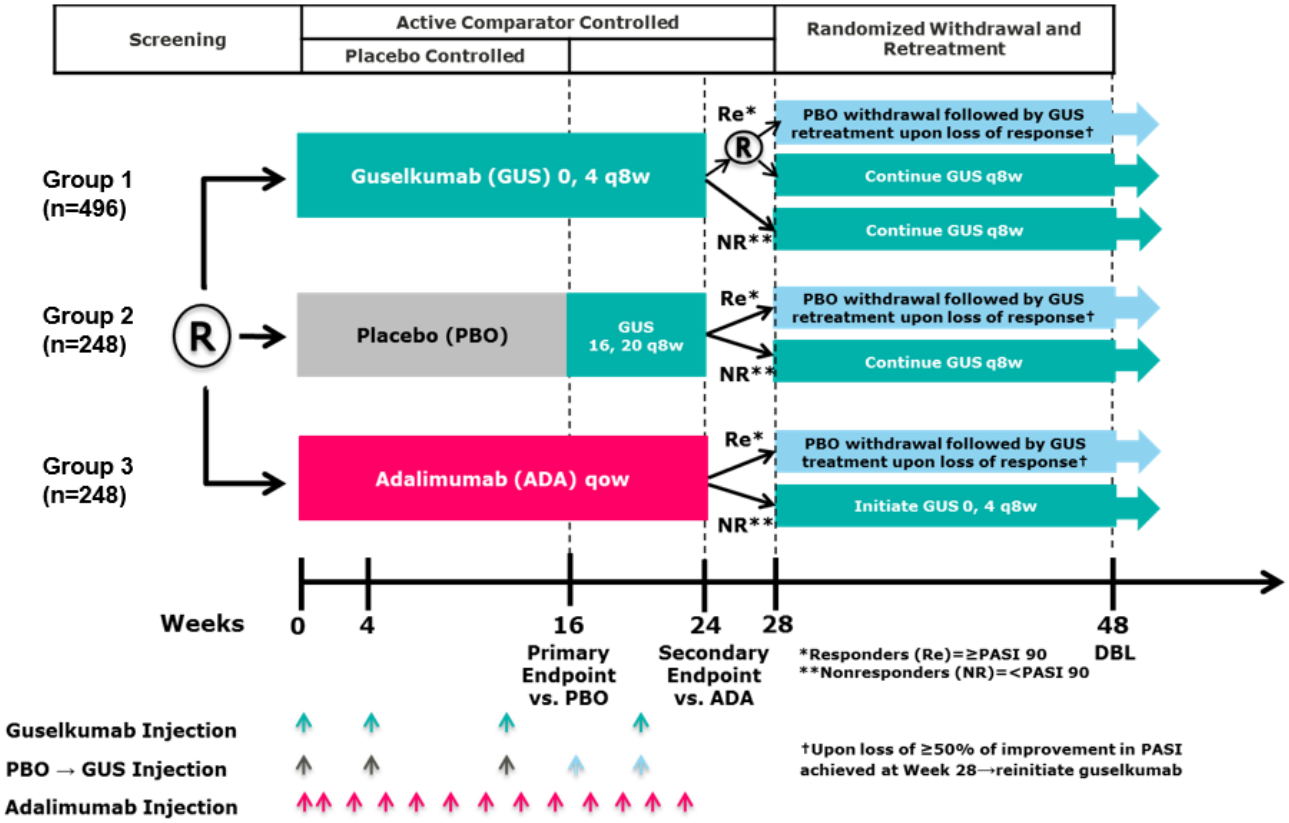
VOYAGE 2 also provides efficacy and safety information on adalimumab PASI 90 non-responders who transitioned to guselkumab treatment at Week 28.

FIGURE 5.3 VOYAGE 1 DESIGN



Abbreviations: ADA: adalimumab; Gus: Guselkumab; PBO: Placebo; Q8W: every 8 weeks; qow: every other week. Source: Medicinrådets Anbefalingsrapport Guselkumab Psoriasis [9]

FIGURE 5.4 VOYAGE 2 DESIGN



Abbreviations: ADA: adalimumab; Gus: Guselkumab; PBO: Placebo; NR: non-responders; Re: responders Q8W: every 8 weeks; qow: every other week. Source: Medicinrådets Anbefalingsrapport Guselkumab Psoriasis [9]

Table 5.2 shows the list of primary and secondary endpoints. The co-primary endpoints in both VOYAGE 1 and VOYAGE 2 were proportion of subjects who achieved IGA 0/1 and proportion of subjects who achieved PASI 90 response at Week 16. The secondary endpoints included PASI 75, 90, 100 and IGA at different time points as well as patient reported outcomes e.g. change of DLQI from baseline to week 16.

Table 5.1 lists the inclusion and exclusion criteria for the trials and Table 5.3 shows the baseline characteristics of patients included in the two trials.

Consort diagrams for both trials can be found in the primary publications [4, 5].

Ohtsuki 2018

Ohtsuki 2018 is a 52-week, phase III, randomized, double-blind, placebo-controlled study with the primary objective to evaluate efficacy and safety of guselkumab in Japanese patients with moderate to severe plaque psoriasis.

The study comprised a placebo-controlled period (week 0–16), a placebo cross-over and active treatment period (week 16–52) and a long-term extension phase (see study design illustration in the primary publication [6]). Eligible patients were randomized (1:1:1) to guselkumab 50 mg, 100 mg or placebo, with injections (s.c.) at week 0, 4, and every 8 weeks (Q8W) thereafter. Patients receiving placebo were crossed over to receive (1:1) guselkumab 50 mg or 100 mg at week 16 and 20 and every Q8W thereafter.

The co-primary end-points were the proportion of patients achieving an IGA cleared/minimal (0/1) and PASI-90 response (≥90% improvement in PASI from baseline) at week 16. The key secondary end-points included the proportion of patients who achieved a PASI-75 response (≥75% improvement in PASI from baseline) and change from baseline in DLQI score at week 16. Other secondary end-points evaluated at week 16 and through week 52 include proportion of patients with IGA 0, IGA 0/1, PASI-50, PASI-75, PASI-90 (≥90% improvement) and PASI-100 (100% improvement); proportion of patients who achieved a DLQI score of 0 or 1 (among patients with a baseline DLQI score of >1); and proportion of patients who achieved a reduction of 5 or more in the DLQI score from baseline (Table 5.2). No data was captured specifically at week 26-28 to enable inclusion of this trial in the indirect comparison at this time horizon, but the week 16 results was included in week 16 indirect comparison as a sensitivity analysis.

Table 5.1 lists the inclusion and exclusion criteria for the trials and Table 5.3 shows the baseline characteristics of patients included in the trial. Although not explicitly stated, the study had an entirely Japanese patient population. The consort diagram of the trial is available in the primary publication [6].

Comparability of populations

The trials were broadly similar in terms of patient characteristics. However, we note that, while four of the trials were in predominantly white or Caucasian populations, the Ohtsuki et al. 2018 trial had an entirely Japanese patient population. The gene pool is naturally different between Japanese and Caucasian patients, which could lead to different metabolism of medicines and response to therapy. Furthermore, the patient baseline characteristics of the Ohtsuki 2018 trial is not comparable with neither the VOYAGE trials nor the reSURFACE trials (see 5.1.1). Importantly, the PASI score as well as body surface area (BSA) involvement are considerably higher in the Japanese patients (PASI ~26 and BSA ~37 versus PASI ~21 and BSA ~29) compared to the participants of the four main trials, whereas the DLQI score is somewhat lower (~10 versus ~14). Finally, the mean body weight approximate 72 kg in the Japanese participants whereas it is ~ 89 kg for the mainly Caucasian patient population. For these reasons the Ohtsuki 2018 trial was only included in a sensitivity analysis.

TABLE 5.1: SUMMARY OF HYPOTHESES, POPULATIONS AND ELIGIBILITY CRITERIA

Trial name	Hypothesis objective	Population	Inclusion criteria	Exclusion criteria
reSURFACE 1 [3]	To assess the efficacy, safety and tolerability of tildrakizumab compared with placebo.	Adults with moderate to severe chronic plaque psoriasis	• Men and women aged ≥ 18 years; • Moderate-to-severe chronic plaque psoriasis (BSA involvement ≥10%, PGA score ≥3, and PASI score ≥12); • Candidates for phototherapy or systemic therapy. • Women of child-bearing potential had to practise abstinence or use medically accepted contraception methods.	• Active or untreated latent tuberculosis • Infection requiring antibiotic treatment within 2 weeks of screening • Severe infection requiring hospitalization or IV antibiotics within 8 weeks of study • Live viral or bacterial vaccination within 4 weeks of the study; • Positive test for HIV, hepatitis B virus infection, or hepatitis C virus infection; • Previous malignancy (except for successfully treated basal cell carcinoma, squamous cell carcinoma of the skin in situ, squamous cell carcinoma with no evidence of recurrence within 5 years, or adequately treated carcinoma in situ of the cervix); • Hospital admission for an acute cardiovascular event, illness, or surgery within 6 months of the trials; • Uncontrolled hypertension • Uncontrolled diabetes; and previous use of tildrakizumab or other interleukin 23 and 17 pathway inhibitors (p40,p19, and interleukin 17 antagonists); • Pregnancy. • Further extensive inclusion criteria were provided in the supplementary appendix, most notably: • Non-plaque forms of psoriasis specifically erythrodermic psoriasis, predominantly pustular psoriasis, medication-induced or medication-exacerbated psoriasis, or new onset guttate psoriasis.

Trial name	Hypothesis objective	Population	Inclusion criteria	Exclusion criteria
reSURFACE 2 [3]	To assess the efficacy, safety and tolerability of tildrakizumab compared with placebo and etanercept.	Adults with moderate to severe chronic plaque psoriasis	Same as reSURFACE 1	Same as reSURFACE 1
VOYAGE 1 [4]	To compare efficacy and safety of guselkumab with adalimumab and placebo in patients with psoriasis treated for 1 year.	Adults with moderate to severe psoriasis	• Age ≥ 18 years • Moderate to severe plaque psoriasis (Investigator global assessment ≥ 3, PASI ≥ 12, body surface area ≥ 10%) for at least 6 months • Candidates for systemic or phototherapy.	• History or current signs of a severe, progressive, or uncontrolled medical condition or had current or history of malignancy (except non-melanoma skin cancer), within 5 years • History or symptoms of active tuberculosis • Had received guselkumab or adalimumab, other anti TNF alpha therapy (within 3 months), other treatment targeting IL-12/23, IL-17, or IL-23 (6 months) or any systemic immunosuppressants (e.g., methotrexate) or phototherapy (4 weeks).
VOYAGE 2 [5]	To evaluate the efficacy, safety, and tolerability of guselkumab to treat patients with moderate to severe plaque-type psoriasis.	Adults with moderate to severe psoriasis	• Age 18-99 years • Moderate to severe plaque psoriasis (Investigator global assessment ≥ 3, PASI ≥ 12, body surface area ≥ 10%) for at least 6 months • Candidates for systemic or phototherapy.	• Non-plaque forms of psoriasis (for example, erythrodermic, guttate, or pustular) • Current drug-induced psoriasis (for example, a new onset of psoriasis or an exacerbation of psoriasis from beta blockers, calcium channel blockers, or lithium) • Prior use of guselkumab or adalimumab • History or current signs or symptoms of severe, progressive, or uncontrolled renal, hepatic, cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, rheumatologic, psychiatric, or metabolic disturbances • Pregnant, nursing, or planning a pregnancy (both men and women) within 5 months following the last administration of study drug • Any condition that, in the opinion of the investigator, would make participation not be in the best interest (for example, compromise the well-being) of the participant or that could

Trial name	Hypothesis objective	Population	Inclusion criteria	Exclusion criteria
				prevent, limit, or confound the protocol-specified assessments
Ohtsuki 2018 [6]	To evaluate efficacy and safety of guselkumab in Japanese patients with moderate to severe plaque-type psoriasis.	Japanese adults with moderate to severe psoriasis	• ≥20 years of age • Moderate to severe plaque-type psoriasis • 6 months or more at PASI ≥ 12 • IGA ≥ 3 • BSA ≥ 10% at baseline • Candidates for phototherapy or systemic treatment for psoriasis *or* • Diagnosis of psoriatic arthritis (PsA) using CASPAR, and with active PsA (defined as ≥3 swollen joints and ≥3 tender joints at baseline and C-reactive protein of 0.3 mg/dL or more at baseline)	• Non-plaque-type psoriasis • Drug induced psoriasis • Latent or active tuberculosis • Chronic or recurrent infectious disease • Malignancy within 5 years (except non-melanoma skin cancer or cervical carcinoma that had been treated, and with no evidence of recurrence within 3 months) • Anaphylactic reactions • History or current signs or symptoms of any severe, progressive or uncontrolled medical disorders • Prior treatment with: - Guselkumab or anti-TNF-a agents within 3 months or five halflives, (whichever was longer) - Biological therapy targeting IL-12, IL-17 or IL-23 within 6 months - Systemic immunosuppressants (e.g. methotrexate, cyclosporin) within 4 weeks - Phototherapy within 4 weeks of enrolment

BSA- body surface area; IV- intravenous; PASI- Psoriasis Area Sensitivity Index; PGA- physicians' global assessment; PsA - psoriatic arthritis.

TABLE 5.2: SUMMARY OF OUTCOMES, ANALYSIS AND DATA MANAGEMENT

Trial identifier	Primary and secondary outcomes	Randomisation and blinding	Subgroup analyses planned	Statistical analysis	Data management: - details of patient withdrawals - missing data imputation
reSURFACE 1 [3]	**Primary outcomes:** Proportion of participants achieving at least 75% improvement in PASI (PASI 75) and the proportion of participants achieving a PGA score of "clear" or "minimal", with at least a two-grade reduction from baseline, at week 12. **Secondary outcomes:** PASI 90 and PASI 100 at week 12, DLQI (proportion of patients with a score of 0 or 1) at week 12 and 28, and PASI 75 in tildrakizumab patients receiving continuous treatment from baseline to the end of week 64.	Participants were randomly assigned (2:2:1) to tildrakizumab 200 mg, tildrakizumab 100 mg, or placebo, then in part 2, those in the placebo group were re-randomised (1:1) to either tildrakizumab 200 or 100 mg. Randomisation was done via computer generated randomisation sequences, and an interactive voice-response system / web-response system. Randomization was done by region. Patients were stratified by bodyweight (≤90 kg or >90 kg) and previous exposure to biologics therapy for psoriasis, and in Japan also for psoriatic arthritis at baseline. The study was double-blind (Investigators, participants, and study personnel) until completion of the studies. Tildrakizumab and its matching placebo or etanercept and its matching placebo were identical in appearance and packaging. Additional placebo doses were administered to maintain masking.	Bodyweight (≤90 kg or >90 kg); Previous exposure to biologics. Results were also reported by the following: • Age (<65, ≥65) • Gender • Race • Region • TNF antagonist response among subjects previously treated for psoriasis (Yes/No) • Psoriatic Arthritis (Yes/No)	Co-primary endpoints were analysed using the Cochran-Mantel-Haenszel test; p-values were not adjusted for multiplicity. Percentage differences and 95% CIs were calculated with the Miettinen-Nurminen method with sample size weights; % differences shown are absolute differences.	Number participants completed/entered stage (reasons for discontinuation; total) Part I (In order: lack of efficacy; adverse effects; lost to follow-up; protocol violation; participant withdrawal): Tildrakizumab 200 mg: 298/308 (NR; 5; 1; 1; 2; 1 pregnancy; total 10) Tildrakizumab 100 mg: 300/309 (1; NR; 2; NR; 3; 3 physician decision; total 9) Placebo: 146/155 (2; NR; 1; 1; 3; also 1 physician decision and 1 progressive disease; total 9) Part 2 (In order: adverse effects; lack of efficacy; lost to follow-up; drug non-compliance; protocol violation; patient withdrawal): Tildrakizumab 200 mg: 279/298 (3; 3; NR; 1; 1; 5; 6 other; total 19) Tildrakizumab 100 mg: 268/299 (NR; 11; 3; 1; NR; 3; 10 other; 2 physician decision; 1 progressive disease; total 31) Placebo- Tildrakizumab 200 mg: 62/72 (1; 3; 1; NR; NR; 2; 2 other; 1 pregnancy; total 10) Placebo- Tildrakizumab 100 mg: 67/74 (NR; 3; 1; NR; NR; 2; 1 other; total 7) Non-responder imputation was pre-specified and was shown for all data, except for DLQI, which were observed data.

Trial identifier	Primary and secondary outcomes	Randomisation and blinding	Subgroup analyses planned	Statistical analysis	Data management: - details of patient withdrawals - missing data imputation
reSURFACE 2 [3]	**Primary outcomes:** Proportion of participants achieving at least 75% improvement in PASI (PASI 75) and the proportion of participants achieving a PGA score of "clear" or "minimal", with at least a two-grade reduction from baseline, at week 12. **Secondary outcomes:** PASI 90 and PASI 100 at week 12, PASI75 and PGA response at Week 28, DLQI (proportion of patients with a score of 0 or 1) at week 12 and 28, and PASI 75 in tildrakizumab patients receiving continuous treatment from baseline to the end of week 52.	Participants were randomly assigned (2:2:1:2) to tildrakizumab 200 mg, tildrakizumab 100 mg, placebo, or etanercept 50 mg. In part 2, the placebo group was re-randomised (1:1) to tildrakizumab 200 mg or 100 mg. In part 3 of both studies, responders (PASI ≥75) and partial responders (PASI ≥50 and PASI <75) to tildrakizumab 200 mg and 100 mg were rerandomized at 28 weeks to continue the same treatment, a different dose of tildrakizumab, or placebo. Randomisation was done as in reSURFACE 1. Patients was stratified by bodyweight (≤90 kg or >90 kg), previous exposure to biologics therapy for psoriasis, non-response to at least one traditional systemic medication, and in Japan also for psoriatic arthritis at baseline. Blinding was done as in reSURFACE 1	Same as reSURFACE 1	Co-primary endpoints were analysed using the Cochran-Mantel-Haenszel test; p-values and a step-down multiplicity strategy was used. Percentage differences and 95% CIs were calculated with the Miettinen-Nurminen method with sample size weights; % differences shown are absolute differences. Descriptive summary statistics by treatment were reported for participants re-randomised from placebo to tildrakizumab 100 mg or 200 mg.	Number participants completed/entered stage (reasons for discontinuation; total) Part I (In order: AE; lack of efficacy; lost to follow-up; protocol violation; participant withdrawal): Tildrakizumab 200 mg: 300/314 (2; 1; 1; 2; 5; 2 other; 1 drug non-compliance; total 14) Tildrakizumab 100 mg: 295/307 (1; NR; 2; 1; 7; 1 pregnancy; total 12) Etanercept: 289/313 (5; NR; 3; NR; 6; 4 other; 4 physician decision; 1 pregnancy ; 1 progressive disease; total 24) Placebo: 142/156 (2; 2; 3; 1; 5; 1 other; total 14) Part 2 (In order: AE; lack of efficacy; lost to follow-up; patient withdrawal): Tildrakizumab 200 mg: 294/300 (2; NR; NR; 3; 1 other; total 6) Tildrakizumab 100 mg: 289/294 (NR; NR; 2; 2; 1 pregnancy; total 5) Etanercept: 277/289 (2; 2; 2; 4; 1 drug non-compliance; 1 pregnancy; total 12) Placebo- Tildrakizumab 200 mg: 69/72 (NR; NR; 1; 1; 1 other; total 3) Placebo- Tildrakizumab 100 mg: 66/70 (1; 2; NR; 1; total 4)
VOYAGE 1 [4]	**Primary outcomes:** Proportion achieving an Investigator Global Assessment score of cleared or minimal	Patients were randomized using a permuted block method at baseline in a 2:1:2 ratio to guselkumab 100 mg at week 0, 4, 12, and every 8 weeks through	NR	Coprimary outcomes and binary outcomes with Cochran-Mantel-Haenszel Chi-square stratified by site,	• Over the 48 weeks 90 participants discontinued: - Up to week 16: - Adalimumab 10 (2 adverse events, 1 lack of efficacy, 4 patient withdrawal, 1

Trial identifier	Primary and secondary outcomes	Randomisation and blinding	Subgroup analyses planned	Statistical analysis	Data management: - details of patient withdrawals - missing data imputation
	disease (0 or 1) and 90% improvement in PASI from baseline (PASI 90) were co-primary endpoints. **Secondary outcomes:** IGA, PASI, scalp specific Investigator Global Assessment, fingernail PGA, NAPSI, PGA of hands and/or feet, DLQI, Psoriasis Symptoms and Signs Diary, Safety, Antibodies.	week 44; placebo at week 0, 4, and 12 followed by guselkumab 100 mg at week 16 and 20, and every 8 weeks through week 44; or adalimumab 80 mg at week 0, 40 mg at week 1, and 40 mg every 2. week through week 47. Central randomization was implemented using an interactive web response system. To maintain the blind, matching placebos were used.		continuous outcomes by ANCOVA with site as a covariate. All statistical analysis was 2-sided with alpha 0.05. Analyses tested in a fixed sequence to control for multiplicity.	lost to follow-up, 1 treatment non-compliance, 1 protocol violation) - Guselkumab 7 (4 adverse events, 1 lost to follow-up, 2 treatment noncompliance) - Placebo 7 (2 adverse events, 2 lack of efficacy, 2 patient withdrawal, 1 lost to follow-up) - from cross over to week 48: - adalimumab 42 (9 adverse events, 11 lack of efficacy, 10 patient withdrawal, 5 lost to follow-up, 3 treatment non-compliance, 1 pregnancy, 3 other) - continued guselkumab 21 (6 adverse events, 3 lack of efficacy, 4 patient withdrawal, 2 lost to follow-up, 3 treatment non-compliance, 1 protocol violation, 2 other) - crossed to guselkumab 2 did not cross over, 3 discontinued (1 adverse event, 1 patient withdrawal, 1 lost to follow-up) • Missing values were considered non-responders for binary endpoints or had baseline values carried forward for continuous endpoints for those who discontinued for lack of efficacy or an adverse event of worsening psoriasis, or who started a protocol-prohibited treatment. Others were considered non-responders for binary endpoints and last observation carried forward for continuous endpoints.
VOYAGE 2 [5]	**Primary outcomes:** Coprimary end points were proportion of	Patients were randomized 2:1:1 using a permuted block method at baseline to guselkumab	NR	Coprimary outcomes and binary outcomes with Cochran-Mantel-	Placebo: 15 (adverse events 2; lack of efficacy 4; lost to follow up 1;

Trial identifier	Primary and secondary outcomes	Randomisation and blinding	Subgroup analyses planned	Statistical analysis	Data management: - details of patient withdrawals - missing data imputation
	patients achieving IGA 0/1 and PASI 90 by week 16 **Secondary outcomes:** • Week 24: Proportion of patients achieving IGA 0, IGA 0/1, PASI 90, or PSSD symptom score 0 • Week 24-48: The time to loss of PASI 90 response • Week 16: Change from baseline in DLQI score, proportion of patients achieving IGA 0/1, PASI 90, PASI 75, ss-IGA 0/1, and change from baseline in PSSD symptom score	100 mg at week 0, 4, 12, and 20; placebo at week 0, 4, and 12, then guselkumab at week 16 and 20; or adalimumab 80 mg at week 0, 40 mg at week 1, and every 2. week thereafter through week 23. Central randomization was implemented using an interactive web response system. To maintain the blind, both guselkumab and adalimumab placebos were administered as necessary.		Haenszel Chi-square stratified by site, continuous outcomes by ANCOVA with site as a covariate. All statistical analysis was 2-sided with alpha 0.05.	withdrawal by subject 7; protocol violation 1) Guselkumab: 18 (adverse events 9; lost to follow up 3; withdrawal by subject 1; protocol violation 3; non-compliance 1; other 1) Adalimumab: (adverse events 4; lack of efficacy 2; lost to follow up 2; protocol violation 1; non-compliance 2) Patients who discontinued treatment due to lack of efficacy or an adverse event of worsening of psoriasis, or started a protocol-prohibited medication/ therapy to improve psoriasis were considered treatment failures. Patients meeting treatment failure criteria before week 16 and patients not returning for week-16 evaluation were considered non-responders for the week-16 primary end point. To control the overall type 1 error rate, the primary and major secondary analyses were tested in a fixed sequence, with the first major secondary end point tested only if the co-primary end points were met, and the subsequent end point(s) tested only if the preceding end point in the sequence was met.
Ohtsuki 2018 [6]	Co-primary end-points were the proportion of patients achieving an	Eligible patients were randomized (1:1:1) to guselkumab 50 mg, 100 mg or placebo, with s.c. injections	NR	Co-primary end-points were assessed in a multiplicity-	Patients who discontinued the study drug because of lack of efficacy, a TEAE of worsening psoriasis or starting a

	IGA cleared/minimal (0/1) and PASI-90 response (≥90% improvement in PASI from baseline) at week 16. **Secondary end-points:** • Proportion of patients who achieved a PASI-75 response at week 16 • Change from baseline in the Dermatology Life Quality Index (DLQI) score at week 16 • Proportion of patients with IGA 0, IGA 0/1, PASI-50, PASI-75, PASI-90 and PASI-100 at week 16 and through to week 52 • Change and % improvement in NAPSI score from baseline • Proportion of patients who had a scalp-specific Investigator's Global Assessment (ss-IGA) score of 0 or 0/1 who had a baseline score of 2 or more • Proportion of patients who achieved a DLQI score of 0 or 1 (among patients with a	at weeks 0, 4, and every 8 weeks (q8w) thereafter. Patients receiving placebo were crossed over to receive (1:1) guselkumab 50 mg or 100 mg at week 16 and 20 and every q8w thereafter. Randomization was performed centrally using a computer-generated randomization scheme, balanced using randomly permuted blocks and stratified by presence of PsA. Study site personnel, investigators and patients were blinded to treatment allocation until week 52 database lock.		adjusted, fixed-sequence testing procedure. Except for PsA, binary efficacy end-points at week 16 (e.g. co-primary end-points) were analyzed using Fisher's exact test; continuous efficacy end-points at week 16 were evaluated using ANCOVA with treatment as a factor and baseline as a covariate; categorical efficacy end-points at week 16 with two or more levels were analyzed using the Cochran– Mantel–Haenszel test.	protocol- prohibited psoriasis treatment were considered nonresponders for binary end-points or had baseline values carried forward for continuous end-points. Last observation was carried forward for other patients with missing data. Safety analyses included all patients receiving one or more study drug administration and were summarized by actual treatment received.

Trial identifier	Primary and secondary outcomes	Randomisation and blinding	Subgroup analyses planned	Statistical analysis	Data management: - details of patient withdrawals - missing data imputation
	baseline DLQI score of >1) • Proportion of patients who achieved a reduction of 5 or more in the DLQI score from baseline • Changes from baseline in the EQ-5D and physical and mental component scores of the SF-36 were assessed through week 48				

AE- adverse event; DLQI- Dermatology quality of life index; IGS- investigators global assessment; IV- intravenous; NAPSI- nail psoriasis severity index; NR- not reported; PASI- Psoriasis Area Sensitivity Index; PGA- physicians' global assessment; PSSD- psoriasis signs and symptoms diary

TABLE 5.3: PARTICIPANTS' BASELINE CHARACTERISTICS

Trial identifier	Intervention	Number of patients randomised	Geography	Age Mean (SD) years	Female Number (%)	Ethnicity	Weight - kg Mean (SD)	BMI Mean (SD)
ReSURFACE 1 [3]	Tildrakizumab 200mg	308	Australia, Canada, Japan, the UK, and the USA	46.9 (13.2)	82 (26.6)	White: 209 (68%) Asian: 83 (27%) Other: 16 (5%)	88·87 (24·09)	NR
	Tildrakizumab 100mg	309		46·4 (13·1)	102 (33.0)	White: 217 (70%) Asian: 70 (23%) Other: 22 (7%)	88·53 (23·87)	NR
	Placebo	155		47·9 (13·5)	55 (35.5)	White: 101 (65%) Asian: 42 (27%) Other: 12 (8%)	87·50 (26·04)	NR
ReSURFACE 2 [3]	Tildrakizumab 200mg	314	Europe, Israel, and the USA	44·6 (13·6)	89 (28.3)	White: 284 (90%) Asian: 14 (4%) Other: 16 (5%)	88·35 (21·23)	NR
	Tildrakizumab 100mg	307		44·6 (13·6)	87 (28.3)	White: 279 (91%) Asian: 9 (3%) Other: 19 (6%)	89·35 (22·12)	NR
	Etanercept 50mg BIW for 12 weeks then QW	313		45·8 (14·0)	91 (29.1)	White: 289 (92%) Asian: 10 (3%) Other: 14 (4%)	87·97 (21·48)	NR
	Placebo	156		46·4 (12·2)	44 (28.2)	White: 144 (92%) Asian: 3 (2%) Other: 9 (6%)	88·74 (22·73)	NR
VOYAGE 1 [4]	Guselkumab 100mg Q8W	329	Australia, Canada, Germany, Hungary, Korea, Republic of, Poland, Russian Federation, Spain, Taiwan, USA	43.9 (12.74)	89 (27.1)	Caucasian: 262 (79.6) Black: 6 (1.8) Asian: 51 (15.5)	NR	29.7 (6.22)
	Adalimumab 40mg Q2W	334		42.9 (12.58)	85 (25.4)	Caucasian: 277 (82.9) Black: 8 (2.4) Asian: 47 (14.1)	NR	29.8 (6.48)
	Placebo	174		44.9 (12.9)	55 (31.6)	Caucasian: 145 (83.3) Black: 3 (1.7) Asian: 23 (13.2)	NR	28.9 (6.89)
VOYAGE 2 [5]	Placebo	248	Australia, Canada, Czechia,	43.3 (12.4)	75* (30.2)*	White: 206 (83.1) Asian: 27 (10.9) Black: 8 (3.2)	NR	29.6 (6.6)

Trial identifier	Intervention	Number of patients randomised	Geography	Age Mean (SD) years	Female Number (%)	Ethnicity	Weight - kg Mean (SD)	BMI Mean (SD)
	Guselkumab 100mg Q8W	496	Germany, Korea, Poland, Russian Federation, Spain, USA	43.7 (12.2)	147* (29.6)*	White: 408 (82.3) Asian: 72 (14.5) Black: 6 (1.2)	NR	29.6 (6.5)
	Adalimumab, 40mg Q2W	248		43.2 (11.9)	78* (31.5)*	White: 200 (80.6) Asian: 37 (14.9) Black: 5 (2.0)	NR	29.6 (6.6)
Ohtsuki 2018 [6]	Placebo	64	Japan	48.3 (10.56)	10* (15.6)*	NR but narrative states all patients were Japanese	71.56 (14.01)	25.42 (4.791)
	Guselkumab 100mg Q8W	63		47.8 (11.07)	16* (25.4)*		74.27 (16.04)	26.33 (5.032)

BIW- twice a week; NR- not reported; PASI- Psoriasis Area Sensitivity Index; QW- once a week; Q2W- every 2 weeks; Q8W- every 8 weeks; SD- standard deviation; USA- United States of America

TABLE 5.3 PARTICIPANTS' BASELINE CHARACTERISTICS. CONTINUED

Trial identifier	Intervention	Number of patients randomised	Disease duration Years Mean (SD)	PASI Mean (SD)	DQLI Mean (SD)	Previously treated with biologics (%)
ReSURFACE 1 [3]	Tildrakizumab 200mg	308	NR	20.7 (8.51)	13.2 (6.87)	23%
	Tildrakizumab 100mg	309	NR	20.0 (7.85)	13.9 (6.68)	23%
	Placebo	155	NR	19.3 (7.07)	13.2 (7.25)	23%
ReSURFACE 2 [3]	Tildrakizumab 200mg	314	NR	19.8 (7.52)	13.2 (7.03)	12%
	Tildrakizumab 100mg	307	NR	20.5 (7.63)	14.8 (7.24)	13%
	Etanercept 50mg BIW for 12 weeks then QW	313	NR	20.2 (7.36)	14.5 (7.20)	12%
	Placebo	156	NR	20 (7.57)	13.7 (6.98)	13%
VOYAGE 1 [4]	Guselkumab 100mg Q8W	329	17.9 (12.27)	22.1 (9.49)	14.0 (7.48)	21.6%
	Adalimumab 40mg Q2W	334	17 (11.27)	22.4 (8.97)	14.4 (7.29)	21.0%
	Placebo	174	17.6 (12.44)	20.4 (8.74)	13.3 (7.12)	19.5%
VOYAGE 2 [5]	Placebo	248	17.9 (11.9)	21.5 (8.0)	15.1 (7.2)	21.8%
	Guselkumab 100mg Q8W	496	17.9 (12.0)	21.9 (8.8)	14.7 (6.9)	20.4%
	Adalimumab, 40mg Q2W	248	17.6 (11.7)	21.7 (9.0)	15.0 (6.9)	19.8%
Ohtsuki 2018 [6]	Placebo	64	13.66 (10.291)	25.92 (12.34)	10.6 (7.74)	15.6%
	Guselkumab 100mg Q8W	63	14.39 (9.227)	26.73 (12.19)	10.3 (7.27)	17.5%

5.1.2 Results per study

Table 5.4 through Table 5.8 below display number of events and number of subjects by arm and by study as reported. The rate of events has been calculated from number of events and number of subjects. For all outcomes, the number of patients randomized to the treatment arm at baseline was used for calculating rates to form rates for the ITT population. The 95% CI has been calculated using the Clopper-Pearson method.

Relative rates were calculated for the active arm relative to placebo. None of the trials had placebo control for more than 16 weeks. Number of events for the placebo arm at week 12-16 was applied at 24-28 week analysis to form relative rates. This alternative was deemed the most appropriate, since efficacy endpoints appear unlikely to significantly increase with placebo beyond week 12 (i.e. curve for PASI change from baseline becomes horizontal before week 12 – see for instance Saurat et al. (2008)[10]. For consistency purposes and lack of a better alternative, an identical approach was taken for safety endpoints as well.

The number of patients with a least one SAE during week 0-28 was not available from the reSURFACE studies. The number of events were calculated as the sum of patients with at least one event during week 0-16 and patients with a least one event during week 17-28. Patients with a SAE in both time-periods will be double counted using this method.

Number of patients with DLQI 0 or 1 was based on number reported. In the VOYAGE trials, it is stated that patients reporting DLQI of 0 or 1 at baseline were excluded from the DLQI response analyses [4, 5, 6]. This means that some patients in the ITT population may not have contributed to the number of events. However, it is important to note that when comparing the different DLQI populations (at baseline, for DLQI 0/1, and for mean change from baseline) the majority of patients excluded from the DLQI 0/1 analysis must actually have had missing baseline values. Therefore, Almirall chose to base the primary DLQI 0/1 analysis on the ITT population for both treatments. In a sensitivity analysis, the indirect comparison of DLQI 0/1 response rates were based on the analysis population applied in the publications (all patients with DLQI data available at base-line and – for the guselkumab studies – also with baseline DLQI score above 1) – see Appendix F.

Tildrakizumab trials

TABLE 5.4: OUTCOMES IN RESURFACE 1

Outcomes at week 12							
Outcome	**Treatment**	**Number of events**	**Number of patients**	**Rate of events**	**95% CI**	**RR**	**95% CI**
PASI75	Placebo	9	155	0.06	(0.03, 0.11)	11.11	(5.88, 20.00)
	Tildrakizumab 100mg	197	309	0.64	(0.58, 0.69)		
PASI90	Placebo	4	155	0.03	(0.01, 0.06)	14.29	(5.00, 33.33)
	Tildrakizumab 100mg	107	309	0.35	(0.29, 0.40)		
SAE	Placebo	1	155	0.01	(0.00, 0.04)	2.50	(0.30, 20.00)
	Tildrakizumab 100mg	5	309	0.02	(0.01, 0.04)		
DLQI 0/1	Placebo	8	155	0.05	(0.02, 0.10)	7.69	(4.00, 16.67)
	Tildrakizumab 100mg	126	309	0.41	(0.35, 0.46)		
Discontinuation	Placebo	9	155	0.06	(0.03, 0.11)	0.50	(0.20, 1.23)
	Tildrakizumab 100mg	9	309	0.03	(0.01, 0.05)		
Outcomes at week 28							
Outcome	**Treatment**	**Number of events**	**Number of patients**	**Rate of events**	**95% CI**	**RR**	**95% CI**
PASI75	Placebo	9	155	0.06	(0.03, 0.11)	12.50	(6.67, 25.00)
	Tildrakizumab 100mg	229	309	0.74	(0.69, 0.79)		
PASI90	Placebo	4	155	0.03	(0.01, 0.06)	20.00	(7.14, 50.00)
	Tildrakizumab 100mg	147	309	0.48	(0.42, 0.53)		
SAE*	Placebo	1	155	0.01	(0.00, 0.04)	5.56	(0.72, 50.00)
	Tildrakizumab 100mg	11	309	0.04	(0.02, 0.06)		
DLQI 0/1	Placebo	8	155	0.05	(0.02, 0.10)	10.00	(4.76, 20.00)
	Tildrakizumab 100mg	152	309	0.49	(0.43, 0.55)		
Discontinuation	Placebo	9	155	0.06	(0.03, 0.11)	6.67	(3.85, 11.11)
	Tildrakizumab 100mg	41	309	0.13	(0.10, 0.18)		

* Number of patients with at least one SAE at week 28 is estimated as the reported number of patients with a least one event during week 0-16 plus the number of patients with at least one event during week 17-28. Patients with an SAE during both time-frames will be double-counted

TABLE 5.5: OUTCOMES IN RESURFACE 2

Outcomes at week 12							
Outcome	**Treatment**	**Number of events**	**Number of patients**	**Rate of events**	**95% CI**	**RR**	**95% CI**
PASI75	Placebo	9	156	0.06	(0.03, 0.11)	11.11	(5.56, 20.00)
	Tildrakizumab 100mg	188	307	0.61	(0.56, 0.67)		
PASI90	Placebo	2	156	0.01	(0.00, 0.05)	33.33	(7.69, 100.00)
	Tildrakizumab 100mg	119	307	0.39	(0.33, 0.44)		
SAE	Placebo	4	156	0.03	(0.01, 0.06)	0.51	(0.13, 2.00)
	Tildrakizumab 100mg	4	307	0.01	(0.00, 0.03)		
DLQI 0/1	Placebo	12	156	0.08	(0.04, 0.13)	5.00	(2.86, 9.09)
	Tildrakizumab 100mg	119	307	0.39	(0.33, 0.44)		
Discontinuation	Placebo	14	156	0.09	(0.05, 0.15)	0.43	(0.21, 0.92)
	Tildrakizumab 100mg	12	307	0.04	(0.02, 0.07)		
Outcomes at week 28							
Outcome	**Treatment**	**Number of events**	**Number of patients**	**Rate of events**	**95% CI**	**RR**	**95% CI**
PASI75	Placebo	9	156	0.06	(0.03, 0.11)	12.50	(6.25, 25.00)
	Tildrakizumab 100mg	216	307	0.7	(0.65, 0.75)		
PASI90	Placebo	2	156	0.01	(0.00, 0.05)	50.00	(10.00, 100.0)
	Tildrakizumab 100mg	161	307	0.52	(0.47, 0.58)		
SAE*	Placebo	4	156	0.03	(0.01, 0.06)	1.64	(0.55, 5.00)
	Tildrakizumab 100mg	13	307	0.04	(0.02, 0.07)		
DLQI 0/1	Placebo	12	156	0.08	(0.04, 0.13)	6.67	(3.85, 11.11)
	Tildrakizumab 100mg	157	307	0.51	(0.45, 0.57)		
Discontinuation	Placebo	14	156	0.09	(0.05, 0.15)	0.65	(0.33, 1.28)
	Tildrakizumab 100mg	18	307	0.06	(0.04, 0.09)		

* Number of patients with at least one SAE at week 28 is estimated as the reported number of patients with a least one event during week 0-16 plus the number of patients with at least one event during week 17-28. Patients with an SAE during both time-frames will be double-counted

Guselkumab trials

TABLE 5.6: OUTCOMES IN VOYAGE 1

Outcomes at week 16							
Outcome	**Treatment**	**Number of events**	**Number of patients**	**Rate of events**	**95% CI**	**RR**	**95% CI**
PASI75	Placebo	10	174	0.06	(0.03, 0.10)	16.67	(8.33, 33.33)
	Guselkumab 100mg	300	329	0.91	(0.88, 0.94)		
PASI90	Placebo	5	174	0.03	(0.01, 0.07)	25.00	(11.11, 50.00)
	Guselkumab 100mg	241	329	0.73	(0.68, 0.78)		
SAE	Placebo	3	174	0.02	(0.00, 0.05)	1.41	(0.38, 5.26)
	Guselkumab 100mg	8	329	0.02	(0.01, 0.05)		
DLQI 0/1*	Placebo	7	174	0.04	(0.02, 0.08)	14.29	(6.67, 25.00)
	Guselkumab 100mg	180	329	0.55	(0.49, 0.60)		
Discontinuation	Placebo	7	174	0.04	(0.02, 0.08)	0.53	(0.19, 1.49)
	Guselkumab 100mg	7	329	0.02	(0.01, 0.04)		
Outcomes at week 24-28							
Outcome	**Treatment**	**Number of events**	**Number of patients**	**Rate of events**	**95% CI**	**RR**	**95% CI**
PASI75 (week 24)	Placebo	10	174	0.06	(0.03, 0.10)	16.67	(8.33, 33.33)
	Guselkumab 100mg	300	329	0.91	(0.88, 0.94)		
PASI90 (week 24)	Placebo	5	174	0.03	(0.01, 0.07)	25.00	(11.11, 50.0)
	Guselkumab 100mg	264	329	0.8	(0.76, 0.84)		
SAE	Placebo	N/A	N/A	N/A	N/A	N/A	N/A
	Guselkumab 100mg	N/A	N/A	N/A	N/A		
DLQI 0/1*	Placebo	7	174	0.04	(0.02, 0.08)	14.29	(6.67, 25.00)
	Guselkumab 100mg	195	329	0.59	(0.54, 0.65)		
Discontinuation	Placebo	N/A	N/A	N/A	N/A	N/A	N/A
	Guselkumab 100mg	N/A	N/A	N/A	N/A		

* Patients with DLQI of 0 at baseline was excluded in the response analysis reported in [4]

TABLE 5.7: OUTCOMES IN VOYAGE 2

Outcomes at week 16							
Outcome	**Treatment**	**Number of events**	**Number of patients**	**Rate of events**	**95% CI**	**RR**	**95% CI**
PASI75	Placebo	20	248	0.08	(0.05, 0.12)	11.11	(7.14, 16.67)
	Guselkumab 100mg	428	496	0.86	(0.83, 0.89)		
PASI90	Placebo	6	248	0.02	(0.01, 0.05)	33.33	(12.50, 50.0)
	Guselkumab 100mg	347	496	0.7	(0.66, 0.74)		
SAE	Placebo	3	248	0.01	(0.00, 0.03)	1.33	(0.36, 5.00)
	Guselkumab 100mg	8	496	0.02	(0.01, 0.03)		
DLQI 0/1	Placebo	8	248	0.03	(0.01, 0.06)	16.67	(7.69, 33.33)
	Guselkumab 100mg	254	496	0.51	(0.47, 0.56)		
Discontinuation	Placebo	15	248	0.06	(0.03, 0.10)	0.60	(0.31, 1.18)
	Guselkumab 100mg	18	496	0.04	(0.02, 0.06)		
Outcomes at week 24-28							
Outcome	**Treatment**	**Number of events**	**Number of patients**	**Rate of events**	**95% CI**	**RR**	**95% CI**
PASI75 (week 24)	Placebo	20	248	0.08	(0.05, 0.12)	11.11	(7.14, 16.67)
	Guselkumab 100mg	442	496	0.89	(0.86, 0.92)		
PASI90 (week 24)	Placebo	6	248	0.02	(0.01, 0.05)	33.33	(14.29,100.0)
	Guselkumab 100mg	373	496	0.75	(0.71, 0.79)		
SAE (week 28)	Placebo	3	248	0.01	(0.00, 0.03)	3.03	(0.89, 10.00)
	Guselkumab 100mg	18	496	0.04	(0.02, 0.06)		
DLQI 0/1* (week 28)	Placebo	8	248	0.03	(0.01, 0.06)	16.67	(9.09, 33.33)
	Guselkumab 100mg	283	496	0.57	(0.53, 0.61)		
Discontinuation (week 28)	Placebo	15	248	0.06	(0.03, 0.10)	0.87	(0.47, 1.61)
	Guselkumab 100mg	26	496	0.05	(0.03, 0.08)		

* Patients with DLQI of 0 at baseline was excluded in the response analysis reported in [5]

TABLE 5.8: OUTCOMES IN OHTSUKI 2018

Outcomes at week 16							
Outcome	**Treatment**	**Number of events**	**Number of patients**	**Rate of events**	**95% CI**	**RR**	**95% CI**
PASI75	Placebo	4	64	0.06	(0.02, 0.15)	14.29	(5.26, 33.33)
	Guselkumab 100mg	53	63	0.84	(0.73, 0.92)		
PASI90	Placebo	0	64	0.00	(0.00, 0.06)	100.00	(5.56, inf)
	Guselkumab 100mg	44	63	0.70	(0.57, 0.81)		
SAE	Placebo	2	64	0.03	(0.00, 0.11)	0.51	(0.05, 5.56)
	Guselkumab 100mg	1	63	0.02	(0.00, 0.09)		
DLQI 0/1	Placebo	4	64	0.06	(0.02, 0.15)	10.00	(4.00, 25.00)
	Guselkumab 100mg	41	63	0.65	(0.52, 0.77)		
Discontinuation	Placebo	12	64	0.19	(0.10, 0.30)	0.08	(0.01, 0.63)
	Guselkumab 100mg	1	63	0.02	(0.00, 0.09)		

* Patients with DLQI of 0 at baseline was excluded in the response analysis reported in [6].
Abbreviations: inf: infinite

5.1.3 Comparative analyses

Methods applied in quantitative syntheses

Risk ratios

In order to compare tildrakizumab 100mg and guselkumab 100mg, a Bucher [11] indirect comparison has been calculated using placebo as common comparator. This involves three steps for each endpoint separately:

(1) Pairwise meta-analysis of placebo and tildrakizumab to estimate a risk ratio
(2) Pairwise meta-analysis of placebo and guselkumab to estimate a risk ratio
(3) Combining risk ratios obtained in (1) and (2) to estimate a risk ratio of tildrakizumab and guselkumab

Step 1 and 2 were originally conducted with placebo as point of origin whereas step 3 originally was conducted with guselkumab as the point of origin. Values provided throughout this document have been inverted to reflect analyses with active treatment (step 1 and 2) and tildrakizumab (step 3) as the points of origin. Please note that all forest plots presented in Appendix B originate from the original analysis and therefore have placebo as the point of origin.

Risk ratios can vary by study. If they vary considerably, the pairwise meta-analyses need to be performed using a random effects (RE) model. Otherwise, a fixed effect (FE) model may be used. It needs to be noted, though, that it is very difficult to estimate variations in-between studies if only a small number of studies are considered, as is the case here.

Heterogeneity is the term used to describe variability in intervention effects among studies due to clinical and/or methodological differences. It can be quantified through the use of the I^2 statistic. This statistic provides an estimate of the percentage of the variability in effect estimates that is due to heterogeneity rather than chance. The Cochrane Handbook [12] suggests I^2 values between 0% and 40% may not be important, and those between 30% and 60% "may represent moderate heterogeneity". To assess heterogeneity, I^2 statistics have been calculated for each pairwise comparison.

If a comparison was reported by one study only, then no meta-analysis was undertaken. In this case, the risk ratio which was taken for step 3 above was identical to the one reported by the single study.

Results for both FE and RE models have been produced.

No adjustments for multiplicity have been made, and all risk ratios are reported with their 95% confidence interval.

Absolute risk reductions

Absolute risk reductions (ARR) in % points were calculated based on observed results of guselkumab arms and relative risk ratios obtained as described above. The following steps were undertaken:

1. If *PR* denotes the assumed proportion of events for tildrakizumab 100mg, then:

$$PR = \frac{\text{sum of all events in tildrakizumab 100mg arms across all studies}}{\text{sum of all subjects in tildrakizumab 100mg arms across all studies}}$$

2. If *RR* denotes the risk ratio of tildrakizumab 100mg to guselkumab 100mg as obtained before, and *ARR* denotes the absolute risk reduction, then:

$$ARR = (RR - 1) * PR$$

To estimate 95% confidence interval for ARR, the ARR at the confidence limits for RR was calculated using the formula above but assuming that the proportion of patient with events (*PR*) is constant, i.e., ignoring the sample variation in this estimate.

Results compared at week 24-28

Forest plots to illustrate the results of the pairwise meta-analyses are presented in Appendix B. Apart from discontinuations, heterogeneity was very low. The following table displays the I^2 statistics for each direct comparison by PASI level. Note that there are no I^2 statistics for SAE and discontinuations for the comparison of placebo and guselkumab 100mg. The reason is that only one study reported these outcomes, and therefore no meta-analysis was undertaken.

TABLE 5.9: HETEROGENEITY ASSESSMENT RESULTS, WEEK 24-28

Treatment 1	Treatment 2	I^2
PASI 75		
Placebo	Tildrakizumab 100mg	0.0%
Placebo	Guselkumab 100mg	0.0%
PASI 90		
Placebo	Tildrakizumab 100mg	0.0%
Placebo	Guselkumab 100mg	0.0%
SAE		
Placebo	Tildrakizumab 100mg	3.9%
Placebo	Guselkumab 100mg	NA
DLQI 0/1		
Placebo	Tildrakizumab 100mg	0.0%
Placebo	Guselkumab 100mg	0.0%
Discontinuations		
Placebo	Tildrakizumab 100mg	84.5%
Placebo	Guselkumab 100mg	NA

DLQI- Dermatology Life Quality Index; NA- not applicable; PASI- Psoriasis Area Sensitivity Index; SAE- Serious Adverse Events

The high amount of heterogeneity for discontinuations appears to have its origins in a low number of discontinuations for tildrakizumab in the Re-SURFACE 2 study. For this endpoint, the RE model should be considered. For all the other models the FE model appears to be appropriate.

For PASI 75, the risk ratios for guselkumab to tildrakizumab obtained by both models are equal to 1, which signifies that the same number of events are observed for both treatments. For PASI 90, the risk ratios are below 1, favouring guselkumab 100mg, but the 95% CIs do contain 1. Thus, it could not be demonstrated that the two treatments are different for PASI levels 75 and 90.

Regarding SAE, the risk ratios calculated by both models are below 1, which means that more SAEs were observed for guselkumab 100mg. However, the result is again not statistically significant since the 95% CIs contain 1.

For DLQI 0/1, both models calculated the risk ratios as below 1, favouring guselkumab 100mg. The result is statistically significant since the CIs do not contain 1. The statistically significant difference in DLQI 0/1 response rate is largely driven by a substantially higher placebo response in the reSURFACE trials (especially reSURFACE 2) than VOYAGE trials. In the reSURFACE 1 and 2 the placebo response was 5 % and 8 % respectively, compared to only 4 % and 3 % in VOYAGE 1 and 2, respectively. This is in contrast to placebo PASI response rates which seem similar across trials. The absolute difference (calculated from overall results in the VOYAGE trials and estimated RR from the Bucher analysis) is 57.9% but with very wide confidence intervals (4.8% to 43.8%) including the MCID set by the Medicine Council indicating that the added clinical value of this finding is uncertain.

Regarding discontinuations, both models return a risk ratio above 1, which signifies that more discontinuations are estimated to happen for treatments with tildrakizumab 100mg. However, the findings are not statistically significant, since the 95% CIs contain 1.

Details of the risk ratios are displayed in the table below.

TABLE 5.10: SUMMARY OF THE RESULTS OF THE BUCHER METHOD, WEEK 24-28

Outcome	Studies included in the analysis	Fixed/ random effects	Risk ratio (95% CI)						Absolute effect estimate		
			Tildrakizumab (100 mg) to placebo		Guselkumab (100mg) to placebo		Tildrakizumab (100 mg) to guselkumab (100 mg)		Absolute effect comparator	Estimated risk difference* (95% CI)	
PASI 75	reSURFACE 1+2 VOYAGE 1+2	FE	12.5	(7.69, 20.0)	12.5	(9.09, 6.67)	1.00	(0.57, 1.75)	89.90%	0.0%	(-38.8%, 67.8%)
		RE	12.5	(7.69, 20.0)	12.5	(9.09,16.67)	1.00	(0.57, 1.75)		0.0%	(-38.8%, 67.8%)
PASI 90	reSURFACE 1+2 VOYAGE 1+2	FE	25	(11.11, 50)	33.33	(16.67,50.0)	0.81	(0.30, 2.17)	77.20%	-14.4%	(-53.9%, 90.6%)
		RE	25	(11.11, 50)	33.33	(16.67,50.0)	0.81	(0.30, 2.17)		-14.4%	(-53.9%, 90.6%)
SAE	reSURFACE 1+2 VOYAGE 2	FE	2.17	(0.82, 5.88)	3.03	(0.89, 10.0)	0.72	(0.15, 3.45)	3.60%	-1.0%	(-3.0%, 8.8%)
		RE	2.22	(0.81, 5.88)	3.03	(0.89, 10.0)	0.74	(0.15, 3.57)		-1.0%	(-3.1%, 9.3%)
DLQI 0/1	reSURFACE 1+2 VOYAGE 1+2	FE	7.69	(5, 12.5)	16.67	(10.0, 25.0)	0.47	(0.24, 0.92)	57.90%	-30.6%	(-43.8%, -4.8%)
		RE	7.69	(5, 12.5)	16.67	(10.0, 25.0)	0.47	(0.24, 0.92)		-30.6%	(-43.8%, -4.8%)
Discontinuations	reSURFACE 1+2 VOYAGE 2	FE	1.19	(0.74, 1.92)	0.87	(0.47, 1.61)	1.39	(0.63, 3.03)	2.90%	1.1%	(-1.1%, 5.9%)
		RE	1.22	(0.36, 4.17)	0.87	(0.47, 1.61)	1.41	(0.36, 5.56)		1.2%	(-1.9%, 13.2%)

CI- confidence interval; DLQI- Dermatology Life Quality Index; FE- fixed effects; PASI- Psoriasis Area Sensitivity Index; RE- random effects; SAE- Serious Adverse Events

* Positive numbers imply more events are predicted for patients treated with tildrakizumab 100mg, compared to those treated with guselkumab 100mg.

Appendix G presents the analysis of DLQI response rate based on the analysis population in the original publications. The conclusion of this analysis is the same as above; the confidence interval for the RR does not include 1 but the confidence interval for ARR includes the protocol-defined MCID.

Importantly DLQI 0/1 response rates only assess one tail of the entire DLQI data distribution (score range from 0-30), and thus if the two distributions are not completely analogous, DLQI 0/1 data may not capture the full extent of the relationship between the two treatment. Alternatively, the effect on DLQI could be assessed by a mean of the distribution, for which mean change from baseline appears the most appropriate measure of treatment effect. This sensitivity analysis is provided in appendix E.

The analysis of change from baseline to week 24-28 (see Table 5.11) showed that the treatment effect on this parameter is similar for guselkumab 100mg and tildrakizumab 100mg. The change from baseline to week 24-28 for guselkumab 100mg compared to tildrakizumab 100mg was -0.70 points (95%CI: -2.86, 1.46). This analysis supports that no significant or clinical important difference is to be expected on patient quality of life for patients treated with tildrakizumab 100mg compared to patient treated with guselkumab 100mg.

TABLE 5.11 RESULT OF BUCHER INDIRECT COMPARISON. MEAN DIFFERENCE IN DLQI CHANGE FROM BASELINE TO WEEK 24-28

	Mean difference	95% CI	
Tildrakizumab 100mg compared to guselkumab 100mg	0.70	-1.46	2.86

In addition to the results presented here, results have been estimated using indirect comparison of reSURFACE and VOYAGE trials at week 12-16 (appendix C) and in a sensitivity analysis including also the Ohtsuki trial trial of guselkumab [6] in a Japanese population (appendix D). These analyses yielded identical findings.

The overall conclusion of all three indirect comparison is that there was no statistically significant difference between guselkumab and tildrakizumab for PASI 75, PASI 90, SAE and rate of discontinuations at either timepoint. For DLQI 0/1 the risk ratios were statistically significant in favour of guselkumab. Thus, for all critical endpoints (PASI 75 and SAEs) and all but one important endpoint no difference was detected between the two treatments.

Narrative comparison of outcomes after one year of treatment

Trial period, trial geography, patient flow, and patient baseline characteristics are detailed in section 4.2, and as it can be seen here, the two reSURFACE and VOYAGE trials appear comparable regarding these characteristics. Details on trial design for each of these four trials can be found in section 4.2. At week 28 in the reSURFACE trials, patients on either dose of tildrakizumab who were PASI 75 or PASI 50 responders were re-randomized to either their existing tildrakizumab dosing regimen, the alternative dose of tildrakizumab or placebo (options varied between the two treatment arms and

trials - see 4.2 for details). Non-responders were discontinued from their respective trial. Using a similar concept, PASI 90 responders on guselkumab were re-randomized to either their existing treatment or placebo at week 28 in the VOYAGE 2 trial (see 4.2 for details), whereas non-responders were switched to guselkumab 100 mg Q8W. In the VOYAGE 1 trial, no re-randomization was conducted throughout the trial (see 4.2 for details).

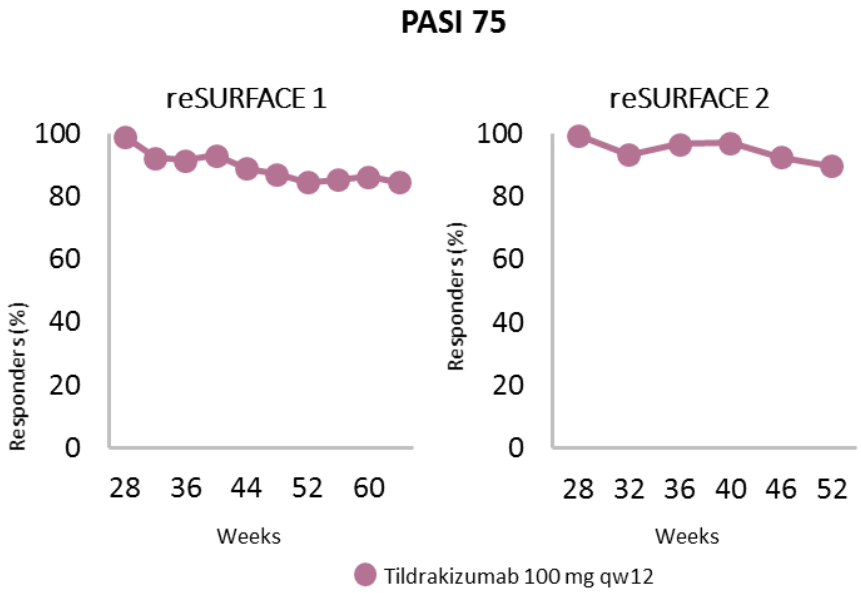
These major trial design differences significantly obscure narrative comparison of tildrakizumab and guselkumab for most outcomes after one year of treatment. An examination of complications for each outcome is provided below:

- **PASI response rates**: Due to the re-randomization at week 28 in the reSURFACE trials, it is not possible to calculate response rates for the ITT population after one year of tildrakizumab treatment, and therefore, one-year data from these studies cannot be compared to VOYAGE 1 during which patients continue the same treatment throughout one year. Moreover, since responders at week 28 are defined differently in the reSURFACE trials (PASI75) compared to VOYAGE 2 (PASI90), a direct comparison between response rates from these trials is not meaningful. A general comparative description of maintenance of response for the reSURFACE trials and the VOYAGE 2 trial until one year of treatment may however provide some value and is provided below.
- **DLQI 0/1 response rates**: Any meaningful comparison is not possible due to the same argumentation as above for PASI response rates.
- **SAE**: Given the assumption that risk of SAE is largely independent of study design as long the target population and dosing regimen is constant, it seems possible to narratively compare the two treatments on this outcome throughout one year of therapy.
- **Discontinuation rate**: Since non-responders (< PASI 50) are discontinued at week 28 in the reSURFACE trials in contrast to VOYAGE 2, during which all patients continue the trial, comparison of discontinuation data after one year of treatment is not relevant.

Comparative description of maintenance of response throughout one year of treatment

Data for PASI 75 responders on tildrakizumab 100 mg Q12W, who continued their treatment in part 3 of the reSURFACE trials, are depicted in Figure 5.5. In reSURFACE 1, 85 % of patients, who obtained a PASI 75 response on tildrakizumab 100 mg and continued their treatment in part 3, maintained their PASI 75 response at the end of part 3 (i.e. week 64; non-responder imputation). At the end of part 3 (i.e. week 52) of reSURFACE 2, 90 % of PASI 75 responders, who continued on tildrakizimab 100 mg, sustained their response (non-responder imputation; [3]). Thus, approximately 9 out of 10 patients on tildrakizumab 100 mg appear to maintain a highly clinically meaningful response (PASI 75) over a period of half a year.

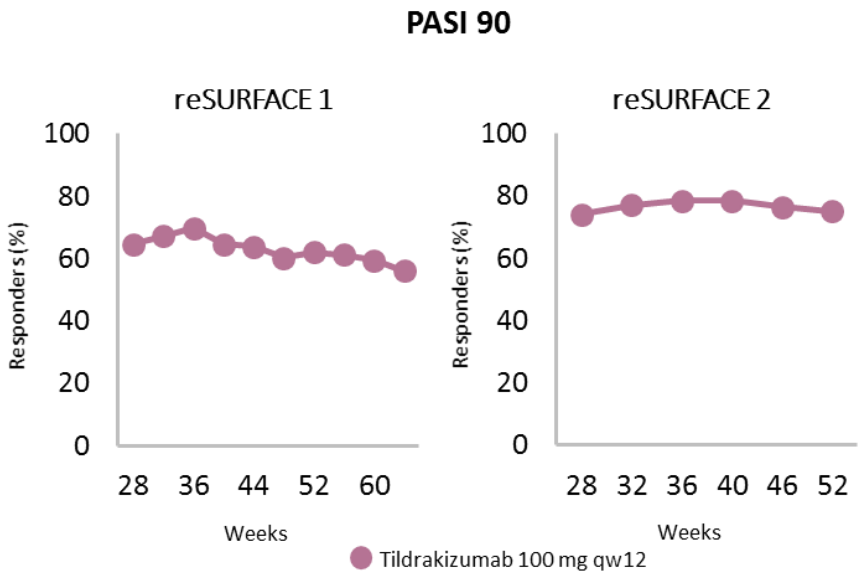
FIGURE 5.5 PASI 75 RESPONSE OVER TIME IN WEEK 28 PASI 75 RESPONDERS WHO CONTINUED TILDRAKIZUMAB 100 MG



Non-responder imputation. Source: Adapted from [3]

At week 28, 65 % and 74 % of the PASI 75 responders, who continued tildrakizumab 100 mg, were also PASI 90 responders in reSURFACE 1 and 2, respectively. Of these PASI 75 responders, 56 % and 75 % had a PASI 90 response at the end of part 3 of reSURFACE 1 and 2, respectively (see Figure 5.6; non-responder imputation; Almirall data on file). Thus, these data again substantiate that a clinical response on tildrakizumab 100 mg is largely maintained over time.

FIGURE 5.6 PASI 90 RESPONSE OVER TIME IN WEEK 28 PASI 75 RESPONDERS WHO CONTINUED TILDRAKIZUMAB 100 MG



Non-responder imputation. Source: Almirall data on file

Among partial responders (i.e. > PASI50 but < PASI75) at week 28 in reSURFACE 1 who continued on tildrakizumab 100 mg, 63 % enhanced their response to PASI75 on tildrakizumab 100 mg (non-

responder imputation; [3]). The corresponding figures for reSURFACE 2 were 62 % on tildrakizumab 100 mg during part 3 (non-responder imputation; [3]). Thus, the skin symptoms of a substantial proportion of partial responders at week 28 continued to improve throughout one year of treatment.

Data curve for PASI 90 responders on guselkumab 100 mg Q8W, who continued their treatment throughout week 48 of the VOYAGE 2 trial can be found in [5]. At week 48, 89.6 % of patients, who obtained a PASI 90 response on guselkumab 100 mg and continued their treatment, maintained their response[5]. In conclusion, in line with tildrakizumab results approximately 9 out of 10 patients on guselkumab 100 mg Q8W maintained a highly clinically meaningful response (PASI 90) over a period of half a year. However, this comparison should be interpreted with caution due to the difference in responder definition (PASI 75 versus PASI 90) as well as data endpoint (week 52/64 versus week 48).

Narrative comparison of SAE rates

At the cut-off for our literature search (20th of November 2018), SAE rates after one year of treatment have not been reported in peer-reviewed manuscripts for the two reSURFACE trials as well as the VOYAGE 2 trial. However, EMA's European public assessment report for either treatment provide SAE per 100 patient-years from a pooled safety analysis of relevant clinical trials. Data from the two VOYAGE trials were included in the analysis for guselkumab, whereas the analysis for tildrakizumab included the two reSURFACE trials as well as a phase IIb study (NCT01225731) in the same target population [1, 13]. The inclusion of the phase IIb trial may appear confounding, but an unpublished analysis of data solely from the reSURFACE trials return the exact same value as the analysis published in the EPAR for Ilumetri. For tildrakizumab, the SAE rate per 100 patient years was found to be 5.81 through the base period of the trials (week 64, 52 and 52 for reSURFACE 1, reSURFACE 2 and phase IIb, respectively) whereas the risk for guselkumab was 6.05 SAE per 100 patient years after 48 weeks of treatment [1, 13]. Thus, the risk of SAE appeared very low and similar for the two treatments throughout one year of therapy.

5.1.4 Subgroup analysis of Ilumetri trials

Patients with failure on treatments with IL-12/23 target

Ustekinumab (Stelara) is currently the only anti-psoriasis treatment available which inhibits the combination of IL-12 and IL-23 via the common p40 subunit (European marketing authorization since 15th of January 2009[14]. In addition to tildrakizumab, the only other specific IL-23 (p19) inhibitor, guselkumab (Tremfya), obtained marketing authorization on the 9th of November 2017[13].

The two reSURFACE trials were conducted in the period between December 2012 to October 2015, which precludes patients that have failed on a IL-23p19 treatment to enter these trials [3]. Additionally, previous use of treatments targeting IL23 via the p40 or p19 subunit was a specific exclusion criterion for both the reSURFACE 1 and reSURFACE 2 trials [3]. Finally, no other trial investigating tildrakizumab in moderate to severe psoriasis has been conducted since the conclusion of the reSURFACE trials. Hence, tildrakizumab efficacy/safety data for patients with a treatment failure on either ustekinumab or guselkumab are currently not available.

Patients with failure on biologic therapy

Both reSURFACE 1 and 2 enrolled patients who had been exposed to previous biologic treatment (excluding p40 and p19 IL-23 as well as IL-17 antagonists; [3]). However, these patients had not necessarily experienced a failure on previous biologic treatment, and moreover, the clinical trial data do not allow for differentiation between patients who are true failures on previous biologic

treatment and patients who merely have been exposed to these drugs[3]. Thus, Table 5.12 shows PASI 90 response rates for patient who are naïve to biologics versus a group of biologic-experienced patients. As shown, no clinically relevant difference (i.e. Δ ≥15 %) was found between patients who are naïve to biologic therapy and biologic-exposed patients including an unknown number of patients that have actually failed on biologic treatment.

TABLE 5.12: PASI 90 RESPONSE RATES FOR BIOLOGIC-NAIVE VERSUS BIOLOGIC-EXPOSED PATIENTS AT WEEK 12 AND WEEK 28

PASI 90 response rates	Biologic-exposed (*n* = 110)	Biologic-naïve (*n* = 506)	Absolute difference (Δ)	Δ ≥ 15 %
Week 12	33 (30.0 %)	193 (38.1 %)	- 8.1 p.p.	No
Week 28	50 (45.5 %)	258 (50.9 %)	- 5.4 p.p.	No

Intention-to-treat population. Non-responder imputation. PASI- Psoriasis Area Sensitivity Index; p.p.- percentage points.
Source: Almirall Data on file

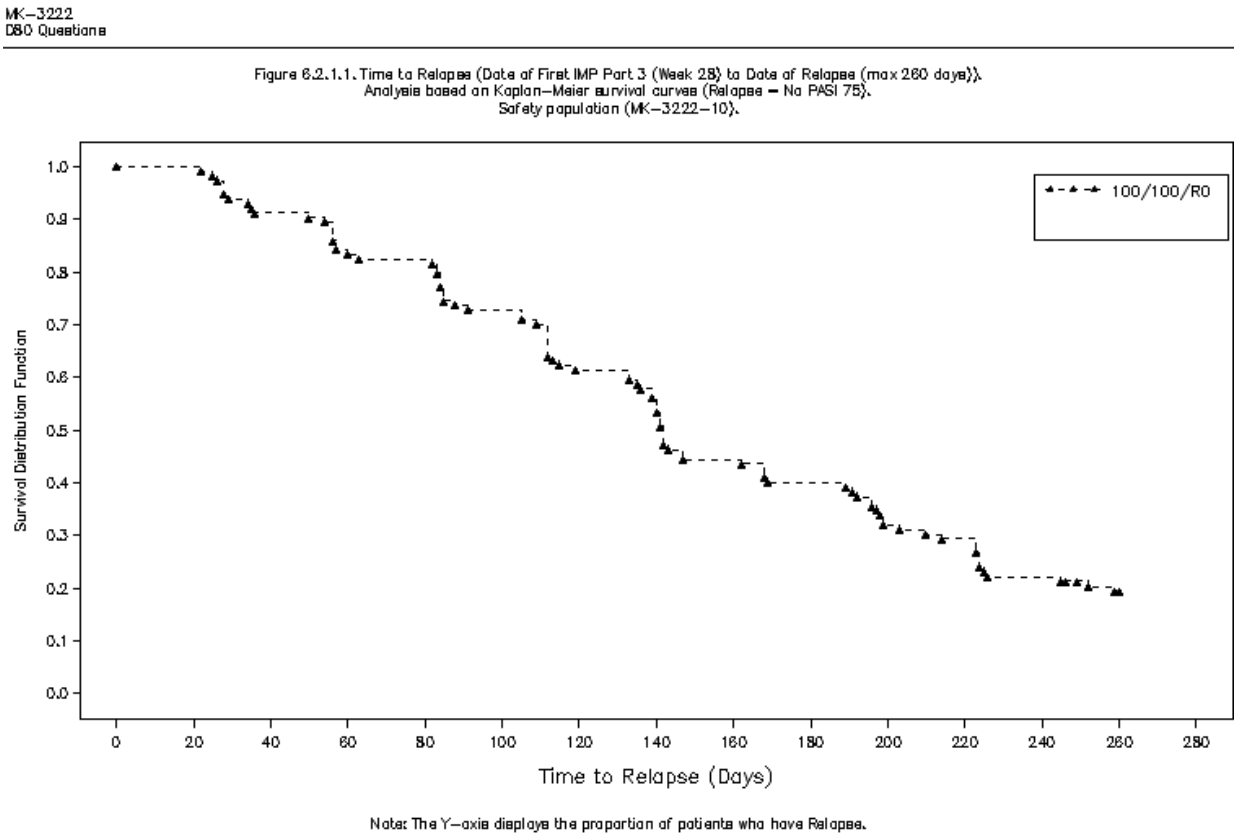
6 Other considerations

The Expert Committee for psoriasis has asked Almirall to provide additional information regarding a number of specific questions pertaining to the clinical use of tildrakizumab in a Danish setting. Almirall has attempted to address these very relevant questions using all available data, but given the current early stage of tildrakizumab's lifecycle, a proportion of the results cannot be expected to be published in peer-reviewed manuscripts.

6.1 Possibility to pause treatment

In the reSURFACE 1 trial, PASI75 responders on tildrakizumab 100 mg were re-randomized to either placebo or continue their previous treatment. Thus, relapse data for the withdrawal group may provide insight to the possibility of treatment pause. Relapse was defined as loss of PASI 75 response, and as depicted in Figure 6.1, the median time to loss of PASI 75 response from re-randomization at week 28 was 142 days, which corresponds to 226 days since the last tildrakizumab dose of 100 mg [15]. At the end of part 3 (i.e. week 64), 54 % of participants in the withdrawal group had lost the PASI 75 response[15]. In comparison, only 15 % of patients who continued tildrakizumab 100 mg in to part 3 lost their PASI 75 response [3].

FIGURE 6.1 TIME TO LOSS OF PASI 75 RESPONSE IN RESURFACE 1 AFTER RE-RANDOMIZATION TO PLACEBO AT WEEK 28



Relapse: Loss of PASI75 response. Last tildrakizumab dose administered at week 16 (12 weeks before). Source: Adapted from Thaci et al. (2018) [15]

Alternatively, relapse may be defined as loss of more than 50 % of the achieved PASI improvement. With this alternative definition, the median time to relapse from re-randomization at week 28 was 226 days, which corresponds to 310 days since the last tildrakizumab dose of 100 mg [15]).

6.2 Possibility of dose reduction of dose interval prolongation

No data from the reSURFACE trials exist on dose reduction from tildrakizumab 100 mg or dose interval prolongation. However, in a recent phase IIb trial (NCT01225731) patients who obtained a PASI 75 response at week 16 were re-randomized to continue tildrakizumab 100 mg Q12W or a dose of 25 mg Q12W. 97 % of the participants who continued the 100 mg dosing regimen maintained their response at week 52, which is statistically significantly ($P < 0.005$) superior to patients who underwent dose reduction to 25 mg (70 %)[16].

6.3 Elaboration on possibility to use 200 mg for patients with certain characteristics

Overall, there are no discernable difference between the two doses of tildrakizumab regarding efficacy or safety for the general patient population included in the phase III trials. Therefore, the recommended dose for tildrakizumab is 100 mg at week 0, 4, and every 12th week thereafter according to the SmPC of Ilumetri:

"The recommended dose in adults is 100 mg by subcutaneous injection at weeks 0, and 4 and every 12 weeks thereafter. In patients with certain characteristics (e.g. high disease burden, body weight ≥90kg) 200 mg may provide greater efficacy."

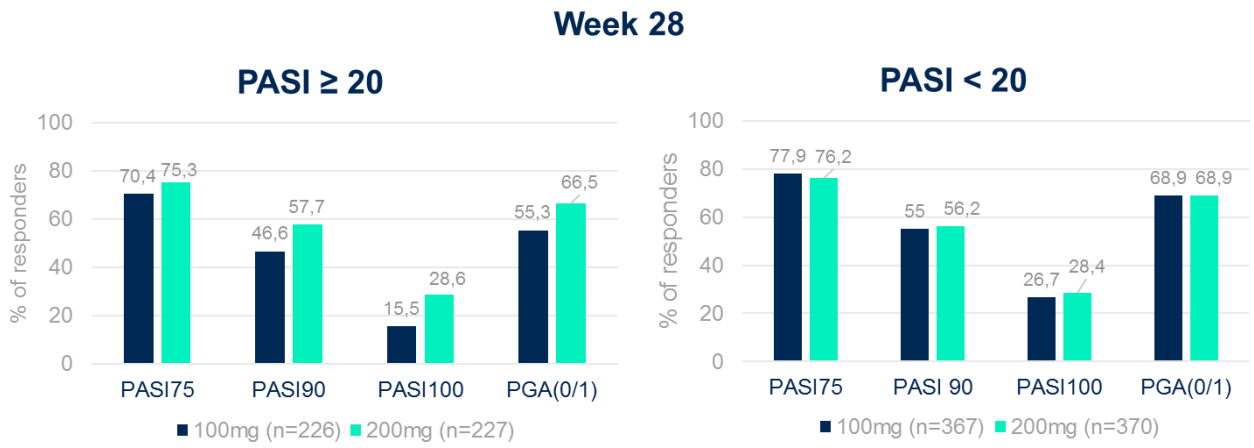
The term "high disease burden" is not clearly defined neither in the SmPC nor in the EPAR for Ilumetri. In the EPAR, "high disease burden" is mentioned in the context of a baseline PASI or BSA of more than 20. For the purpose of this discussion, we will focus on the PASI definition.

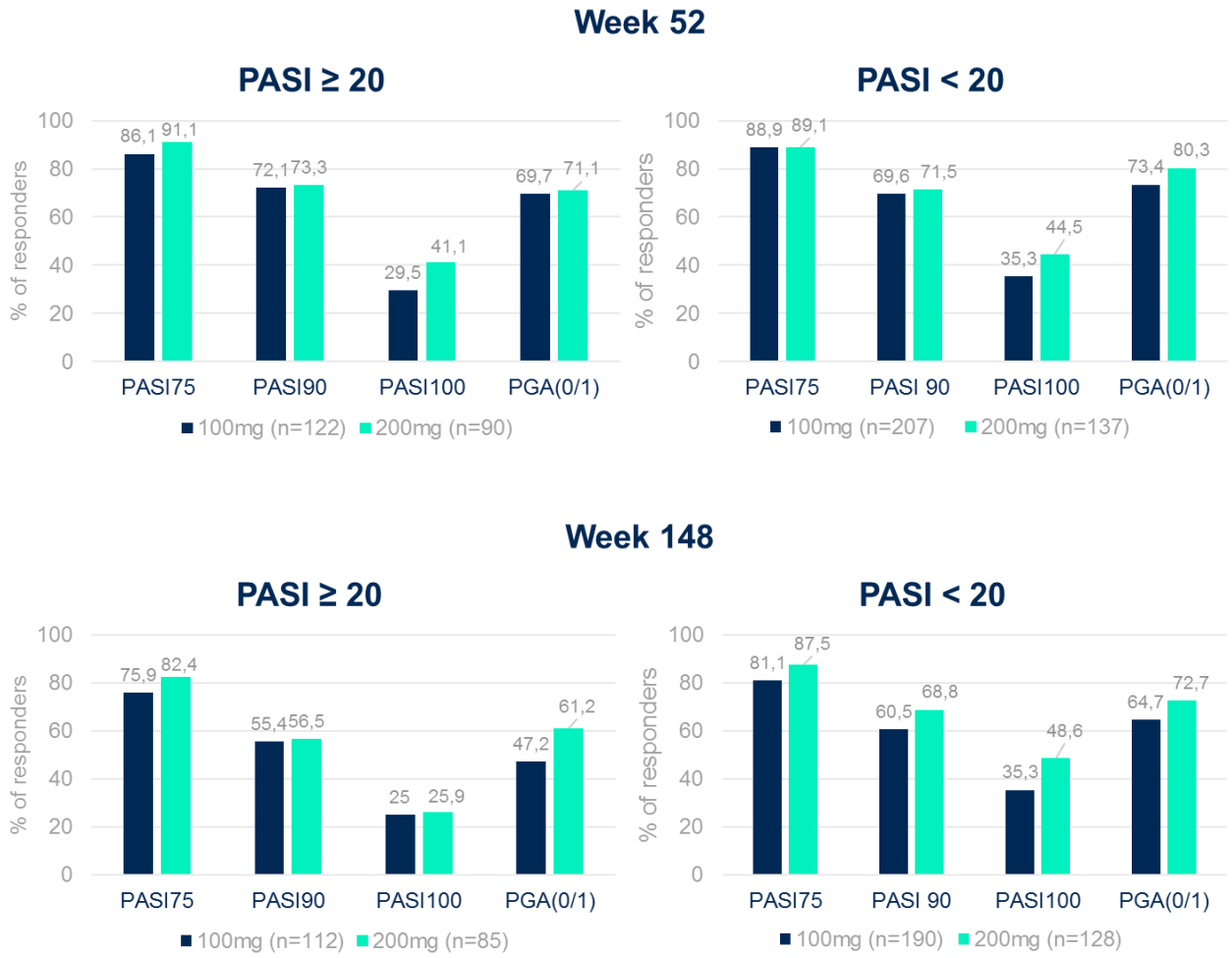
There are no clinical pharmacology data to support the use of a higher dose in patients with higher baseline PASI, and pharmacology analysis do not provide a clear-cut argument for using 200 mg in patients with a body weight above 90 kg. For instance, EMAs EPAR for Ilumetri concludes that "*While the population PK analysis showed a slight decrease in exposure with increased body mass, increased tildrakizumab exposure was not linked to greater clinical response*." However, "*There is a point that in lower weight patients < 90 kg the 100mg may be sufficient dose, as body weight was identified as most influential covariate on tildrakizumab PK. Supportively, from the pharmacokinetic point of view, subgroup analysis regarding covariate weight indicates that exposure in terms of steady state AUCss following 100 mg Q12W for patients ≤90 kg and following 200 mg Q12W for patients > 90 kg will be more balanced across the patient population*."

In addition to these clinical pharmacology data, unpublished post-hoc sub-analyses of efficacy endpoints (pooled analysis of both reSURFACE trials) were considered during the decision process to include the possibility to use 200 mg for patients with high disease burden (baseline PASI > 20) and/or body weight > 90 kg in the SmPC.

Figure 6.2 depicts various efficacy response rates over time by baseline PASI. For patients with a baseline PASI > 20 there might be a minor trend towards better efficacy for the 200 mg dose regarding stricter outcomes such as PASI 90 or 100 at week 28, but the absolute difference does not exceed 15 p.p. Moreover, these minor differences seem to more or less diminish at later time points.

FIGURE 6.2 EFFICACY AT DIFFERENT TIME POINTS BY BASELINE PASI

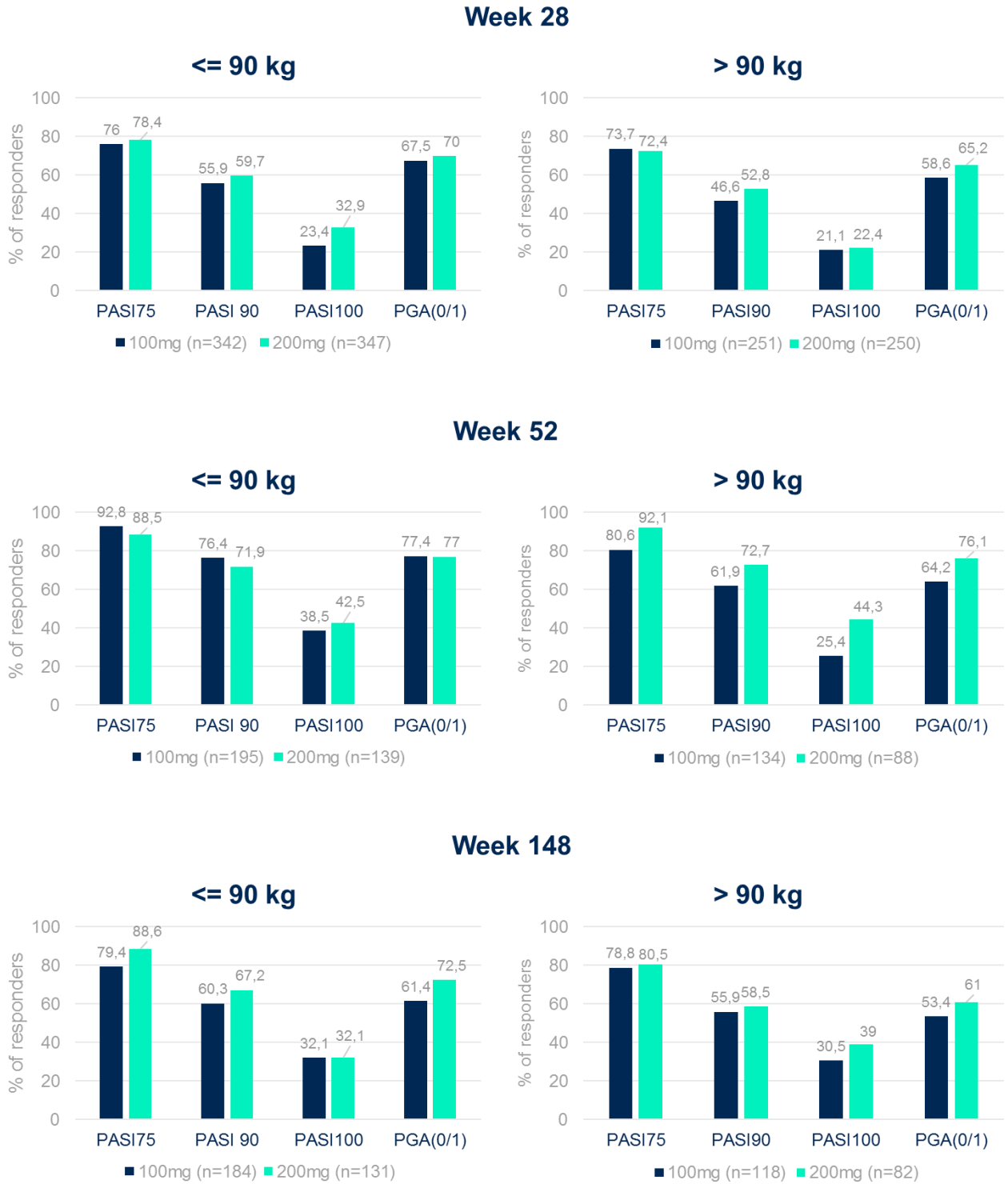




Non-responder imputation. Pooled analysis from reSURFACE 1 and 2. Source: Almirall data on file.

Efficacy endpoints at different time points grouped by body weight is shown in Figure 6.3. At week 28, it is not possible to detect a tendency towards a better response of 200 mg in patients with a body weight of more than 90 kg compared to patient with a body weight less than 90 kg. There might be a minor trend towards better response to the 200 mg dose for patients above 90 kg at week 52, but at week 148, no apparent difference is evident.

FIGURE 6.3 EFFICACY AT DIFFERENT TIME POINTS BY BODY WEIGHT



Non-responder imputation. Pooled analysis from reSURFACE 1 and 2. Source: Almirall data on file.

In conclusion, according to the criteria for added clinical value set in the Danish Medicine Council's protocol there is limited evidence for the difference between the two dosages. Therefore, Almirall recommends inclusion of the 100 mg dose as standard dosing option in the Danish national recommendations.

6.4 Relationship between loading dose and maintenance dose

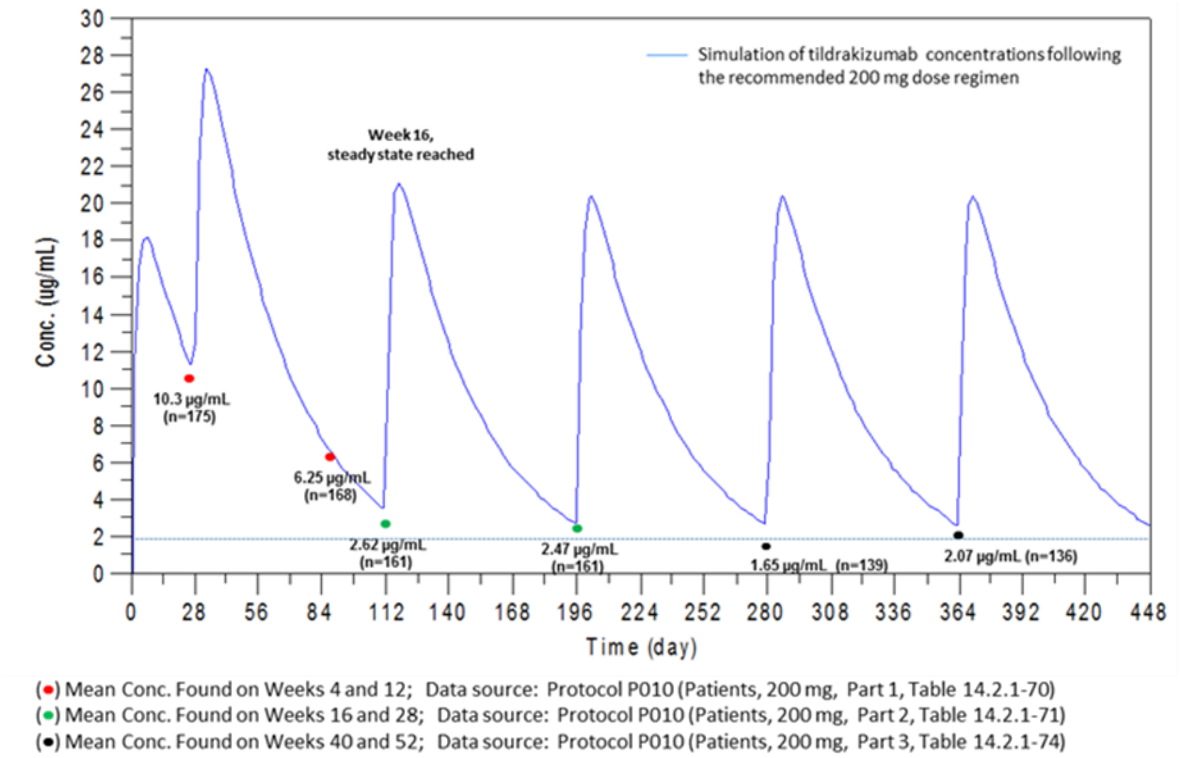
The optimal dose regimen selected for tildrakizumab was based on the phase II and III trial program, where it was clearly demonstrated that the recommended dose regimen (Week 0 and Week 4 followed with Q12W dosing thereafter) provided the best onset of action and efficacy during the induction and maintenance phases, respectively.

Data from phase I [17] and phase II [16] trials and as well as PK/PD relationships based on a mean half-life of 23,4 days [1], showed that less frequent dossing (e.g. Weeks 0, 4 and 8; [17] yield a more rapid onset of activity. This supported the need for a loading dose at Week 4. Dosing frequency beyond 12 weeks was not expected to result in adequate levels to support sustained clinical response. The two phase III trials ratified the findings obtained in phase II. It should be noticed that the current dose regimen has been demonstrated to be optimal, efficacious and safe in the two phase III trials and that no such information is available for a less frequent schedule during the first 12 weeks of treatment.

Given the long tildakizumab half-life (23,4 days; [1]) a relatively low maintenance dose is needed to keep serum concentrations at therapeutic levels (that is 100 mg QW12), however, this comes with the caveat that longer time is required to reach therapeutic level using a maintenance dosing regimen only. Therefore, considering the linear and time-independent pharmacokinetics of tildrakizumab [1], the administration of the second dose at approximately its half-life (that is, at week 4) is translated to a 2-fold increase in the peak plasma levels and, importantly, into trough concentrations (concentrations at the end of the dosing interval) similar to those of the steady state. Figure 6.4 below describes this well-known tildrakizumab PK profile (notice that Figure 6.4 corresponds to a dose of 200 mg, but the PK behaviors it is exactly the same for a 100 mg dose but with 2-fold lower concentrations).

In summary, the Week 4 tidrakizumab dose followed with Q12W dosing thereafter, provide the best onset of action and efficacy during the induction and maintenance phases, respectively.

FIGURE 6.4 TILDRAKIZUMAB SERUM CONCENTRATION-TIME PROFILE FOR RESURFACE 1

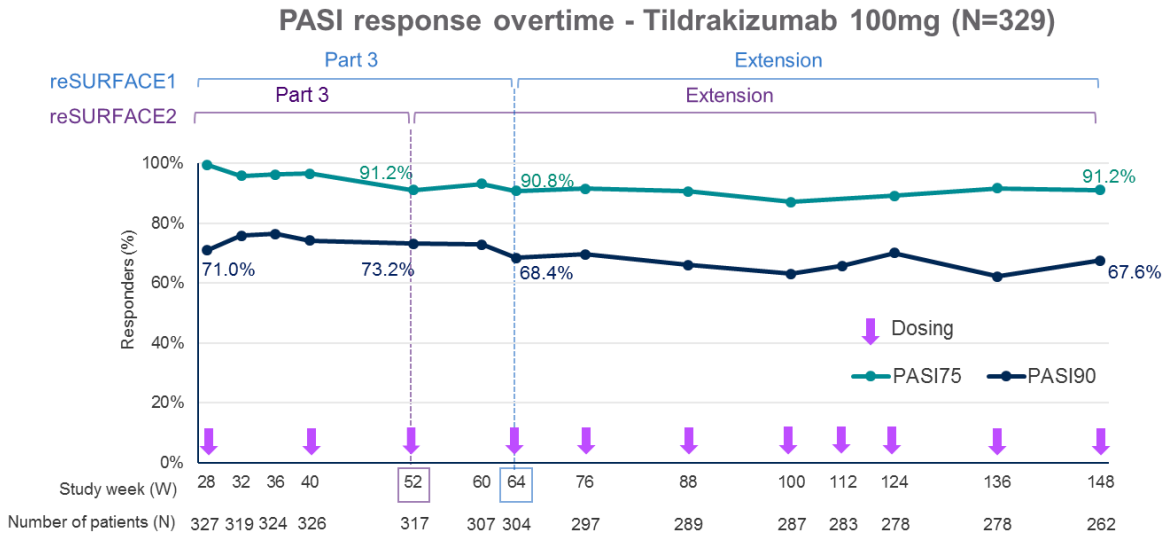


Source: Almirall data on file. Blue line represent simulated concentrations after 200 mg at 0 and 4 followed by Q12W thereafter. Filled circles represent mean experimental concentration trough values found in psoriasis patients (≤ 90 kg) in reSURFACE 1 at the same simulated doses.

6.5 Maintenance of response between dosing every 12 weeks

Insights to maintenance of response between doses of tildrakizumab 100 mg every 12 weeks may be uncovered by exploring long term efficacy data. Figure 6.5 depicts pooled PASI 75 and PASI 90 response rate from week 28 to week 148, and as also shown, tildrakizumab is dosed a week 28, 40, 52, 64, 76, 88, 100, 112, 124, 136, and 148 (purple arrows). The response rates appear to be largely maintained and, thus, there is no pattern of a decrease in response rates between doses[15]

FIGURE 6.5 LONG-TERM PASI RESPONSE RATES THROUGH WEEK 148



No imputation of missing data. Pooled analysis from reSURFACE 1 and 2. Adapted from [15]

7 References

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4. Blauvelt A, Papp KA, Griffiths CEM, Randazzo B, Wasfi Y, Shen Y-K, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: Results from the phase III, double-blinded, placebo- and active comparator-controlled VOYAGE 1 trial. J Am Acad Dermatol. 2017;76(3):405-17.
5. Reich K, Armstrong AW, Foley P, Song M, Wasfi Y, Randazzo B, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the treatment of patients with moderate to severe psoriasis with randomized withdrawal and retreatment: Results from the phase III, double-blind, placebo- and active comparator-controlled VOYAGE 2 trial. J Am Acad Dermatol. 2017;76(3):418-31.
6. Ohtsuki M, Kubo H, Morishima H, Goto R, Zheng R, Nakagawa H. Guselkumab, an anti-interleukin-23 monoclonal antibody, for the treatment of moderate to severe plaque-type psoriasis in Japanese patients: Efficacy and safety results from a phase 3, randomized, double-blind, placebo-controlled study. Journal of Dermatology. 2018;45(9):1053-62.
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9. Medicinrådet. Baggrund for Medicinrådets anbefaling vedrørende guselkumab som mulig standardbehandling til moderat til svær plaque psoriasis. København: Medicinrådet; 2018 15. Marts.
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12. Higgins JPT, Altman DG, Sterne JAC. Section 12.4.1: Confidence intervals. 2011. In: Cochrane Handbook for Systematic Reviews of Interventions [Version 510][updated March 2011] [Internet]. The Cochrane Collaboration. Available from: https://handbook-5-1.cochrane.org/chapter_12/12_4_1_confidence_intervals.htm.
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14. EMA. Assessment Report. Stelara. EMEA/H/C/000958. European Medicines Agency. Committee for Medicinal Products for Human Use, CHMP; 2009 9 February.
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week 28: pooled analysis through 3 years (148 weeks) from reSURFACE 1 and reSURFACE 2 phase 3 trials. EADV; 2018 12-16 SEPTEMBER; Paris.
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17. Kopp TER, Christine Bangert, Edward Bowman, Elli Greisenegger, Ann Horowitz, Harald Kittler, Wendy Blumenschein, Terrill McClanahan, Thomas Marbury, Claus Zachariae, Danlin Xu, Xiaoli (Shirley) Hou, Anish Mehta, Anthe Zandvliet, Diana Montgomery, Frank van Aarle & Sauzanne Khalilieh. A Rising Multiple-Dose Tolerability, Safety, and Pharmacokinetic Study of Intravenous Tildrakizumab in Patients With Psoriasis Nature Protocol Exchange2015 [Available from: https://www.nature.com/protocolexchange/protocols/3721.
18. Thomson Reuters. Endnote [X8 for Windows & Mac]. Philadelphia: Thomson Reuters; 2015.

APPENDIX A: Literature search

1 Search strategy

The literature search was designed to identify trials of tildrakizumab and guselkumab in patients with moderate to severe psoriasis. The searches included two concepts and was structured as follows:

Psoriasis AND (tildrakizumab OR guselkumab)

The searches were undertaken in the databases shown in Table A.1 and full search strategies are presented in Figure A.1.

TABLE A.1. DATABASES SEARCHED TO IDENTIFY STUDIES FOR THE SYSTEMATIC REVIEW ITC

Database / information source	Interface / URL
MEDLINE, MEDLINE In-Process and MEDLINE(R) Daily Epub Ahead of Print	Ovid SP
Cochrane Central Register of Controlled Trials (CENTRAL)	Cochrane Library / Wiley

FIGURE A.1: DETAILED SEARCH STRATEGIES

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 to November 20, 2018>

Search Strategy:

---

1 psoria$.ti,ab,kf. (43984)

2 exp Psoriasis/ (36568)

3 (Guselkumab or Tremfya$2 or CNTO 1959 or CNTO1959 or 089658A12D or 1350289-85-8).ti,ab,kf,nm,rn. (88)

4 (ilumetri or ilumya or tildrakizumab or MK 3222 or MK3222 or SCH 900222 or SCH900222 or DEW6X41BEK or 1326244-10-3).ti,ab,kf,nm,rn. (59)

5 or/1-2 (49385)

6 or/3-4 (111)

7 5 and 6 (95)

Database: Cochrane Central Register of Controlled Trials Issue 11 of 12, November 2018

Search Strategy:

#1 psoria* 6347

#2 [mh Psoriasis] 2797

#3 (Guselkumab or Tremfya* or "CNTO 1959" or CNTO1959 or 089658A12D or "1350289-85-8") 70

```
#4          (ilumetri or ilumya or tildrakizumab or MK 3222 or MK3222 or SCH 900222
or SCH900222 or DEW6X41BEK or "1326244-10-3")    38

#5          #1 or #2     6347

#6          #3 or #4     100

#7          #5 and #6 in Trials      89
```

The database search results were loaded into EndNote bibliographic software [18]. The records were de-duplicated using several algorithms.

2 Study Selection

The detailed eligibility criteria are presented in Table A.2.

TABLE A.2: ELIGIBILITY CRITERIA

	Inclusion criteria	Exclusion criteria
Population	Adult patients (≥18 years of age) with moderate to severe chronic plaque psoriasis	Children younger than 18 years
Intervention	• Tildrakizumab (Ilumetri) (100mg week 0, 4, Q12W) • Guselkumab (Tremfya) (100mg week 0,4, Q8W)	Studies without either of these interventions
Comparators	• Placebo	NA
Outcomes	• Severity of psoriasis: Psoriasis Area Severity Index (PASI) 75 or 90 • % patient with DLQI 0/1 • Frequency of Serious Adverse Events • Withdrawals for any cause Outcomes based on ITT analysis	NA
Study Design	Phase III randomized controlled trials (RCTs)	• Phase I, II or IV RCTs • Case studies • Case reports • Non-randomised controlled trials
Limits	• English language publications only • Studies published as full text articles in peer review journals	• Non-English language publications • Conference abstracts

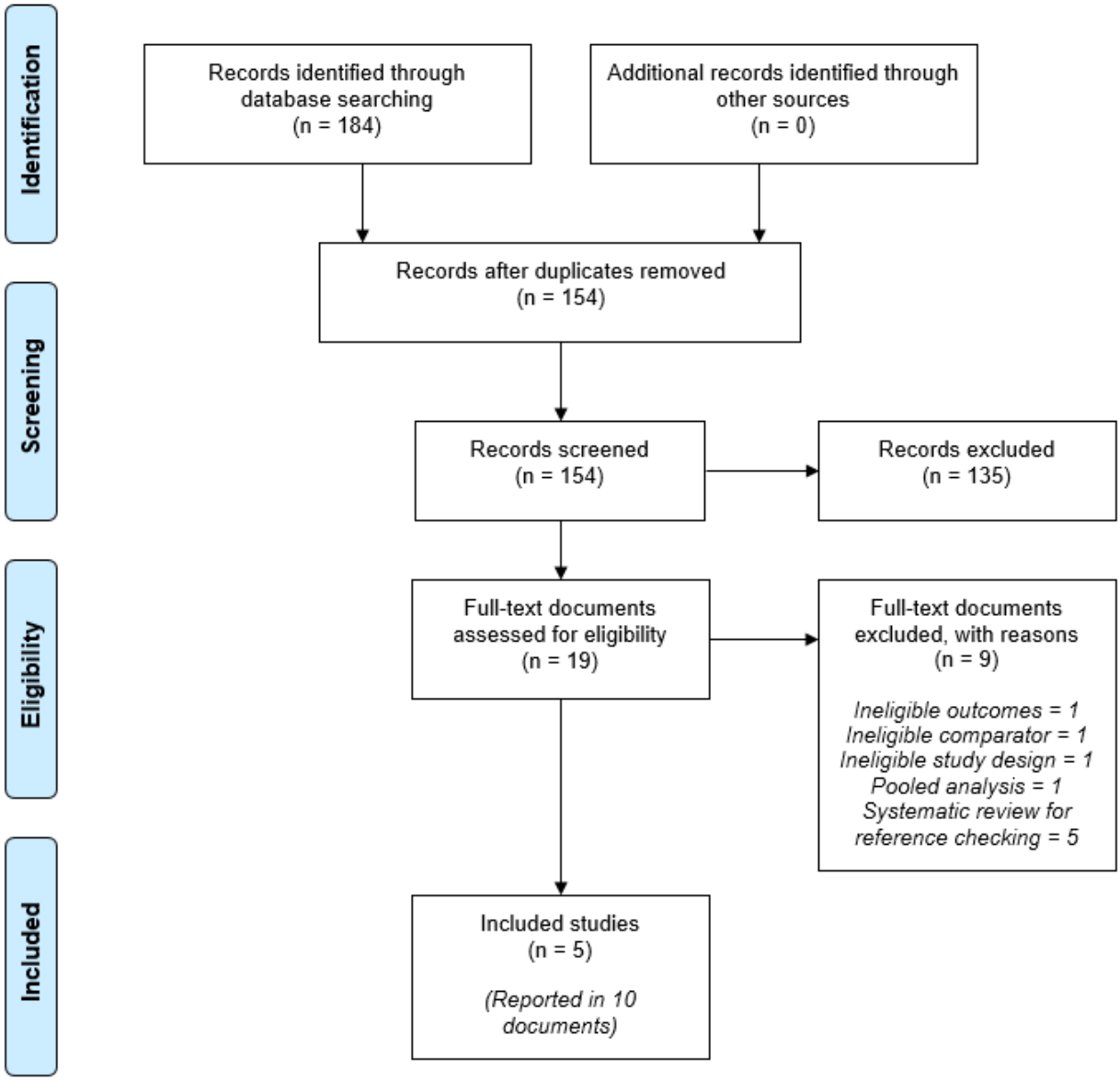
The search results were rapidly assessed according to their relevance in providing information in relation to the review. Obviously irrelevant records, such as animal studies, commentaries and news items, and records on issues unrelated to the topic of interest were removed. Two reviewers assessed the titles and abstracts independently for relevance to the eligibility criteria. A third reviewer adjudicated any disagreements.

Full texts of potentially relevant studies were obtained and assessed in detail for relevance to the review's eligibility criteria. This produced a list of eligible and ineligible studies. Where results for one study were reported in more than one paper, all related papers were identified and grouped together to ensure that participants in individual studies were only included once.

Two reviewers independently undertook the record selection, with a third reviewer adjudicating any disagreements. Studies excluded after assessment of the full document are listed in an excluded studies table with the reasons for exclusion (Appendix A).

The PRISMA study flow diagram (Figure A.2) shows the number of records identified by the search and the numbers excluded at various selection stages.

FIGURE A.2: PRISMA FLOW DIAGRAM



3 Full text publication excluded

TABLE A.3 EXCLUDED STUDIES (N:9) WITH REASONS FOR EXCLUSION

Reference	Reason for Exclusion
Bilal J, Berlinberg A, Bhattacharjee S, Trost J, Riaz IB, Kurtzman DJB. A systematic review and meta-analysis of the efficacy and safety of the interleukin (IL)-12/23 and IL-17 inhibitors ustekinumab, secukinumab, ixekizumab, brodalumab, guselkumab and tildrakizumab for the treatment of moderate to severe plaque psoriasis. J Dermatolog Treat. 2018;29(6):569-78.	Systematic review for reference checking only
Bilal J, Berlinberg A, Bhattacharjee S, Trost J, Riaz IB, Kurtzman DJB. A systematic review and meta-analysis of the efficacy and safety of the interleukin (IL)-12/23 and IL-17 inhibitors ustekinumab, secukinumab, ixekizumab, brodalumab, guselkumab and tildrakizumab for the treatment of moderate to severe plaque psoriasis. J Dermatolog Treat. 2018;29(6):569-78.	Systematic review for reference checking only
Blauvelt A, Reich K, Papp KA, Kimball AB, Gooderham M, Tyring SK, et al. Safety of tildrakizumab for moderate-to-severe plaque psoriasis: pooled analysis of three randomized controlled trials. Br J Dermatol. 2018;179(3):615-22.	Pooled analysis
Hu C, Yao Z, Chen Y, Randazzo B, Zhang L, Xu Z, et al. A comprehensive evaluation of exposure-response relationships in clinical trials: application to support guselkumab dose selection for patients with psoriasis. J Pharmacokinet Pharmacodyn. 2018;45(4):523-35.	Ineligible outcomes
Langley RG, Tsai TF, Flavin S, Song M, Randazzo B, Wasfi Y, et al. Efficacy and safety of guselkumab in patients with psoriasis who have an inadequate response to ustekinumab: results of the randomized, double-blind, phase III NAVIGATE trial. Br J Dermatol. 2018;178(1):114-23.	Ineligible comparator
Nakamura M, Lee K, Jeon C, Sekhon S, Afifi L, Yan D, et al. Guselkumab for the Treatment of Psoriasis: A Review of Phase III Trials. Dermatol Ther. 2017;7(3):281-92.	Systematic review for reference checking only
Sofen H, Smith S, Matheson RT, Leonardi CL, Calderon C, Brodmerkel C, et al. Guselkumab (an IL-23-specific mAb) demonstrates clinical and molecular response in patients with moderate-to-severe psoriasis. J Allergy Clin Immunol. 2014;133(4):1032-40.	Ineligible study design
Sbidian E, Chaimani A, Garcia-Doval I, Do G, Hua C, Mazaud C, et al. Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis. Cochrane Database Syst Rev. 2017;12:CD011535.	Systematic review for reference checking only
Tausend W, Downing C, Tyring S. Systematic review of interleukin-12, interleukin-17, and interleukin-23 pathway inhibitors for the treatment of moderate-to-severe chronic plaque psoriasis: ustekinumab, briakinumab, tildrakizumab, guselkumab, secukinumab, ixekizumab, and brodalumab. J Cutan Med Surg. 2014;18(3):156-69.	Systematic review for reference checking only

APPENDIX B: Forest Plots, Week 24-28 analysis

Below the forest plots from the comparisons of active treatment to placebo are presented. Please note that the RR are presented as the rate of placebo to the rate of active treatment in all plots as described in section 5.1.3. The RR presented in section 5.1.1 are inverted (rate of events on active treatment compared to placebo).

FIGURE B.1: TILDRAKIZUMAB: FOREST PLOT FOR PASI 75 AT 24-28 WEEKS

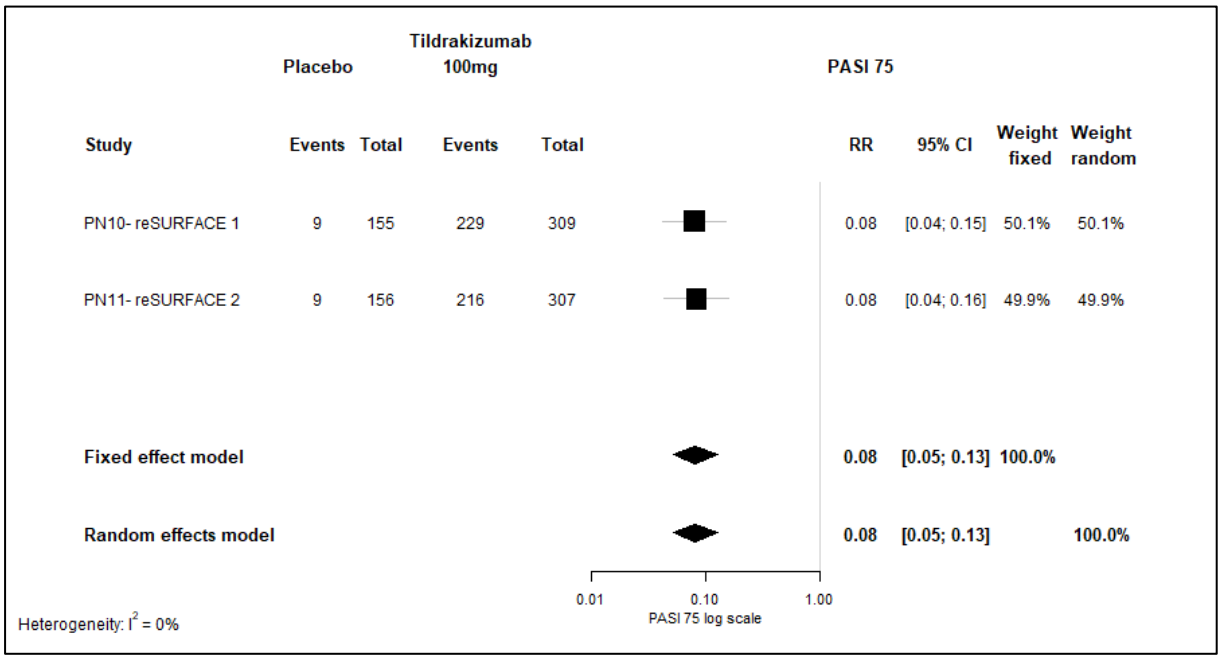


FIGURE B.2: TILDRAKIZUMAB: FOREST PLOT FOR PASI 90 AT 24-28 WEEKS

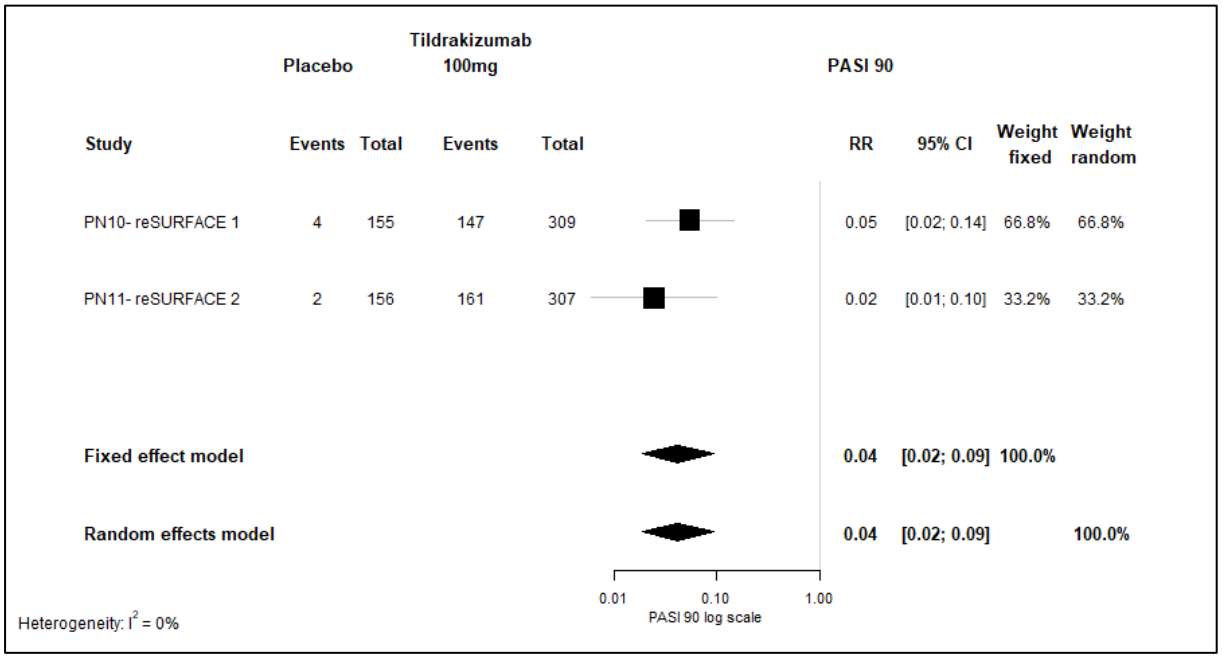


FIGURE B.3: TILDRAKIZUMAB: FOREST PLOT FOR SAE AT 24-28 WEEKS

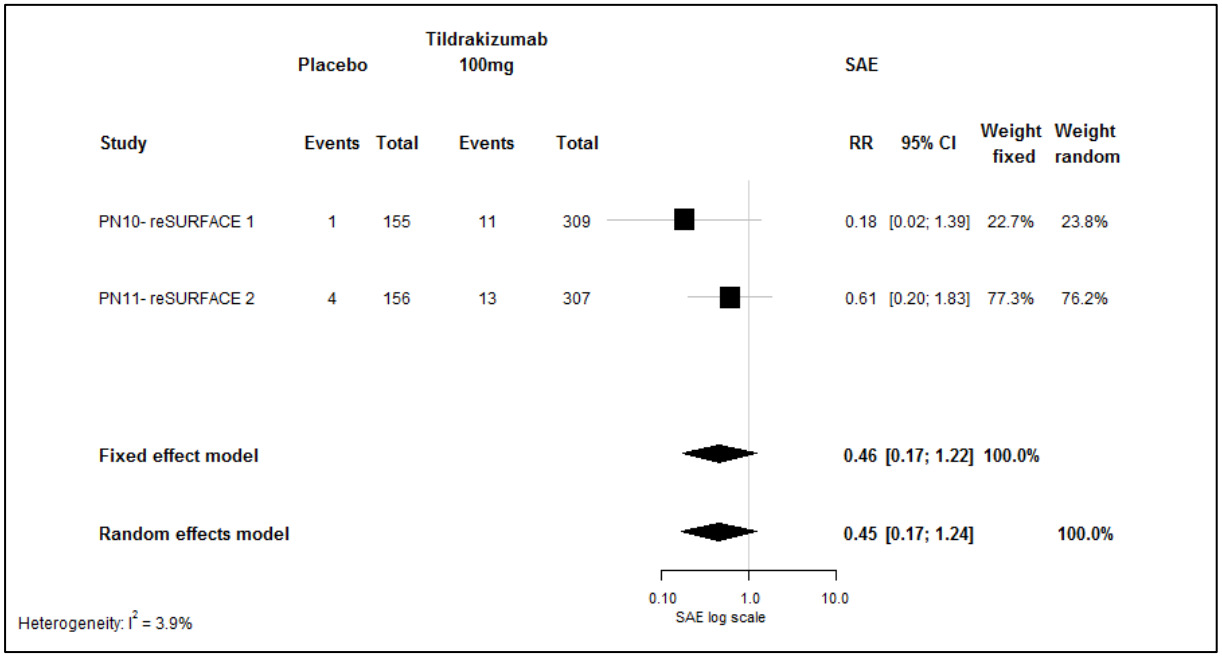


FIGURE B.4: TILDRAKIZUMAB: FOREST PLOT FOR DLQI 0/1 AT 24-28 WEEKS

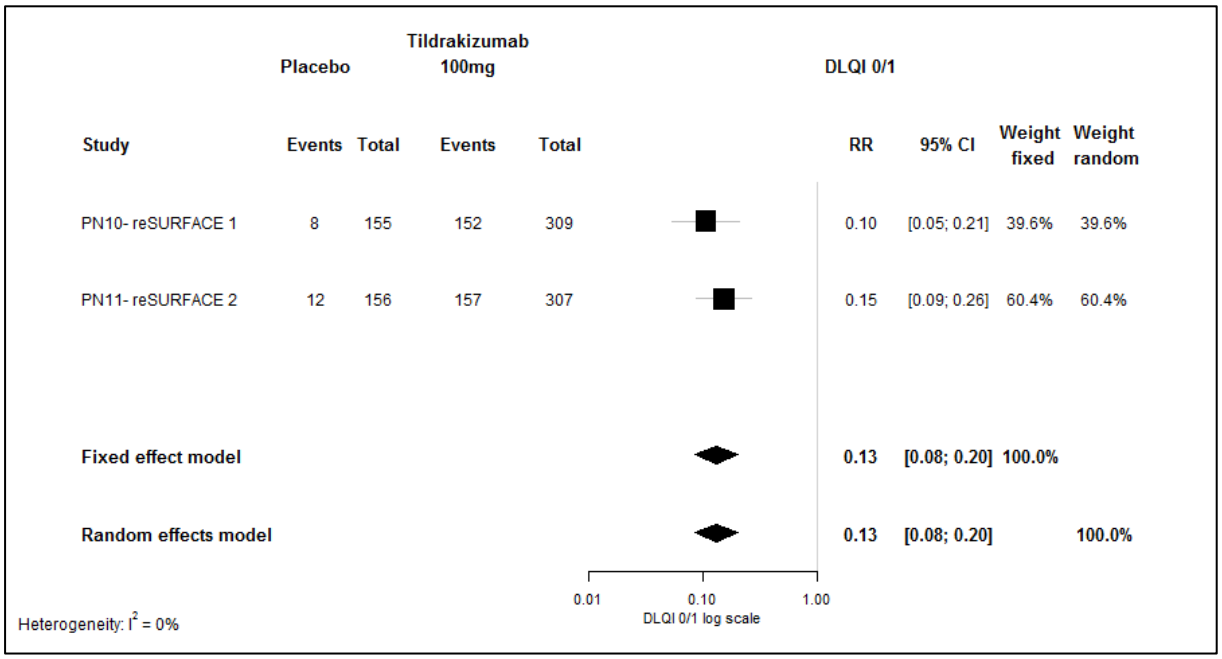


FIGURE B.5: TILDRAKIZUMAB: FOREST PLOT FOR DISCONTINUATIONS AT 24-28 WEEKS

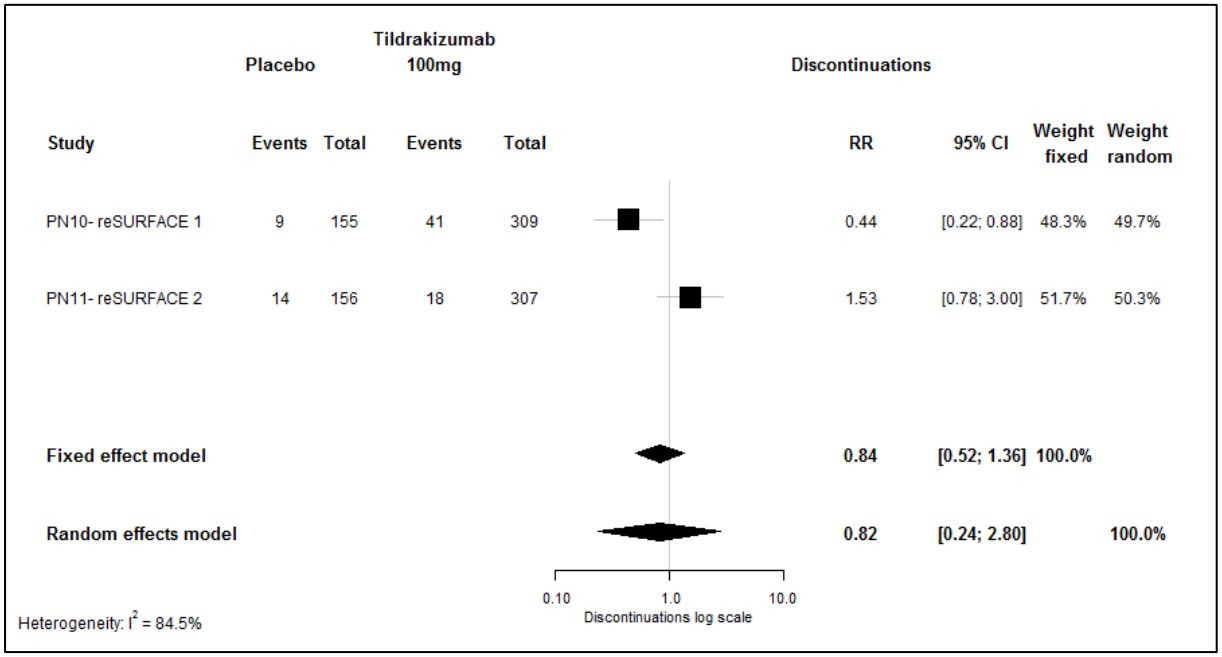


FIGURE B.6: GUSELKUMAB: FOREST PLOT FOR PASI 75 AT 24-28 WEEKS

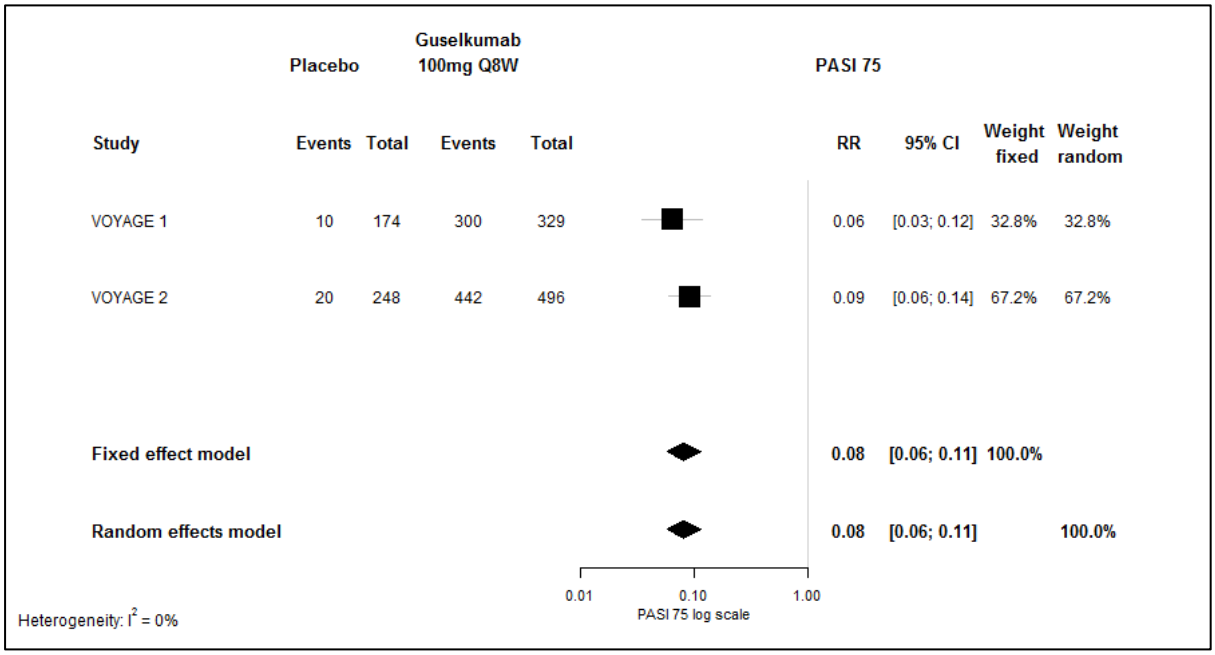


FIGURE B.7: GUSELKUMAB: FOREST PLOT FOR PASI 90 AT 24-28 WEEKS

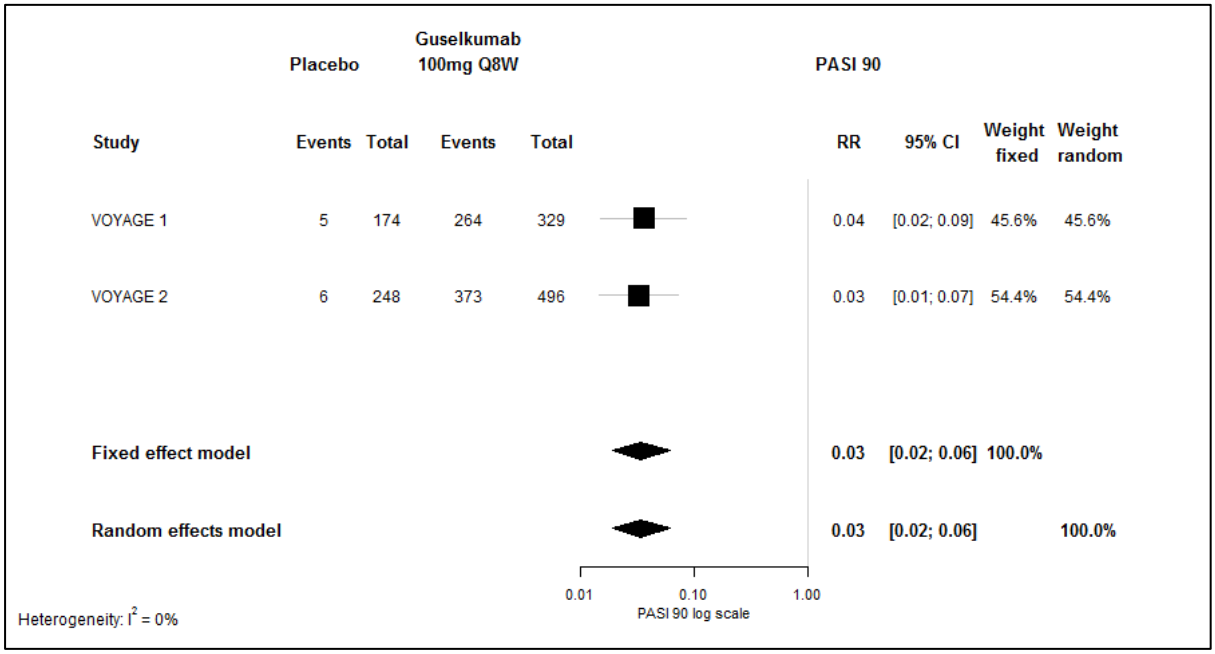
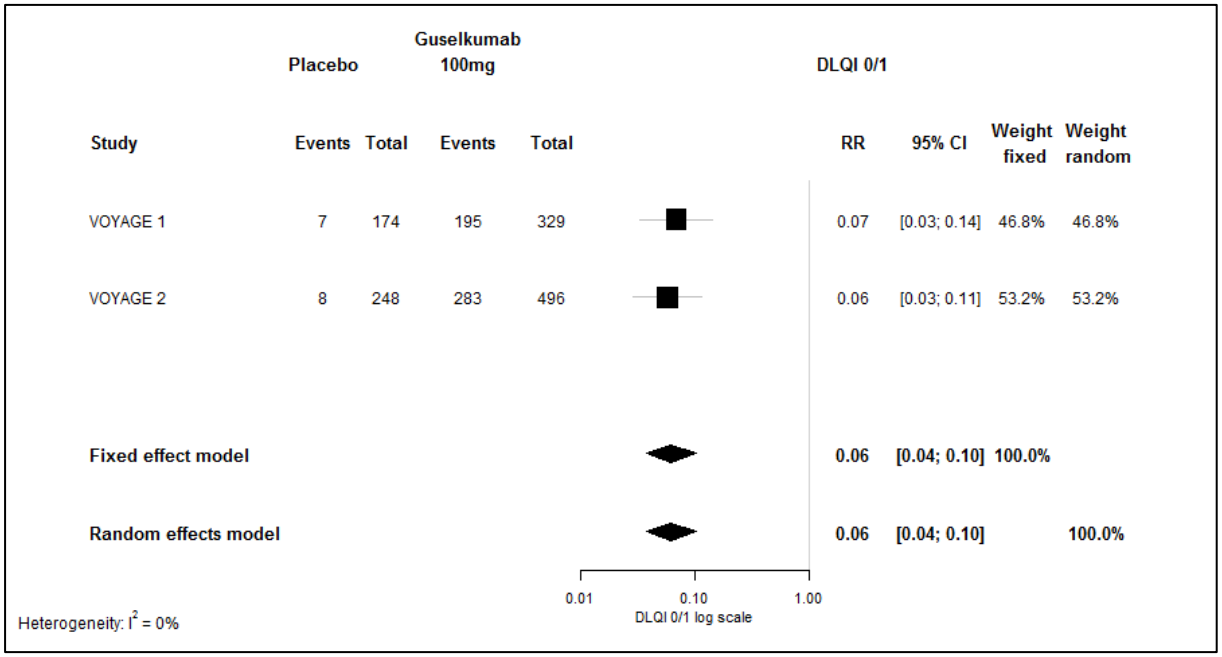


FIGURE B.8: GUSELKUMAB: FOREST PLOT FOR DLQI 0/1 AT 24-28 WEEKS



APPENDIX C: Indirect comparison Week 12-16

1 Forest Plots, Week 12-16

Below the forest plots from the comparisons of active treatment to placebo are presented. Please note that the RR are presented as the rate of placebo to the rate of active treatment in all plots as described in section 5.1.3. The RR presented in Table C.2. are inverted (rate of events on active treatment compared to placebo).

FIGURE C.1: TILDRAKIZUMAB: FOREST PLOT FOR PASI 75 AT 12-16 WEEKS

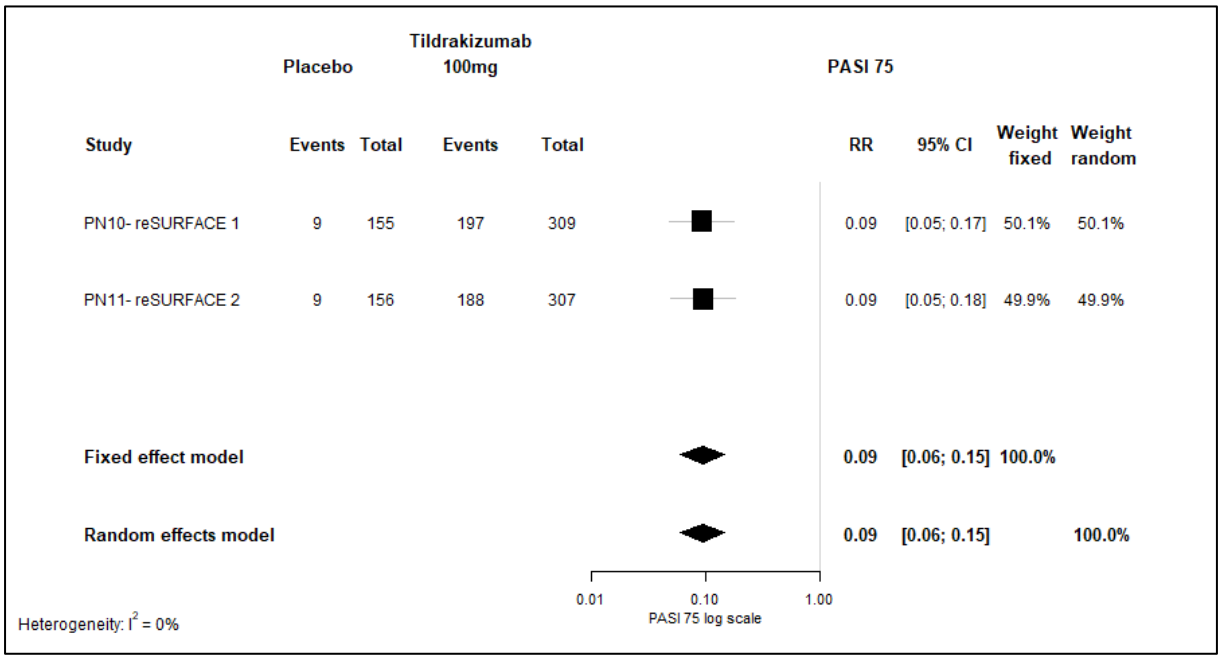


FIGURE C.2: TILDRAKIZUMAB: FOREST PLOT FOR PASI 90 AT 12-16 WEEKS

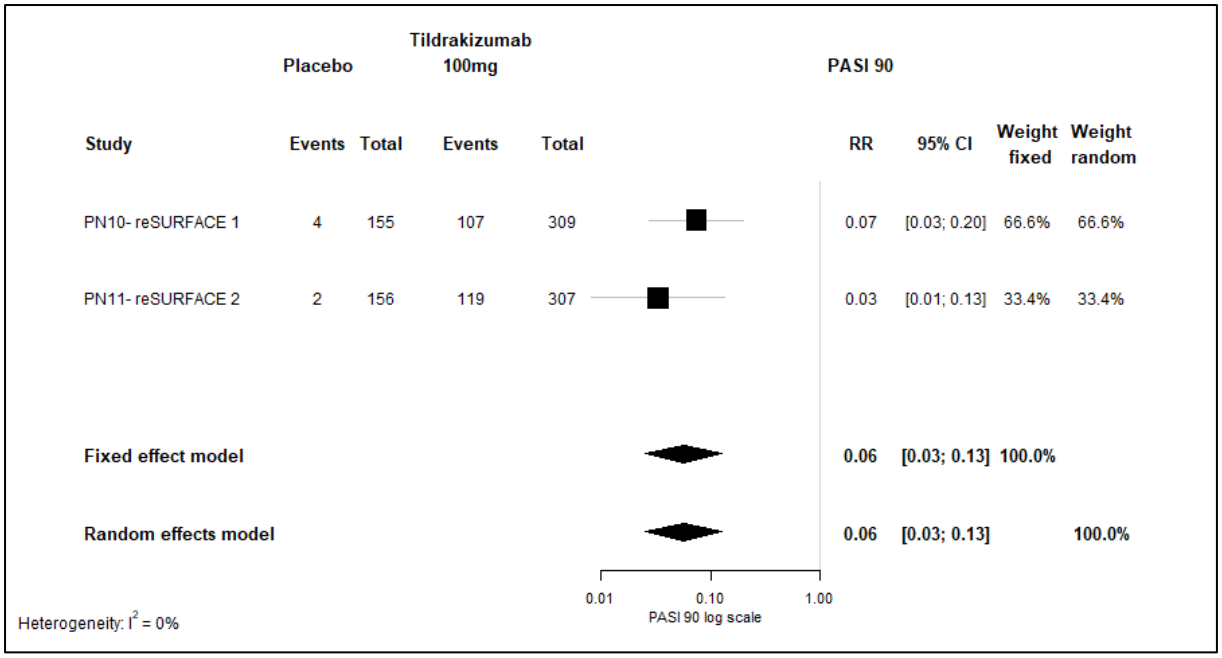


FIGURE C.3: TILDRAKIZUMAB: FOREST PLOT FOR SAE AT 12-16 WEEKS

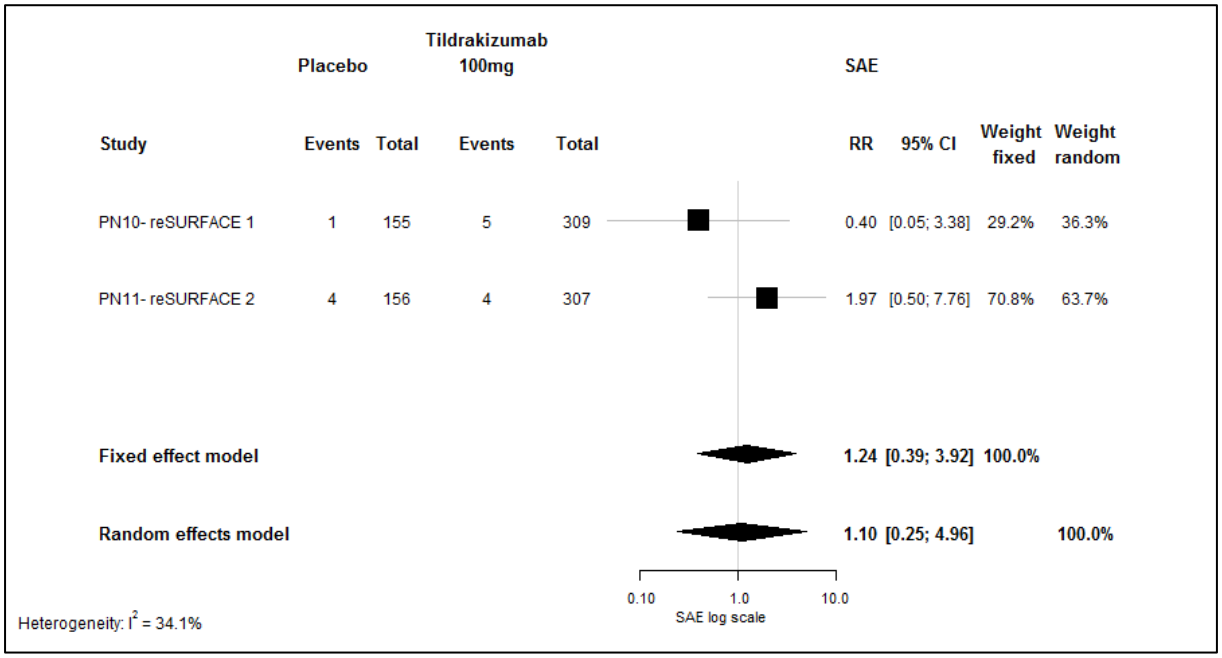


FIGURE C.4: TILDRAKIZUMAB: FOREST PLOT FOR DLQI 0/1 AT 12-16 WEEKS

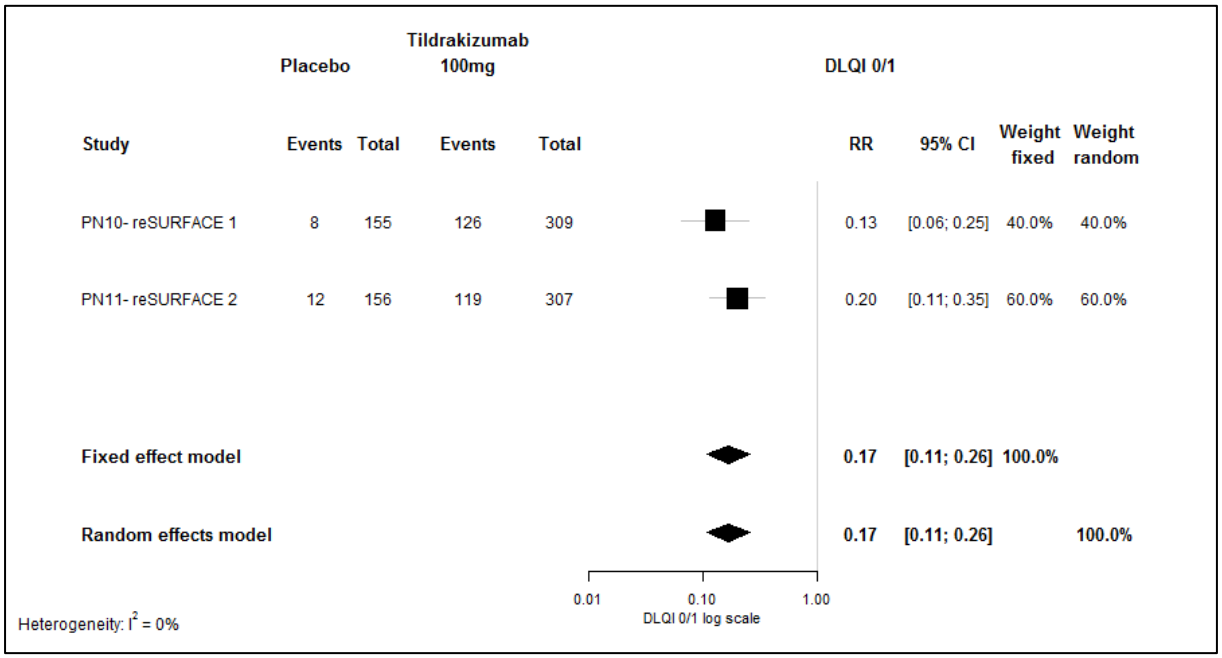


FIGURE C.5: TILDRAKIZUMAB: FOREST PLOT FOR DISCONTINUATIONS AT 12-16 WEEKS

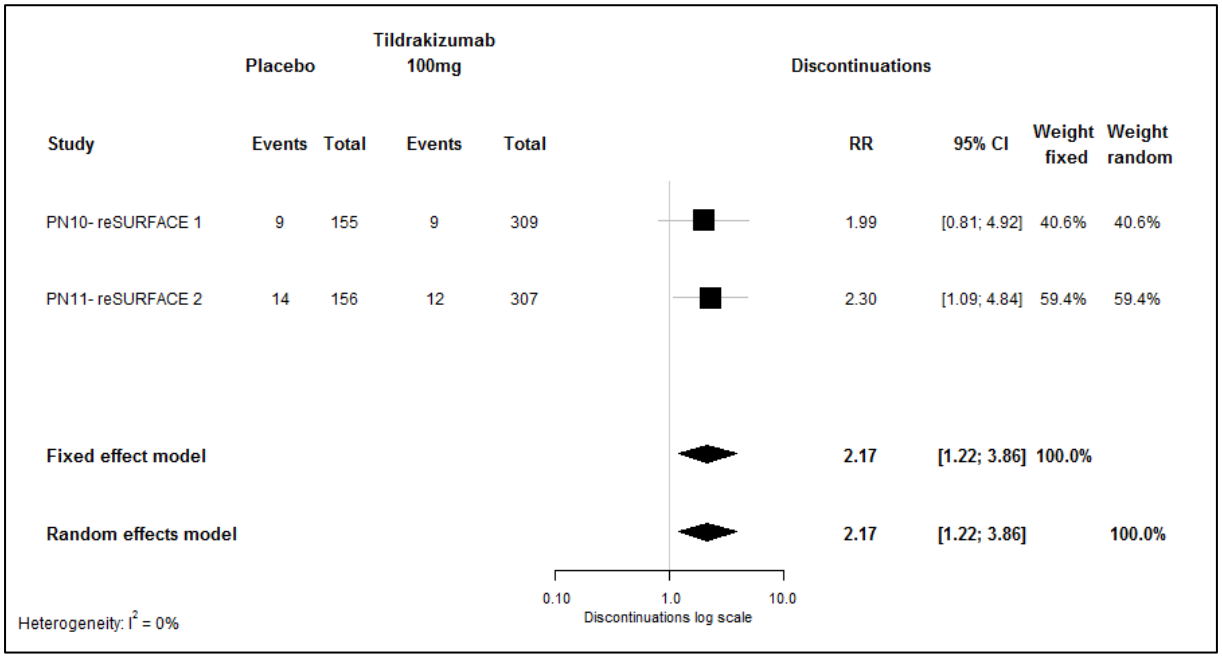


FIGURE C.6: GUSELKUMAB: FOREST PLOT FOR PASI 75 AT 12-16 WEEKS

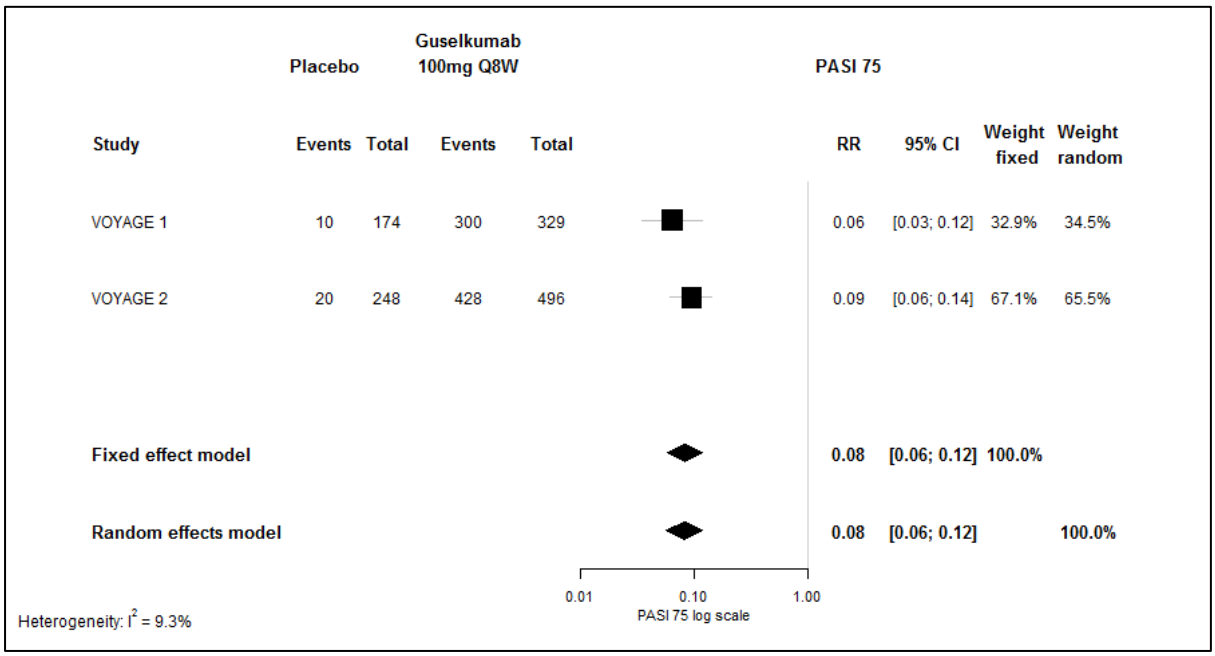


FIGURE C.7: GUSELKUMAB: FOREST PLOT FOR PASI 90 AT 12-16 WEEKS

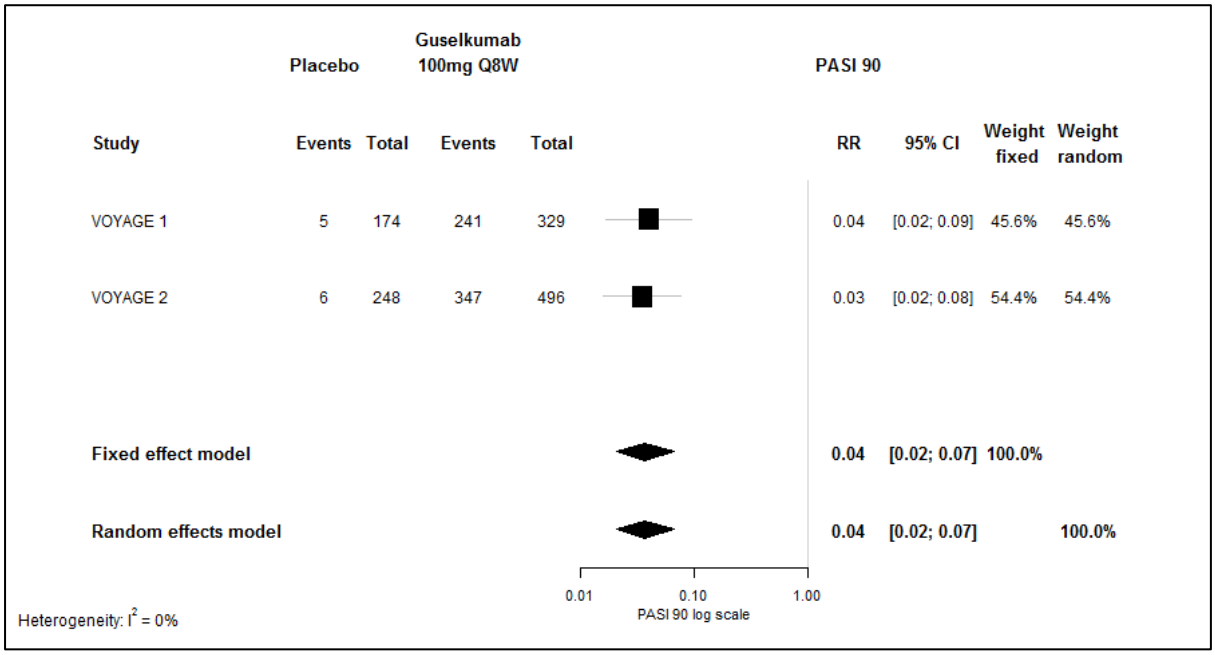


FIGURE C.8: GUSELKUMAB: FOREST PLOT FOR SAE AT 12-16 WEEKS

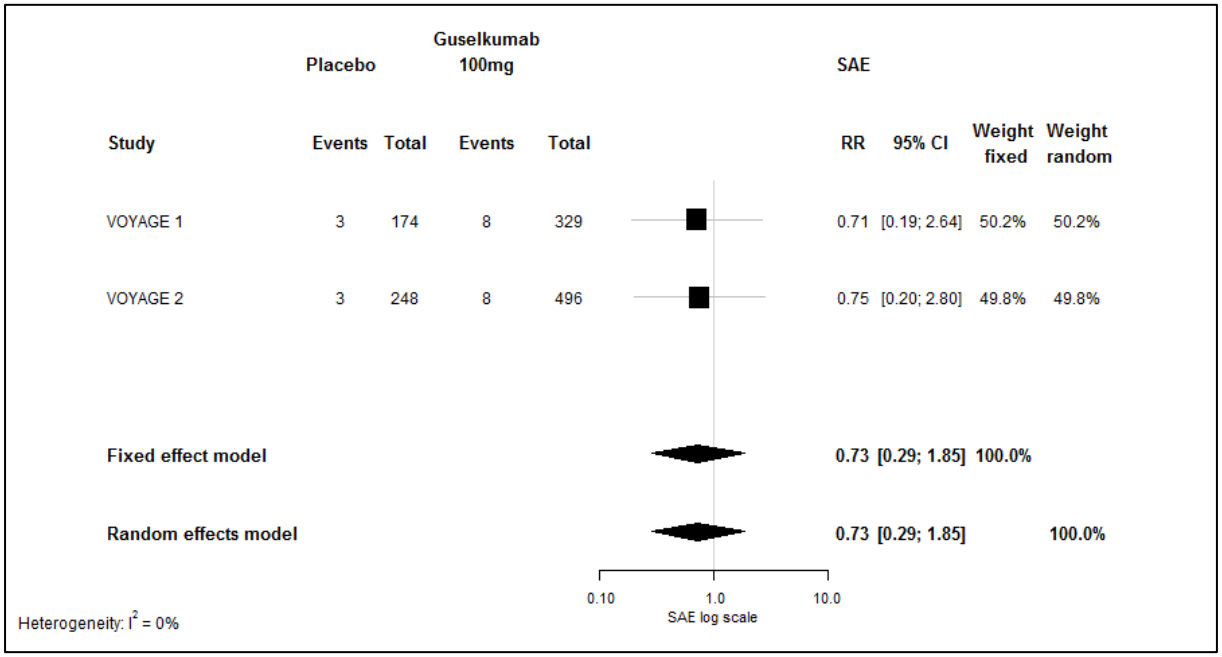


FIGURE C.9: GUSELKUMAB: FOREST PLOT FOR DLQI 0/1 AT 12-16 WEEKS

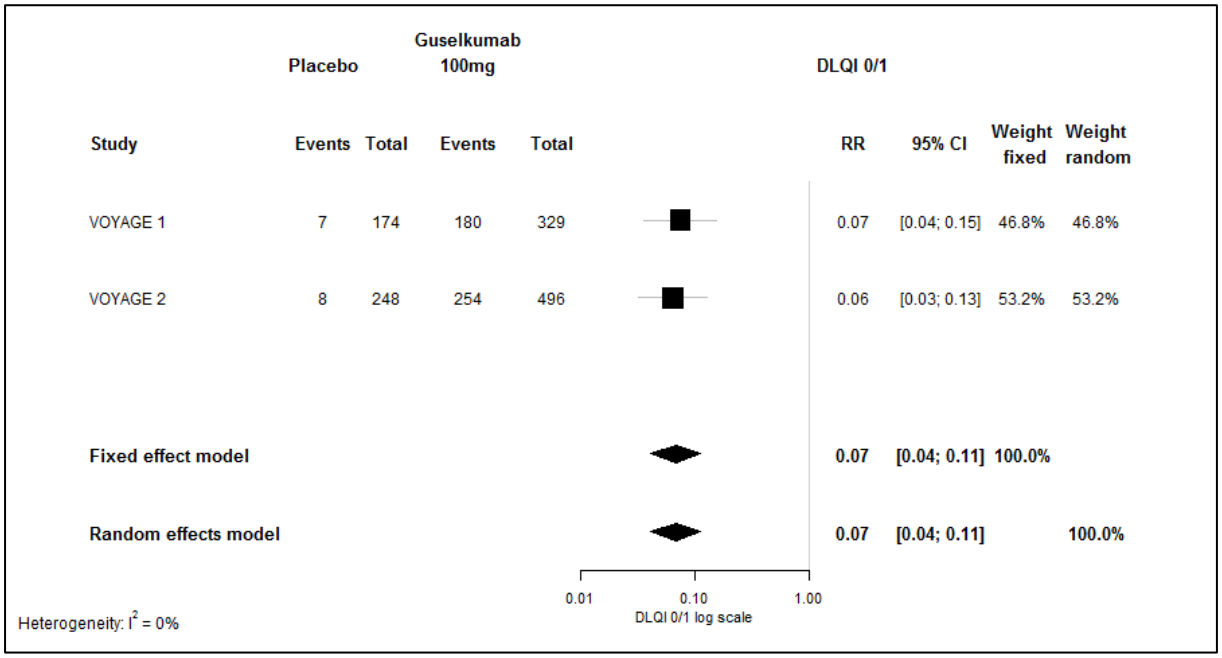
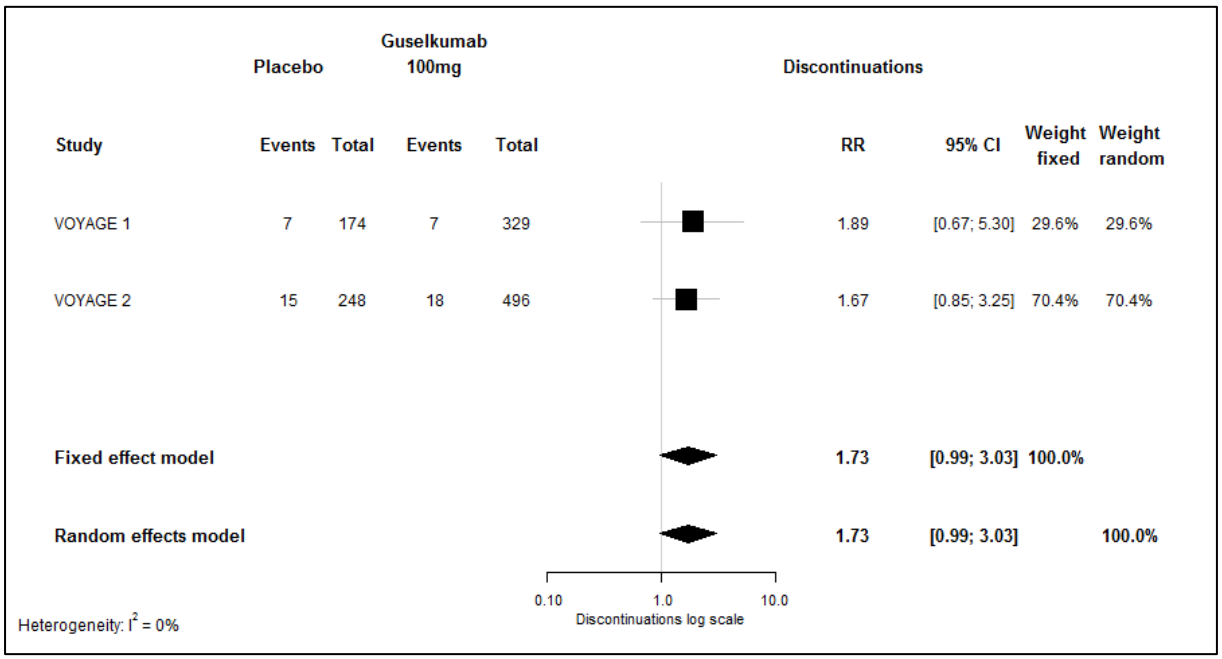


FIGURE C.10: GUSELKUMAB: FOREST PLOT FOR DISCONTINUATIONS AT 12-16 WEEKS



2 Assessment of Heterogeneity

Table C.1 displays the I^2 statistics for each direct comparison by outcome. As noted above, where few studies are available to assess heterogeneity (as is the case here), the I^2 statistic has relatively limited value.

TABLE C.1: HETEROGENEITY ASSESSMENT RESULTS, WEEK 12-16

Treatment 1	Treatment 2	I^2
PASI 75		
Placebo	Tildrakizumab 100mg	0.0%
Placebo	Guselkumab 100mg	9.3%
PASI 90		
Placebo	Tildrakizumab 100mg	0.0%
Placebo	Guselkumab 100mg	0.0%
SAE		
Placebo	Tildrakizumab 100mg	34.1%
Placebo	Guselkumab 100mg	0.0%
DLQI 0/1		
Placebo	Tildrakizumab 100mg	0.0%
Placebo	Guselkumab 100mg	0.0%
Discontinuations		
Placebo	Tildrakizumab 100mg	0.0%
Placebo	Guselkumab 100mg	0.0%

DLQI- Dermatology Life Quality Index; PASI- Psoriasis Area Sensitivity Index; SAE- Serious Adverse Events

A visual inspection of the forest plots presenting the input study results (see above) and the I^2 statistics reveals a moderate amount of heterogeneity for the SAE tildrakizumab results, and both the FE and RE models could be considered. The moderate amount of heterogeneity is caused by one very low event count in a placebo arm, and studies disagree about which treatment produces more SAEs. However, given the low heterogeneity in all other endpoints, the FE model can be considered for all endpoints including SAE. For comparisons with an I^2 value of 0% the FE and RE models yield identical results.

3 Risk ratios

Table C.2 displays risk ratios of all outcomes of interest, as obtained by analyses outlined in Section 5.1.3, using FE and RE models. A risk ratio equal to 1 means that both treatments involved in the comparison produce the same number of events, while a risk ratio greater than 1 signifies that the first mentioned treatment produces more events. To translate the risk ratios into absolute risk reductions, calculations have been undertaken as outlined in Section 5.1.3 in the main application document for those outcomes where the 95% CI for RR crosses 1. Positive numbers mean fewer events for patients treated with tildrakizumab 100mg, compared to those treated with guselkumab 100mg.

For both PASI levels and both models, the risk ratios of tildrakizumab 100mg to guselkumab 100mg are below 1, which favours guselkumab 100mg. However, the 95% confidence intervals (CIs) contain 1. Therefore, no significant difference could be detected between the two treatments for PASI levels 75 and 90.

Regarding SAEs and discontinuations, the risk ratios of guselkumab 100mg to tildrakizumab 100mg are again below 1 for both models. This means that more SAEs/discontinuations were observed for guselkumab 100mg in relation to tildrakizumab 100mg. As before, the 95% CIs contain 1, indicating that no significant difference between the two treatments could be detected.

The risk ratios of tildrakizumab 100mg to guselkumab 100mg for DLQI 0/1 are below 1 for both models, favouring guselkumab 100mg. Confidence intervals crosses 1. The ARR is estimated at 31.1%-points but with wide confidence intervals (95%CI: 10.9, 41.5). The clinical importance of this finding is uncertain. Appendix E presents a sensitivity of the week 12-16 indirect comparison of DLQI treatment effect indicating that there is no significant differences between in the overall distributions of DLQI change from baseline in the tildrakizumab trials compared to the guselkumab trials. This further raises doubt as to the clinical relevance of the statistically significant difference in the RR of DLQI 0/1 response found above.

Details of the risk ratios are displayed in the table below.

TABLE C.2: SUMMARY OF THE RESULTS OF THE BUCHER METHOD, WEEKS 12-16

Outcome	Studies included in the analysis	Fixed/ random effects	Risk ratio (95% CI)						Absolute effect estimate		
			Tildrakizumab (100 mg) to placebo		Guselkumab (100mg) to placebo		Tildrakizumab (100 mg) to guselkumab (100 mg)		Absolute effect comparator	Estimated risk difference* (95% CI)	
PASI 75	reSURFACE 1+2 VOYAGE 1+2	FE	11.11	(6.67, 16.67)	12.5	(8.33,16.67)	0.88	(0.50, 1.56)	88.20%	-10.1%	(-43.9%, 49.6%)
		RE	11.11	(6.67, 16.67)	12.5	(8.33,16.67)	0.88	(0.49, 1.59)		-10.8%	(-44.8%, 51.8%)
PASI 90	reSURFACE 1+2 VOYAGE 1+2	FE	16.67	(7.69, 33.33)	25	(14.29, 50)	0.65	(0.24, 1.72)	71.30%	-25.3%	(-54.2%, 51.6%)
		RE	16.67	(7.69, 33.33)	25	(14.29, 50)	0.65	(0.24, 1.72)		-25.3%	(-54.2%, 51.6%)
SAE	reSURFACE 1+2 VOYAGE 1+2	FE	0.81	(0.26, 2.56)	1.37	(0.54, 3.45)	0.59	(0.13, 2.63)	1.90%	-0.8%	(-1.6%, 3.1%)
		RE	0.91	(0.2, 4)	1.37	(0.54, 3.45)	0.66	(0.11, 3.85)		-0.6%	(-1.7%, 5.4%)
DLQI 0/1	reSURFACE 1+2 VOYAGE 1+2	FE	5.88	(3.85, 9.09)	14.29	(9.09, 25)	0.41	(0.21, 0.79)	52.60%	-31.1%	(-41.5%, -10.9%)
		RE	5.88	(3.85, 9.09)	14.29	(9.09, 25)	0.41	(0.21, 0.79)		-31.1%	(-41.5%, -10.9%)
Discontinuations	reSURFACE 1+2 VOYAGE 1+2	FE	0.46	(0.26, 0.82)	0.58	(0.33, 1.01)	0.80	(0.36, 1.79)	3.00%	-0.6%	(-1.9%, 2.4%)
		RE	0.46	(0.26, 0.82)	0.58	(0.33, 1.01)	0.80	(0.36, 1.79)		-0.6%	(-1.9%, 2.4%)

CI- confidence interval; DLQI- Dermatology Life Quality Index; FE- fixed effects; PASI- Psoriasis Area Sensitivity Index; RE- random effects; SAE- Serious Adverse Events

* Positive numbers imply that more events are predicted for patients treated with tildrakizumab 100mg, compared to those treated with guselkumab 100mg.

APPENDIX D: Indirect comparison week 12-16. Sensitivity analysis

The sensitivity analysis is based on the studies used for the "weeks 12-16" analysis in appendix C and the additional study Ohtsuki 2018 which included only Japanese patients. The additional study compares placebo and guselkumab 100mg at week 12-16.

1 Forest Plots, Week 12-16, sensitivity analysis

Below the forest plots from the comparisons of active treatment to placebo are presented. Please note that the RR are presented as the rate of placebo to the rate of active treatment in all plots. The RR presented in Table D.2. are inverted (rate of events on active treatment compared to placebo).

Forest plots referring to comparisons of placebo and tildrakizumab 100mg can be found in Appendix C.

FIGURE D.1: GUSELKUMAB: FOREST PLOT FOR PASI 75 AT 12-16 WEEKS, SENSITIVITY ANALYSIS

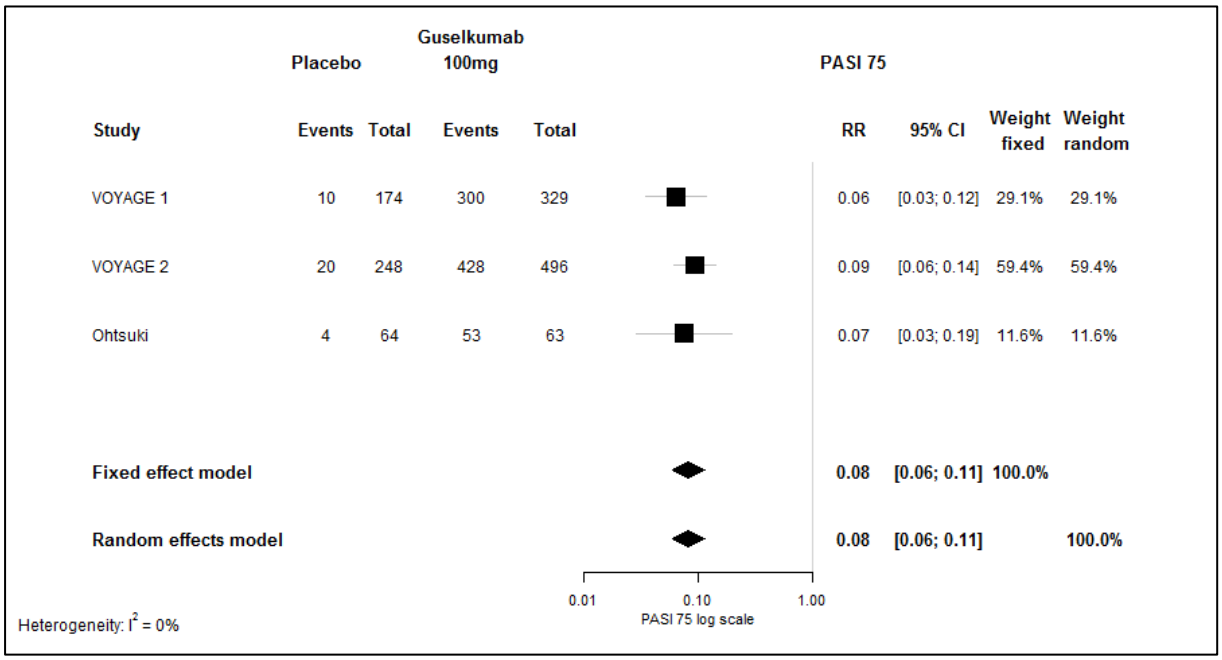


FIGURE D.2: GUSELKUMAB: FOREST PLOT FOR PASI 90 AT 12-16 WEEKS, SENSITIVITY ANALYSIS

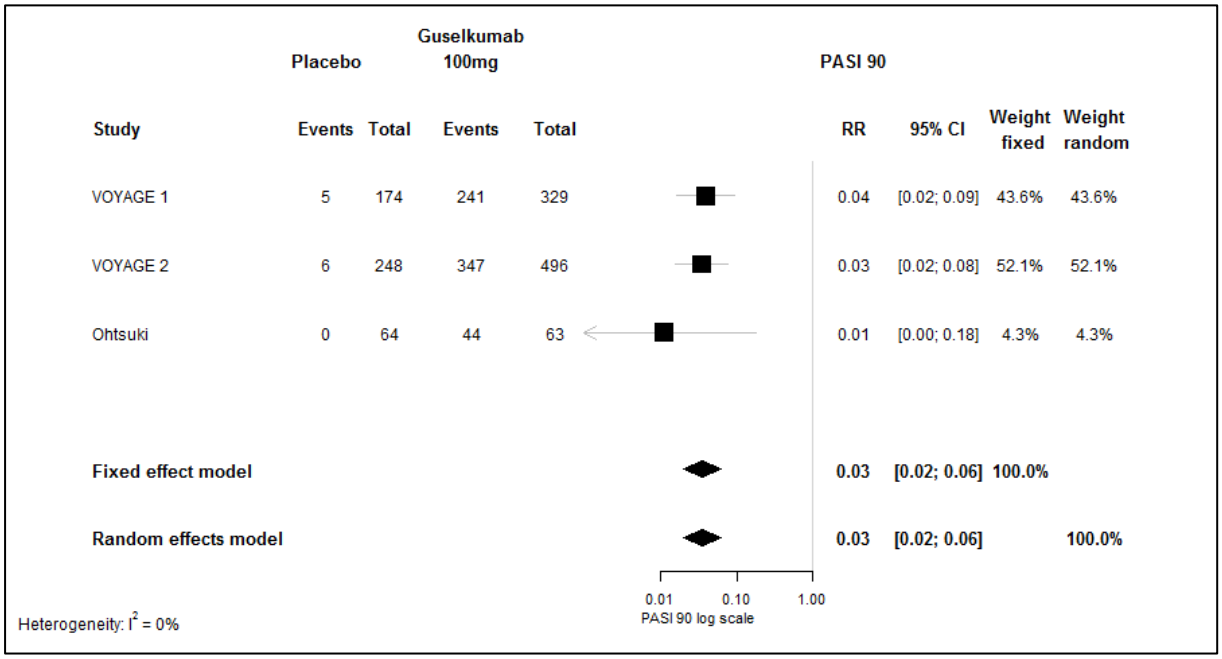


FIGURE D.3: GUSELKUMAB: FOREST PLOT FOR SAE AT 12-16 WEEKS, SENSITIVITY ANALYSIS

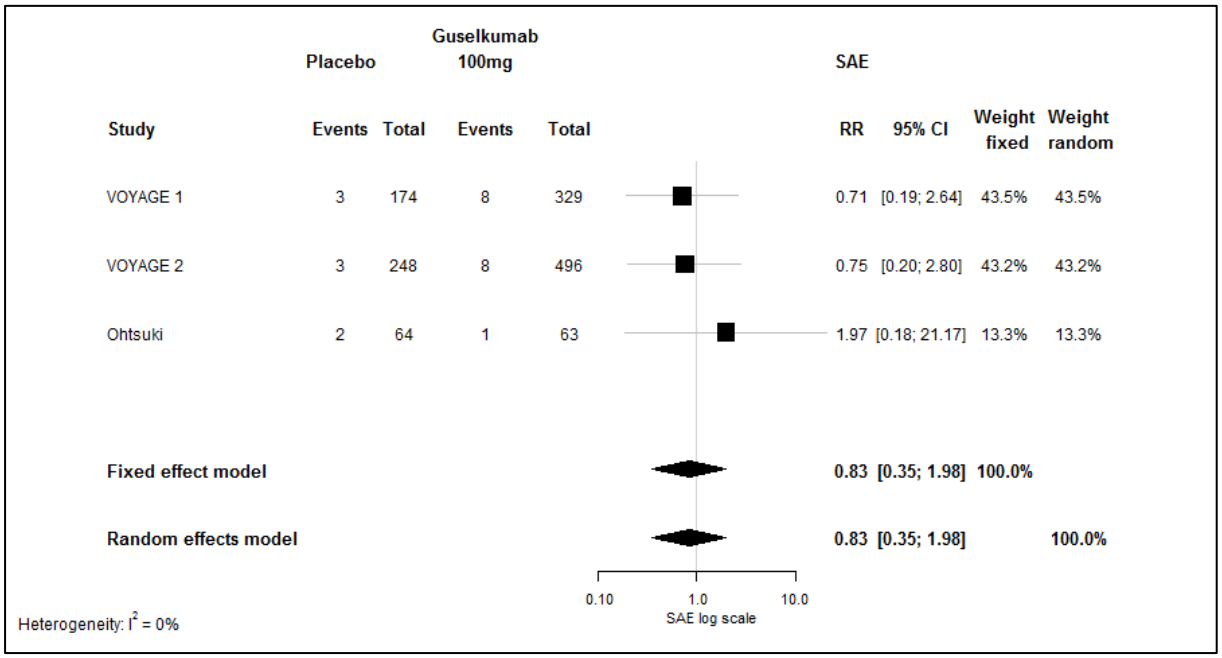


FIGURE D.4: GUSELKUMAB: FOREST PLOT FOR DLQI AT 12-16 WEEKS, SENSITIVITY ANALYSIS

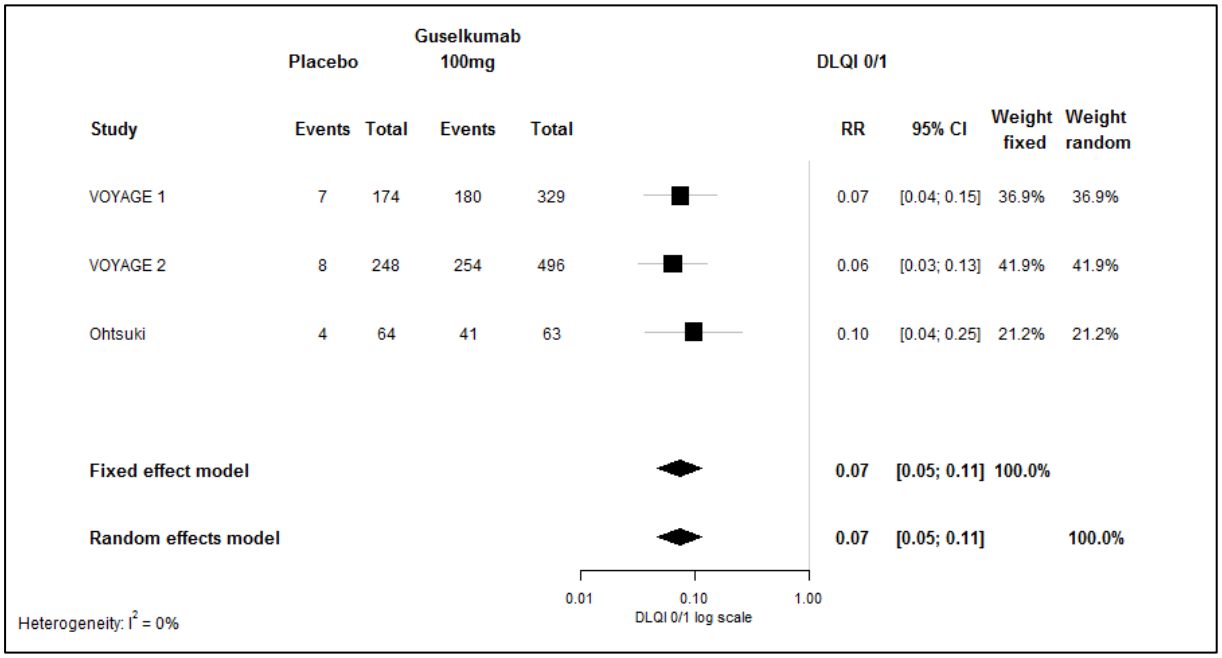
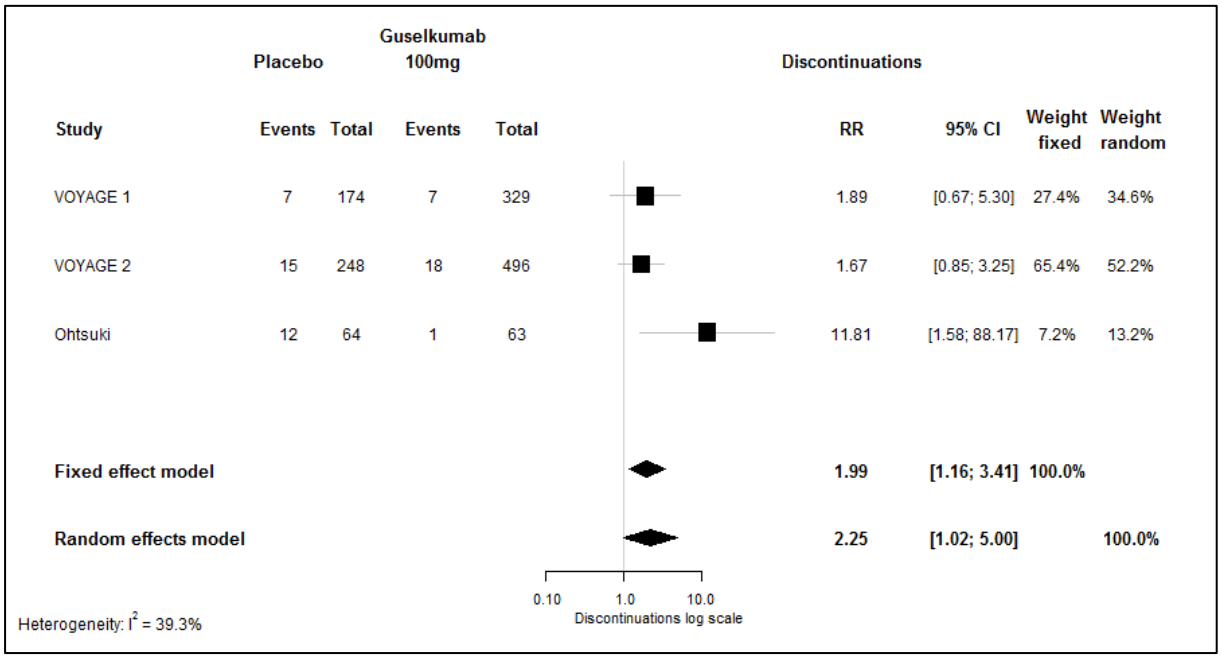


FIGURE D.5: GUSELKUMAB: FOREST PLOT FOR DISCONTINUATIONS AT 12-16 WEEKS, SENSITIVITY ANALYSIS



2 Assessment of Heterogeneity

The addition of the Ohtsuki study has little impact on the observed amount of heterogeneity, apart from the endpoint of discontinuation. Here the I^2 statistics changes from 0% to 39.3% for the comparison of placebo and guselkumab 100mg, thus adding a moderate amount of heterogeneity.

TABLE D.1: HETEROGENEITY ASSESSMENT RESULTS, WEEKS 12-16, SENSITIVITY ANALYSIS

Treatment 1	Treatment 2	I^2
PASI 75		
Placebo	Tildrakizumab 100mg	0.0%
Placebo	Guselkumab 100mg	0.0%
PASI 90		
Placebo	Tildrakizumab 100mg	0.0%
Placebo	Guselkumab 100mg	0.0%
SAE		
Placebo	Tildrakizumab 100mg	34.1%
Placebo	Guselkumab 100mg	0.0%
DLQI 0/1		
Placebo	Tildrakizumab 100mg	0.0%
Placebo	Guselkumab 100mg	0.0%
Discontinuations		
Placebo	Tildrakizumab 100mg	0.0%
Placebo	Guselkumab 100mg	39.3%

DLQI- Dermatology Life Quality Index; PASI- Psoriasis Area Sensitivity Index; SAE- Serious Adverse Events

Similar to the main analysis at weeks 12-16, the FE model can be considered for all endpoints. As before, the very low number in one placebo arm drives the observed amount of heterogeneity up for SAEs.

3 Risk ratios

Adding the Ohtsuki 2018 study does not change any conclusions in terms of significance.

For the outcomes PASI 75, PASI 90, and SAE guselkumab 100mg is estimated to produce more events, but differences to tildrakizumab 100mg are not statistically significant. For DLQI 0/1, the confidence interval for the estimated RR is below 1. ARR is estimated at 29.9% with wide 95% confidence intervals (9.6, 40.9). For discontinuations, the risk ratios were below 1, favouring tildrakizumab 100mg, but not in a significant way. Now the risk ratios have moved closer to values around 1, and the RE model even calculates a value favouring guselkumab 100mg. Still, as before, observed differences are not significant.

Details of the risk ratios are displayed in the table below.

TABLE D.2: SUMMARY OF THE RESULTS OF THE BUCHER METHOD, WEEKS 12-16, SENSITIVITY ANALYSIS

Outcome	Studies included in the analysis	Fixed/ random effects	Risk ratio (95% CI)						Absolute effect estimate		
			Tildrakizumab (100 mg) to placebo		Guselkumab (100mg) to placebo		Tildrakizumab (100 mg) to guselkumab (100 mg)		Absolute effect comparator	Estimated risk difference* (95% CI)	
PASI 75	reSURFACE 1+2 VOYAGE 1+2 Ohtsuki 2018	FE	11.11	(6.67, 16.67)	12.50	(9.09,16.67)	0.88	(0.5, 1.54)	88.00%	-10.8%	(-43.8%, 47.4%)
		RE	11.11	(6.67, 16.67)	12.50	(9.09,16.67)	0.88	(0.5, 1.54)		-10.8%	(-43.8%, 47.4%)
PASI 90		FE	16.67	(7.69, 33.33)	33.33	(16.67,50.00)	0.61	(0.23, 1.64)	71.20%	-27.5%	(-54.9%, 45.5%)
		RE	16.67	(7.69, 33.33)	33.33	(16.67,50.00)	0.61	(0.23, 1.64)		-27.5%	(-54.9%, 45.5%)
SAE		FE	0.81	(0.26, 2.56)	1.20	(0.51, 2.86)	0.68	(0.16, 2.86)	1.90%	-0.6%	(-1.6%, 3.5%)
		RE	0.91	(0.20, 4.00)	1.20	(0.51, 2.86)	0.75	(0.13, 4.35)		-0.5%	(-1.6%, 6.4%)
DLQI 0/1		FE	5.88	(3.85, 9.09)	14.29	(9.09, 20.00)	0.44	(0.24, 0.82)	52.50%	-29.9%	(-40.9%, -9.6%)
		RE	5.88	(3.85, 9.09)	14.29	(9.09, 20.00)	0.44	(0.24, 0.82)		-29.9%	(-40.9%, -9.6%)
Discontinuations		FE	0.46	(0.26, 0.82)	0.50	(0.29, 0.86)	0.92	(0.42, 2.00)	2.90%	-0.2%	(-1.7%, 2.9%)
		RE	0.46	(0.26, 0.82)	0.44	(0.2, 0.98)	1.04	(0.39, 2.78)		0.1%	(-1.8%, 5.2%)

CI- confidence interval; DLQI- Dermatology Life Quality Index; FE- fixed effects; PASI- Psoriasis Area Sensitivity Index; RE- random effects; SAE- Serious Adverse Events

* Positive numbers imply that more events are predicted for patients treated with tildrakizumab 100mg, compared to those treated with guselkumab 100mg.

APPENDIX E: DLQI sensitivity analysis. Change from baseline

In this appendix a sensitivity analysis was performed on DLQI response to treatment using Bucher indirect comparison of guselkumab 100mg and tildrakizumab 100 mg with placebo as the common comparator.

Table E.1 shows the baseline DLQI and change from baseline to the end of placebo-controlled phase (week 12-16) and change from baseline to week 24-28. DQLI change from baseline data was not reported in Reich et al. (2017)[3] but is reported here based on the clinical study report from the two studies. Overall the mean and standard deviation of DLQI at baseline was consistent, however with a tendency to lower mean scores being reported in the Japanese study[6].

TABLE E.1 REPORTED DLQI SCORE AT BASELINE AND CHANGE FROM BASELINE IN INCLUDED STUDIES

		Baseline			Week 16			Week 24		
		N	mean	SD	N	Change from baseline	SD	N	Change from baseline	SD
VOYAGE 1	Guselkumab 100mg	322	14	7.48	322	-11.2	7.24	322	-11.6	7.55
	PBO	170	13.3	7.12	170	-0.6	6.36	NA	NA	NA
VOYAGE 2	Guselkumab 100mg	495	14.7	6.9	496	-11.3	6.8	495	-11.9	7
	PBO	248	15.1	7.2	248	-2.6	6.9	NA	NA	NA
Ohtsuki 2018	Guselkumab 100mg	63	10.3	7.27	65	-8.5	6.95	NA	NA	NA
	PBO	64	10.6	7.74	64	-0.8	5.4	NA	NA	NA
		Baseline			**Week 12**			**Week 28**		
		N	**mean**	**SD**	**N**	**Change from baseline**	**SD**	**N**	**Change from baseline**	**SD**
reSURFACE 1*	Tildrakizumab 100mg	306	14	6.78	301	-10	6.66	287	-10.8	6.66
	PBO	153	13	7.2	149	-2.1	6.52	NA	NA	NA
reSURFACE 2*	Tildrakizumab 100mg	307	14.8	7.24	307	-10.6	7	294	-11.7	7.19
	PBO	156	13.7	6.98	156	-1.6	5.97	NA	NA	NA

NA: not available; PBO: placebo; SD: standard deviation

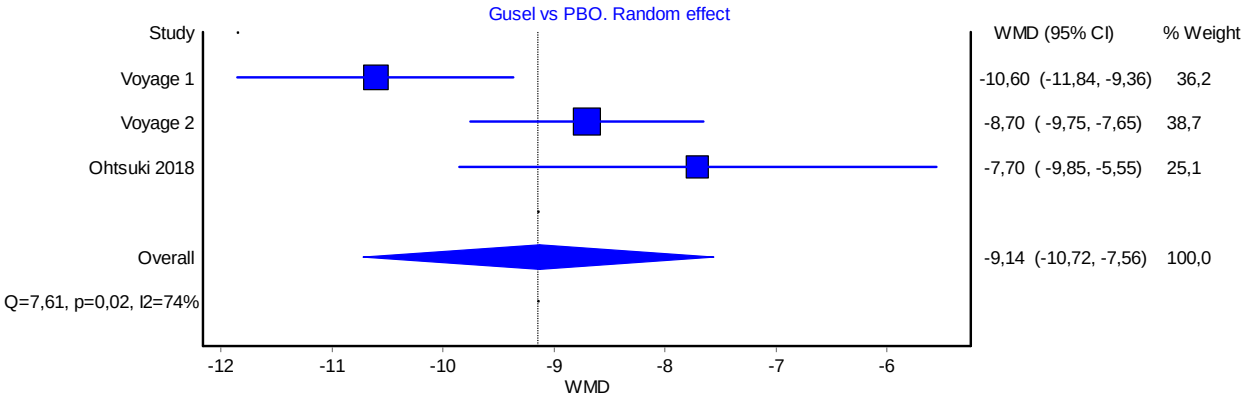
* Data reported for the full analysis set population definition [3]. Source of reSURFACE 1+2: Almirall data on file

1 Week 12-16 meta-analyses and indirect comparison

Figure E.1 shows the forest plot of the meta-analysis of guselkumab studies reporting DQLI change from baseline for guselkumab 100mg and placebo. The overall change from baseline was 9.14 points lower in the guselkumab arms compared to change from baseline in the placebo arm (95%CI -10.72, -7.56). The forest plot suggest that the findings were not consistent across studies which is also apparent from a high I^2 statistics and a low level of significance in the Cochranes Q test of heterogeneity.

In an alternative model excluding the Ohtsuki 2018 trial, the lack of consistency in results remain high with a I^2 of 81% and a Cochranes Q statistic of 5.26; p=0.02 (data not shown). The pooled mean difference in DLQI change from baseline for guselkumab compared to placebo in this analysis was -9.62 (95% CI: -11.48, -7.76) (data not shown). Because the alternative analysis gave wider confidence intervals, the former model using data from all three studies were used in indirect comparison.

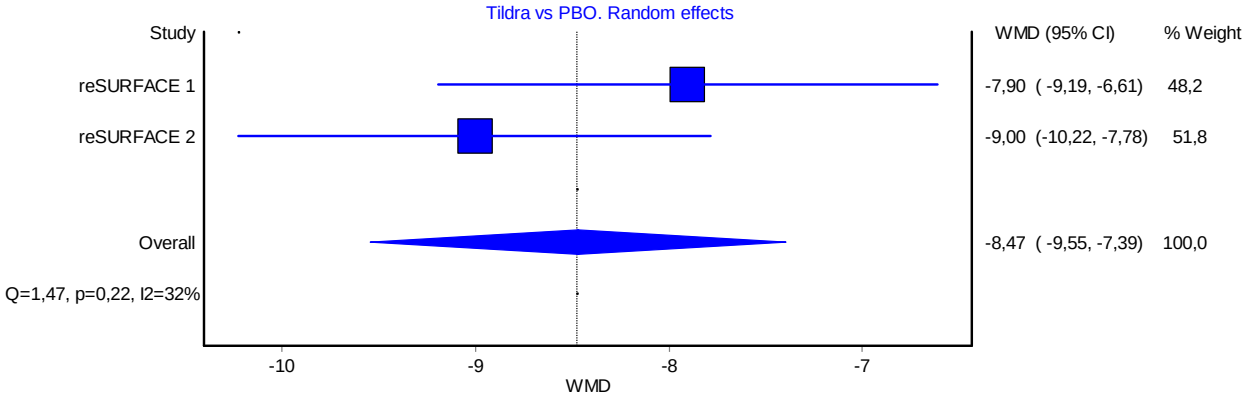
FIGURE E.1 FOREST PLOT OF META-ANALYSIS OF DLQI CHANGE FROM BASELINE TO WEEK 16 IN GUSELKUMAB STUDIES. RANDOM EFFECTS MODEL



WMD: Weighted mean difference. Q: Cochrane's Q statistics; CI: confidence intervals; I2: I^2 heterogeneity measure; gusel: guselkumab

Figure E.2 provides the forest plot from the meta-analysis of tildrakizumab placebo controlled studies. The overall change from baseline was 8.47 points lower in the tildrakizumab 100 mg arms compared to change from baseline in the placebo arm (95%CI -9.55, -7.39).

FIGURE E.2 FOREST PLOT OF META-ANALYSIS OF DLQI CHANGE FROM BASELINE TO WEEK 16 IN TILDRAKIZUMAB. RANDOM EFFECTS MODEL



WMD: Weighted mean difference. Q: Cochrane's Q statistics; CI: confidence intervals; I2: I^2 heterogeneity measure; tildra: tildrakizumab

Table E.2 provides the result of the Bucher indirect treatment comparison using placebo as the common comparator. The difference in change from baseline of tildrakizumab 100 mg compared to guselkumab 100mg was 0.67 points. This means that guselkumab 100mg was associated with a 0.67 larger reduction in the DLQI score from baseline compared to tildrakizumab (i.e., favours guselkumab) but with a 95% confidence interval that contains 1.

TABLE E.2 RESULT OF BUCHER INDIRECT COMPARISON. MEAN DIFFERENCE IN DLQI CHANGE FROM BASELINE TO WEEK 12-16

	Mean difference	95% CI	
Tildrakizumab 100mg compared to guselkumab 100mg	0.67	-1.25	2.58

Results from the sensitivity analysis of treatment effect on DLQI showed no statistical difference in the change from baseline to week 12-16 between guselkumab 100mg and tildrakizumab.

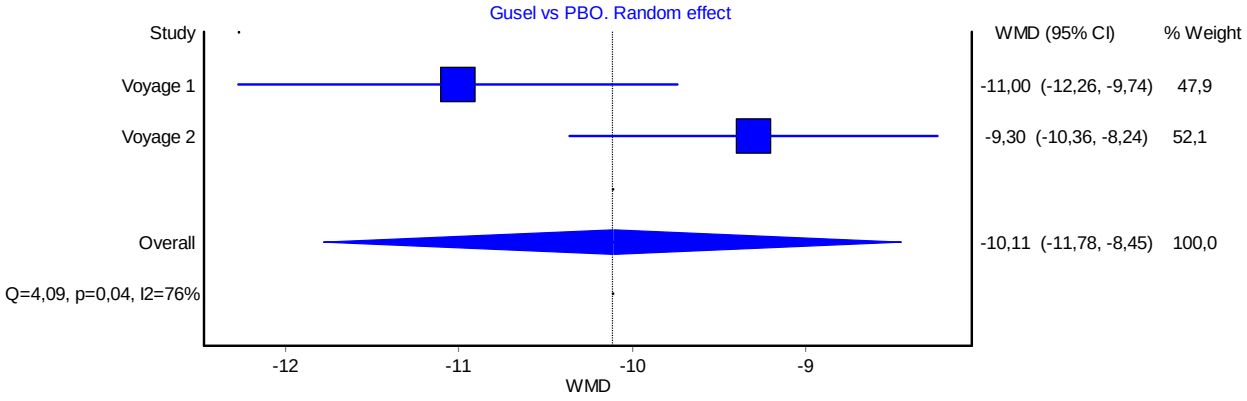
2 Week 24-28 meta-analyses and indirect comparison

As it is apparent form Table E.1 above, the change from baseline in DLQI is mainly taken place in the first 12-16 weeks with the change from base line to week 24-28 being of almost the same magnitude. Although none of the studies had placebo control for longer than the initial 12-16 weeks, an indirect comparison of change in DLQI from baseline to week 24-28 was attempted using placebo as the common comparator. In this analysis – like in the other week 24-28 analyses – the outcome in the placebo arm was carried forward to the later observation period assuming that no change would occur in the placebo arm.

Figure E.3 and Figure E.4 show the forest plots from the meta-analyses of guselkumab studies respectively tildrakizumab studies.

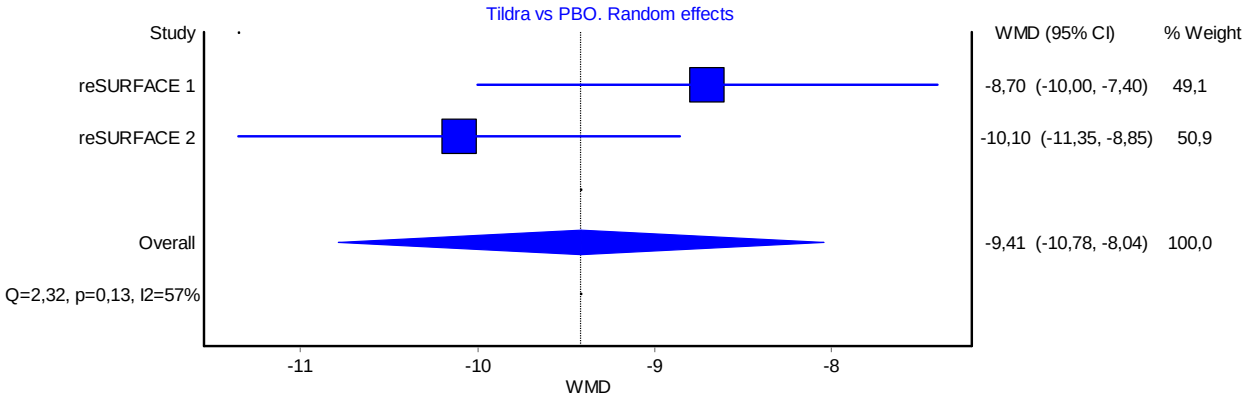
The overall change from baseline was 10.11 points lower in the guselkumab arms compared to change from baseline in the placebo arm (95%CI -11.78, -8.45). Overall change from baseline was -9.41 points in the tildrakizumab 100 mg arms compared to change from baseline in the placebo arm (95%CI -10.78, -8.04).

FIGURE E.3 FOREST PLOT OF META-ANALYSIS OF DLQI CHANGE FROM BASELINE TO WEEK 24 IN GUSELKUMAB STUDIES. RANDOM EFFECTS MODEL



WMD: Weighted mean difference. Q: Cochrane's Q statistics; CI: confidence intervals; I2: I^2 heterogeneity measure; gusel: guselkumab

FIGURE E.4 FOREST PLOT OF META-ANALYSIS OF DLQI CHANGE FROM BASELINE TO WEEK 16 IN TILDRAKIZUMAB. RANDOM EFFECTS MODEL



WMD: Weighted mean difference. Q: Cochrane's Q statistics; CI: confidence intervals; I2: I^2 heterogeneity measure; tildra: tildrakizumab

The result of the Bucher indirect treatment comparison using placebo as the common comparator (Table E.3), shows that guselkumab 100mg was associated with a 0.70 higher change from baseline compared to tildrakizumab but with a 95% confidence interval containing 1.

TABLE E.3 RESULT OF BUCHER INDIRECT COMPARISON. MEAN DIFFERENCE IN DLQI CHANGE FROM BASELINE TO WEEK 24-28

	Mean difference	95% CI	
Tildrakizumab 100mg vs Guselkumab 100mg	0.70	-1.46	2.86

Results from the sensitivity analysis of treatment effect on DLQI showed no statistical difference in the change from baseline to week 24-28 between guselkumab 100mg and tildrakizumab.

APPENDIX F: DLQI sensitivity analysis. Population of analysis

In the main and sensitivity analyses the of the DLQI response rate, the ITT population was used for all studies as the denominator in the DLQI response rate. This differs from the published analysis where different population definitions were used. In the guselkumab studies, the DLQI response rates were calculated based on patients with complete DLQI data at baseline excluding those patients who had a DQLI score at baseline above 1. In the tildrakizumab studies the DLQI response rates were calculated based on patients with complete DLQI data at both time points of measurement. It may be argued that using the ITT population is the better choice for calculation of the response rate because every missing observation of DLQI is counted as non-response. In this appendix the indirect comparison of DLQI response rate is explored using the actual population of analysis from each study directly (i.e. all patients with DLQI data available at base-line and – for the guselkumab studies – also with baseline DLQI score above 1).

Table F.1 gives the number of patients and number of events by time of endpoint assessment. Figures F.1 through Figure F.5 provides the product specific forest plots from meta-analyses of included studies in the week 24-28 analysis, the week 12-16 analysis including only VOYAGE studies for guselkumab, and the week 12-16 sensitivity analysis including all guselkumab studies. Please note that the RR are presented as the rate of placebo to the rate of active treatment in all plots as described in section 5.1.3. The RR presented in Table D.2. are inverted (rate of events on active treatment compared to placebo). The forest plots did not show signs of heterogeneity in any of the meta-analyses.

TABLE F.1: NUMBER OF PATIENTS AND OUTCOMES AT WEEK 12-16 AND WEEK 24-28

Trial identifier	Treatment	DLQI at week 12 -16			DLQI at week 24 - 28		
		Time point (week)	Number analysed	DLQI 0/1 (n)	Time point (week)	Number analysed	DLQI 0/1 (n)
ReSURFACE 1[3]	Placebo	12	150	8	28	150	8
	Tildrakizumab 100mg		304	126		290	152
ReSURFACE 2[3]	Placebo	12	150	12	28	150	12
	Tildrakizumab 100mg		296	119		290	157
VOYAGE 1[4]	Placebo	16	168	7	24	168	7
	Guselkumab 100mg Q8W		320	180		320	195
VOYAGE 2[5]	Placebo	16	246	8	24	246	8
	Guselkumab 100 mg Q8W		246	96		246	101
Ohtsuki 2018 [6]	Placebo	16	61	4	NR	NR	NR
	Guselkumab 100mg Q8W		60	41		NR	NR

FIGURE F.1: TILDRAKIZUMAB: FOREST PLOT FOR DLQI AT 24-28 WEEKS

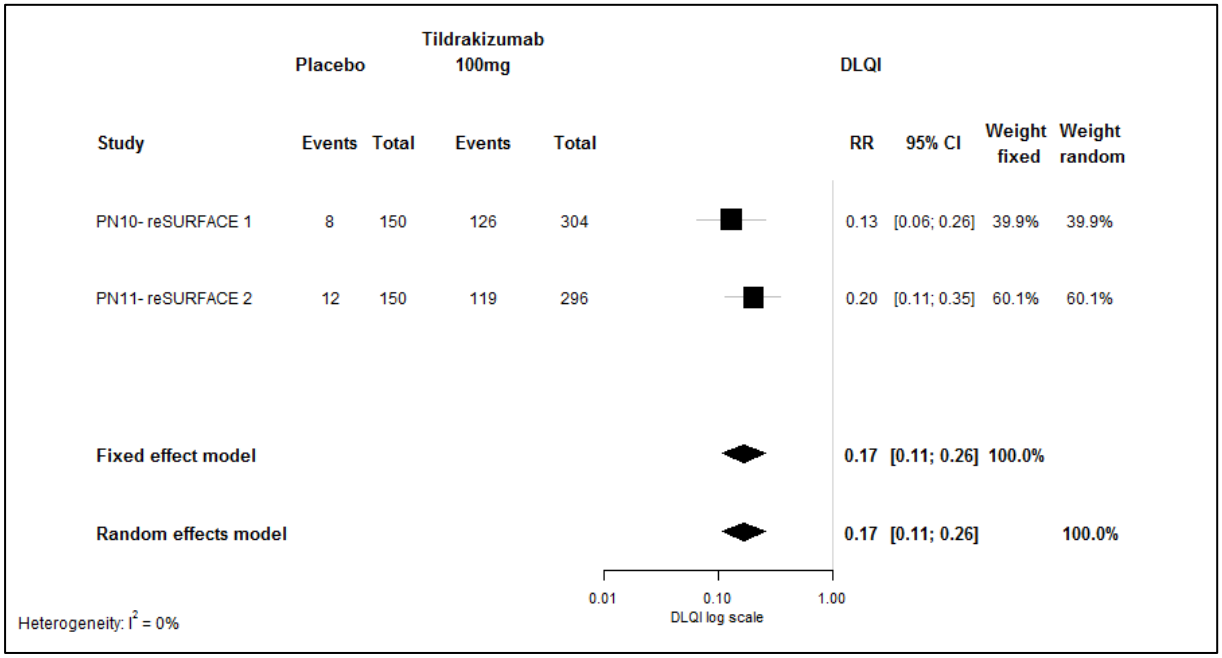


FIGURE F.2: GUSELKUMAB: FOREST PLOT FOR DLQI AT 24-28 WEEKS

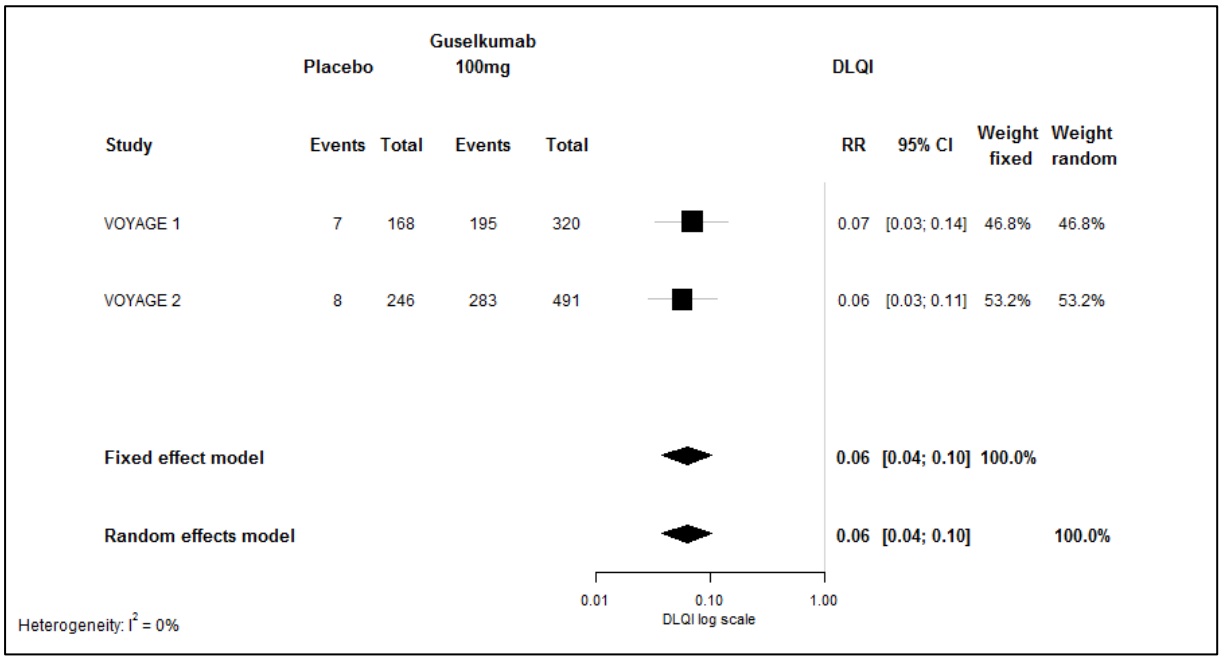


FIGURE F.3: TILDRAKIZUMAB: FOREST PLOT FOR DLQI AT 12-16 WEEKS

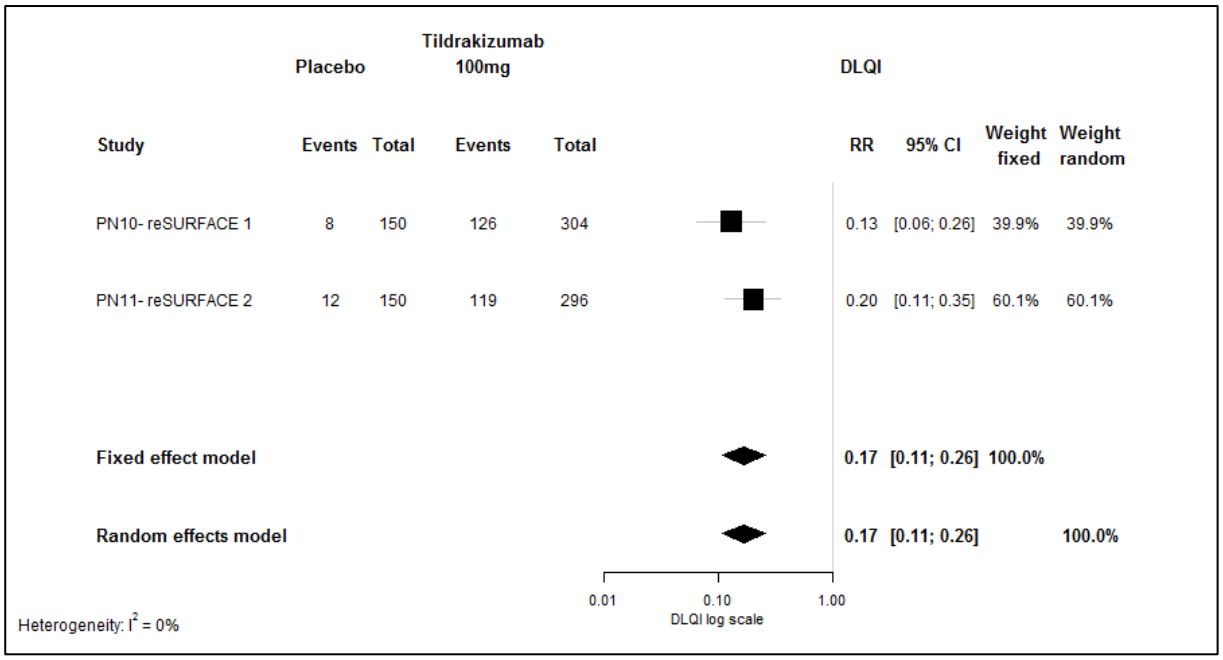


FIGURE F.4: GUSELKUMAB: FOREST PLOT FOR DLQI AT 12-16 WEEKS

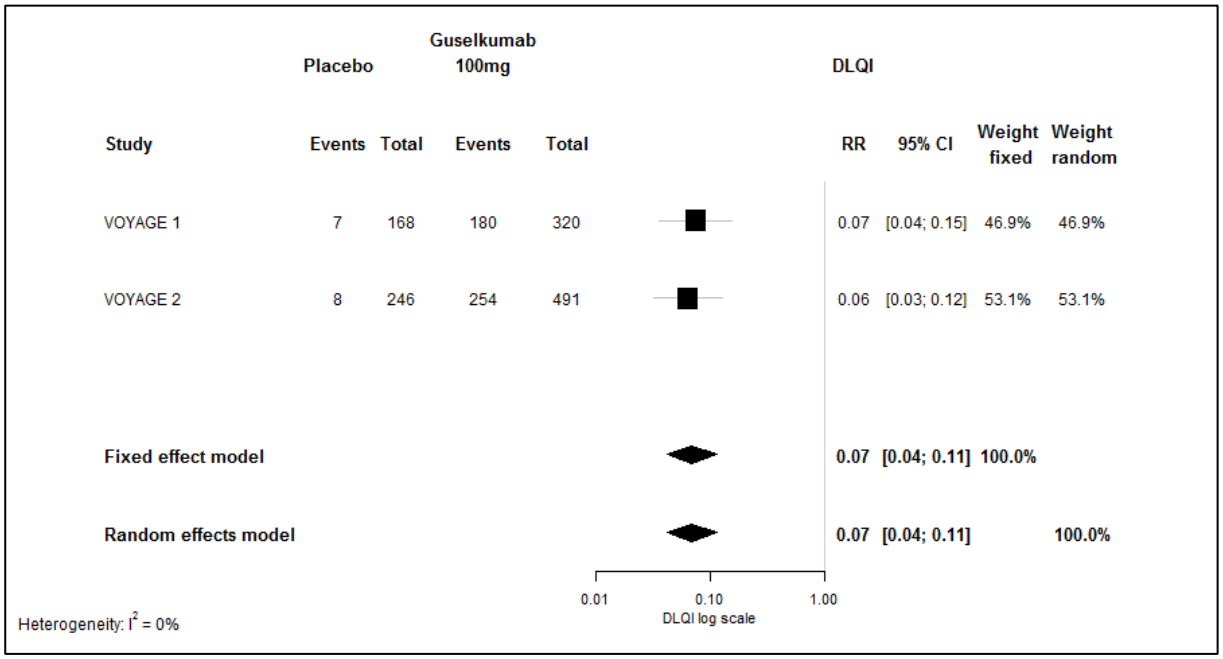


FIGURE F.5: GUSELKUMAB: FOREST PLOT FOR DLQI AT 12-16 WEEKS, SENSITIVITY ANALYSIS

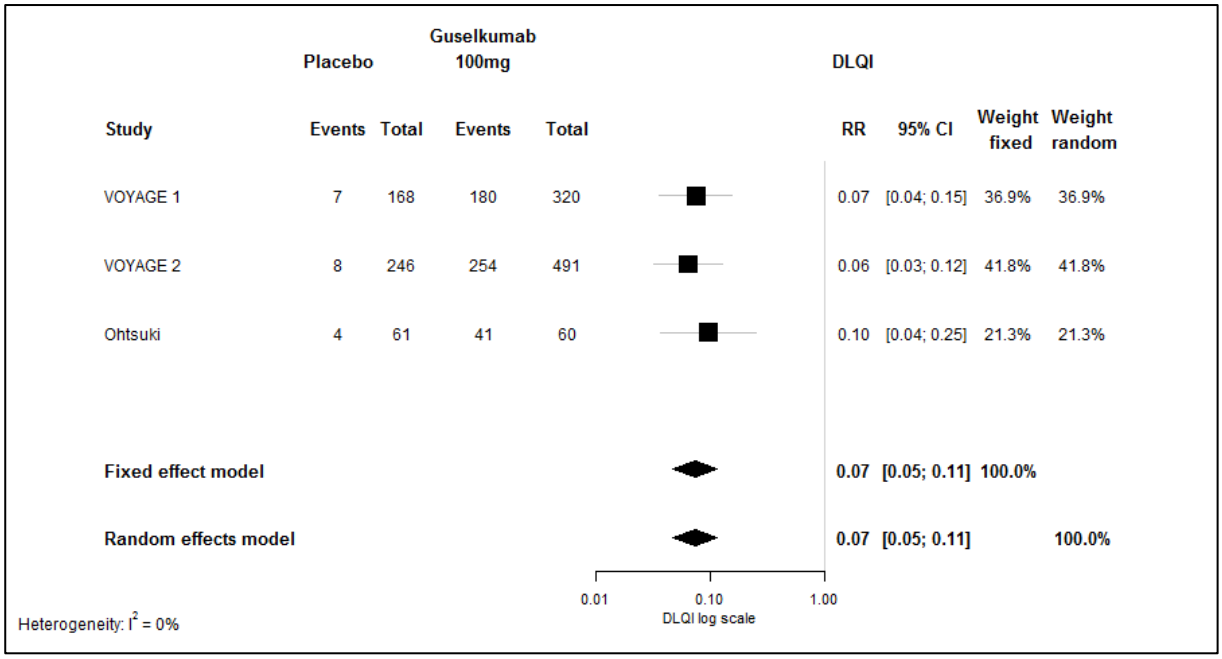


Table F.2 shows the results of the indirect comparison in the alternative DLQI responder analysis based on the number of patients included in the published responder analyses for each product and analysis (week 24-28, week 12-16, week 12-16 sensitivity analysis including the Othsuki 2018 study). The result from each analysis support the conclusion from the ITT-based analyses. The confidence intervals do not include 1 with an upper limit of between 0.79 and 0.93, however the clinical implication of this finding is uncertain with ARR confidence intervals including the MCID set in the Medicine Council protocol.

TABLE F.2: SUMMARY OF THE RESULTS OF THE BUCHER METHOD BY ANALYSIS

Outcome	Studies included in the analysis	Fixed/ random effects	Risk ratio (95% CI)						Absolute effect estimate		
			Tildrakizumab (100 mg) to placebo		Guselkumab (100mg) to placebo		Tildrakizumab (100 mg) to guselkumab (100 mg)		Absolute effect comparator	Estimated risk difference* (95% CI)	
Week 24-28	reSURFACE 1+2 VOYAGE 1+2	FE	7.69	(5, 12.5)	16.67	(10, 25)	0.49	(0.25, 0.93)	58.90%	-30.3%	(-44.1%, -3.9%)
		RE	7.69	(5, 12.5)	16.67	(10, 25)	0.49	(0.25, 0.93)		-30.3%	(-44.1%, -3.9%)
Week 12-16	reSURFACE 1+2 VOYAGE 1+2	FE	5.88	(3.85, 9.09)	14.29	(9.09, 25)	0.41	(0.21, 0.79)	53.50%	-31.8%	(-42.3%, -11.4%)
		RE	5.88	(3.85, 9.09)	14.29	(9.09, 25)	0.41	(0.21, 0.79)		-31.8%	(-42.3%, -11.4%)
Week 12-16. Sensitivity	reSURFACE 1+2 VOYAGE 1+2 Othsuki 2018	FE	5.88	(3.85, 9.09)	14.29	(9.09, 20)	0.44	(0.23, 0.81)	54.50%	-30.7%	(-41.7%, -10.2%)
		RE	5.88	(3.85, 9.09)	14.29	(9.09, 20)	0.44	(0.23, 0.81)		-30.7%	(-41.7%, -10.2%)

CI- confidence interval; DLQI- Dermatology Life Quality Index; FE- fixed effects; PASI- Psoriasis Area Sensitivity Index; RE- random effects
*Positive numbers imply that more events are predicted for patients treated with tildrakizumab 100mg, compared to those treated with guselkumab 100mg.

Medicinrådet

Medicinrådets protokol for vurdering af klinisk merværdi for tildrakizumab til behandling af moderat til svær plaque psoriasis

Handelsnavn	Ilumetri
Generisk navn	Tildrakizumab
Firma	Almirall
ATC-kode	L04AC17
Virkningsmekanisme	Humaniseret monoklonalt antistof rettet mod interleukin (IL)-23.
Administration/dosis	Subkutan injektion 100 mg i uge 0, 4 og hver 12. uge herefter.
Forventet EMA-indikation	Behandling af moderat til svær plaque psoriasis hos voksne (≥ 18 år), som er kandidater til systemisk behandling.
Godkendelsesdato Offentliggørelsesdato Dokumentnummer Versionsnummer	22 oktober 2018 23 oktober 2018 28540 1.0

Fagudvalgets sammensætning og sekretariatets arbejdsgruppe se bilag 1

Indhold

Forkortelser

BSA:	*Body Surface Area*
CI:	Konfidensinterval
DDS:	Dansk Dermatologisk Selskab
Dermbio:	National database for psoriasispatienter i biologisk behandling
DLQI:	*Dermatology life quality index*
EMA:	*European Medicines Agency*
GRADE:	System til vurdering af evidens (*Grading of Recommendations Assessment, Development and Evaluation*)
HR:	*Hazard ratio*
IL:	Interleukin
mAb:	Monoklonalt antistof
OR:	*Odds ratio*
PASI:	*Psoriasis area and severity index*
RR:	Relativ risiko
SAE:	Alvorlig uønsket hændelse (*serious adverse effect*)
TNF:	*Tumor necrosis factor*

1 Formål

Protokollen har til formål at definere de kliniske spørgsmål, der ønskes belyst i vurderingen af tildrakizumab som mulig standardbehandling til patienter (≥ 18 år) med moderat til svær plaque psoriasis uden ledgener, som er kandidater til 2. generations immunmodulerende behandling. I protokollen angives en definition af population, herunder subpopulationer, komparator og effektmål, der skal præsenteres i den endelige ansøgning samt de metoder, der ønskes anvendt til den komparative analyse. Arbejdet med protokollen er igangsat på baggrund af den foreløbige ansøgning om tildrakizumab modtaget den 18. september 2018.

Protokollen danner grundlaget for den endelige ansøgning for vurderingen af den kliniske merværdi af tildrakizumab sammenlignet med dansk standardbehandling. Alle effektmål, der er opgivet i denne protokol, skal besvares med en sammenlignende analyse mellem tildrakizumab og valgte komparator af både absolutte og relative værdier for de udspecificerede populationer i de angivne måleenheder (se tabel 1). Ansøger bedes også rapportere data for de angivne øvrige overvejelser. Litteratursøgning og databehandling udføres som beskrevet i protokollen. Den endelige ansøgning skal udfyldes i Medicinrådets ansøgningsskema, som findes på Medicinrådets hjemmeside.

2 Baggrund

I Danmark, som i øvrige dele af verden, får ca. 2-3 % af befolkningen psoriasis i løbet af livet. Psoriasis er en autoimmun, kronisk, inflammatorisk sygdom, hvor plaque psoriasis er den almindeligste (ca. 80 %) [1,2]. Der findes ikke et definitivt mål for sværhedsgraden af psoriasis. Sygdommen anses som moderat til svær, hvis psoriasis area and severity index (PASI) er over 10, det afficerede overfladeareal (body surface area, BSA) er over 10, eller patientens vurdering af livskvalitet, sædvanligvis vurderet ved dermatology life quality index (DLQI), er over 10. Samlet betegnes dette ”10-reglen” [3,4].

I Dermbios seneste årsrapport (2016) er antallet af patienter, der er i biologisk behandling i Danmark, fortsat stigende. Ved udgangen af 2016 var der registreret 3100 patienter fra 42 indberettende hospitaler og praksis i Danmark [5]. Ca. 40 % af behandlingsregimerne afbrydes, hvor manglende behandlingseffekt er den primære årsag [6]. Desuden ses en del bivirkninger ved behandling med 2. generations immunmodulerende lægemidler, hvor øget infektionstendens er den hyppigst forekommende. Opgørelsen af bivirkninger er dog vanskeliggjort af, at patientgruppen har en række komorbiditeter herunder øget infektionstendens [5,7]. Det forventede antal patienter på landsplan, som er kandidater til 2. generations immunmodulerende behandling, er pr. år ca. 100 nye patienter. Det drejer sig om psoriasispatienter, der opfylder kriterierne for biologisk behandling, og som ikke har psoriasisartropati (PsA). Derudover forventes det, at ca. 100 patienter pr. år fejler på et 2. generations immunmodulerende lægemiddel og skal skifte til et andet lægemiddel [7].

I 2014 blev psoriasis anerkendt af World Health Organisation (WHO) som en alvorlig kronisk sygdom, der ofte er yderst smertefuld og invaliderende. Dette skyldes blandt andet den stigmatisering, som ofte er forbundet med sygdommen [8]. Livskvalitetsundersøgelser viser, at psoriasis kan påvirke patienten på linje med diabetes og hjertekarsygdomme [8].

2.1 Nuværende behandling

2. generations immunmodulerende behandling igangsættes efter kriterier defineret i RADS-behandlingsvejledningen [7] og retningslinjer fra Dansk Dermatologisk Selskab [4]. Disse omfatter bl.a., at patienten skal have psoriasis med svære hudmanifestationer, defineret som PASI ≥ 10, BSA ≥ 10 % eller DLQI ≥ 10.

Til behandling af moderat til svær psoriasis anvendes ni lægemidler med forskellige virkningsmekanismer: tre tumor necrosis factor (TNF-alfa-hæmmere: infliximab, eternacept og adalimumab), et anti-interleukin (IL)-12/23 (ustekinumab), to anti-IL-17 (secukinumab og ixekizumab), et anti-IL-17RA (brodalumab), et anti-IL-23 (guselkumab) og en PDE4-inhibitor (apremilast). De fleste af disse behandlinger virker dæmpende på immunsystemet.

Adalimumab, secukinumab, ixekizumab og ustekinumab anbefales alle som 1. linjebehandlinger til psoriasis begrundet i samme effekt på hudsymptomer og sammenlignelig bivirkningsprofil jf. det foreliggende RADS-baggrundsnotat [7]. Lægemidlerne brodalumab og guselkumab er af Medicinrådet (15. marts 2018) vurderet til at udgøre et klinisk ligestillet alternativ til 1. linjebehandlingerne [9,10].

Patienterne vurderes før opstart, efter 12 ugers behandling og derefter 1 gang årligt. Der er i DDS-guidelines samt RADS' vejledning opstillet kriterier for den forventede effekt på PASI, og hvornår behandlingsskift er nødvendigt. Alle patienter med psoriasis, som sættes i 2. generations immunmodulerende behandling, skal registreres i Dermbio-databasen. For patienter med moderat til svær psoriasis har de biologiske præparater medført en betydelig bedring i behandlingsrespons.

2.2 Tildrakizumab

Ilumetri er en systemisk, biologisk antistofbehandling, der gives som injektion (subkutan á 100 mg i uge 0, 4 og herefter hver 12. uge). Indholdsstoffet tildrakizumab er et monoklonalt humaniseret antistof (mAb), der specifikt binder sig til det ekstracellulære humane interleukin (IL)-23. Herved forhindres, at IL-23 bidrager til immunaktivering, og samtidig begrænses den inflammatoriske reaktion i huden, der spiller en central rolle i udviklingen af psoriasis. Ilumetri er ikke indiceret til patienter med psoriasisartropati. Hos patienter med specifikke karakteristika (bl.a. høj sygdomsbyrde, kropsvægt ≥ 90 kg) kan dosering med 200 mg overvejes [11]. Fagudvalget ønsker denne dosering nærmere uddybet jf. afsnit 6: Andre overvejelser.

3 Kliniske spørgsmål

Hvad er den kliniske merværdi af tildrakizumab til voksne patienter med moderat til svær plaque psoriasis, som er kandidater til 2. generations immunmodulerende behandling og ikke har psoriasisartropati?

Population
Voksne (≥ 18 år) med moderat til svær plaque psoriasis, som er kandidater til 2. generations immunmodulerende behandling[1] og ikke har psoriasisartropati.

Subpopulationen omfatter patienter, som har haft behandlingssvigt på biologiske lægemidler generelt samt specifikt på lægemidler med IL-23 og IL-12/23 target.

- Ved behandlingssvigt er klinisk praksis at skifte til et lægemiddel med et andet target, hvorfor fagudvalget er interesseret i at se behandlingseffekterne for subgruppen af patienter med behandlingssvigt på tidligere lægemidler med (til dels) samme target som tildrakizumab (IL-23-

[1] Ved kandidater til 2. generations immunmodulerende behandling forstås psoriasispatienter, der opfylder de gældende kriterier, jf. RADS' behandlingsvejledning og Dansk Dermatologisk Selskabs retningslinjer. Kriterierne er: (1) at der er tale om patienter med moderat til svær kronisk psoriasis defineret ved 10-reglen, hvor patienten ikke responderer på, har kontraindikationer overfor eller er intolerant (uacceptable bivirkninger) overfor methotrexat og lysbehandling i form af smalspektret UVB eller PUVA, og (2) hvis der er kontraindikationer for methotrexat, bør det, før biologisk behandling påbegyndes, overvejes om patienten kan være kandidat til acitretin behandling [4].

hæmmende og IL-12/23-hæmmende lægemidler). Dette vil i klinisk praksis betyde flere behandlingsmuligheder.
- Derudover er fagudvalget interesseret i at se behandlingseffekterne for patienter med tidligere behandlingssvigt på biologiske lægemidler uanset target.

Intervention
Tildrakizumab, subkutan injektion á 100 mg i uge 0, 4 og herefter hver 12. uge.

Komparator
Effekten af tildrakizumab er jf. den foreløbige ansøgning undersøgt i et direkte sammenlignet studie med lægemidlet etanercept. Idet etanercept i RADS' behandlingsvejledning er placeret i behandlingshierarkiet efter 1. linjelægemidlerne begrundet med den ringere effekt på hudsymptomer, finder både fagudvalget og ansøger (jf. deres foreløbige ansøgning) det mere relevant at sammenligne tildrakizumab med ét af de lægemidler, der aktuelt anbefales som 1. linjebehandling til den generelle patientpopulation med moderat til svær plaque psoriasis. Der foreligger dog ikke head-to-head-studier, der direkte sammenligner effekten af tildrakizumab med effekten af et 1. linjelægemiddel, hvorfor indirekte sammenligning af lægemidlerne vil være nødvendig.

Fagudvalget definerer derfor komparator som ét af de anbefalede 1. linjelægemidler i standarddoser jf. RADS' baggrundsnotat [7] eller et af de to klinisk ligestillede alternativer, brodalumab og guselkumab, jf. Medicinrådets anbefaling den 15. marts 2018 [9,10]. Fagudvalget finder ikke, at der er klinisk belæg for at udvælge ét af de pågældende lægemidler fremfor et andet. For alle effektmål vælges samme komparator.

Effektmål
Tabel 1 summerer de valgte effektmål, herunder deres vigtighed, kategori og mindste klinisk relevante forskel. Begrundelsen er uddybet i afsnit 3.2.

Derudover finder fagudvalget, at en række lægemiddelhåndteringsmæssige overvejelser kan have betydning for patientpræferencer og praktisk håndtering af lægemidler og derfor må tages i betragtning (se afsnit 6).

3.1 Valg af effektmål

Tabel 1. Oversigt over valgte effektmål. For hvert effektmål er angivet deres vigtighed, den mindste klinisk relevante forskel samt indplacering i de fire kategorier (overlevelse, alvorlige symptomer og bivirkninger, livskvalitet og ikke-alvorlige symptomer og bivirkninger).

Effektmål*	Vigtighed	Kategori	Måleenhed	Mindste klinisk relevante forskelle (absolutte værdier)
For den totale population (inkl. subpopulation)				
PASI75	Kritisk	Alvorlige symptomer og bivirkninger	Andel patienter	15 % absolut forskel i respons
PASI90	Vigtig	Alvorlige symptomer og bivirkninger	Andel patienter	15 % absolut forskel i respons
Livskvalitet målt ved DLQI	Vigtig	Livskvalitet	Opnået DLQI score 0-1	15 % absolut forskel i respons
Alvorlige uønskede hændelser (SAEs)	Kritisk	Alvorlige symptomer og bivirkninger	Andel patienter	5 % absolut forskel
Behandlingsophør	Vigtig	Alvorlige symptomer og bivirkninger	Andel patienter	15 % absolut forskel

For subpopulation				
PASI90 hos patienter med tidligere svigt jf. populationsbeskrivelse	Vigtig	*Alvorlige symptomer og bivirkninger*	Andel patienter	15 % absolut forskel (non-inferiør)#

* For alle effektmål ønskes data med længst mulig opfølgningstid.
# Den absolutte forskel er angivet i forhold til patienter, der i deres tidligere behandling har oplevet svigt på biologiske lægemidler generelt samt specifikt på lægemidler med hhv. IL-23 og IL-12/23 target.

For alle kritiske samt vigtige effektmål ønskes både absolutte og relative værdier. For de relative værdier vurderes den kliniske merværdi på baggrund af tildelt kategori ifølge de væsentlighedskriterier, som er beskrevet i Medicinrådets metodehåndbog for vurdering af nye lægemidler. Der ønskes begrundelser, hvis der i den endelige ansøgning afviges fra de angivne effektmål.

For alle effektmål skal der antages hændelsesrater for den valgte komparator. Disse hændelsesrater skal være velbegrundede og skal bruges til beregning af de absolutte forskelle baseret på de estimerede relative forskelle i den indirekte sammenligning. Fagudvalget vil sammenholde de antagne hændelsesrater med danske data (se også beskrivelse i afsnit 5).

Tidshorisont
Den samlede kliniske merværdi af tildrakizumab baseres på en tidshorisont på 1 år. Der skal laves indirekte sammenligning på længst mulig opfølgningstid. Såfremt der ikke findes data op til 1 år, skal de indirekte sammenligninger suppleres med narrative sammenligninger af data for tildrakizumab og valgte komparator ved 1 års behandling på sammenlignelige tidspunkter fx ved uge 52 (se krav vedr. den narrative dataopgørelse sidst i afsnit 5).

Tidshorisonten på 1 år er valgt som tidsenhed for alle effektmål for at kunne vurdere langtidseffekten og derved vedligeholdelsen af den kliniske effekt.

Kritiske effektmål

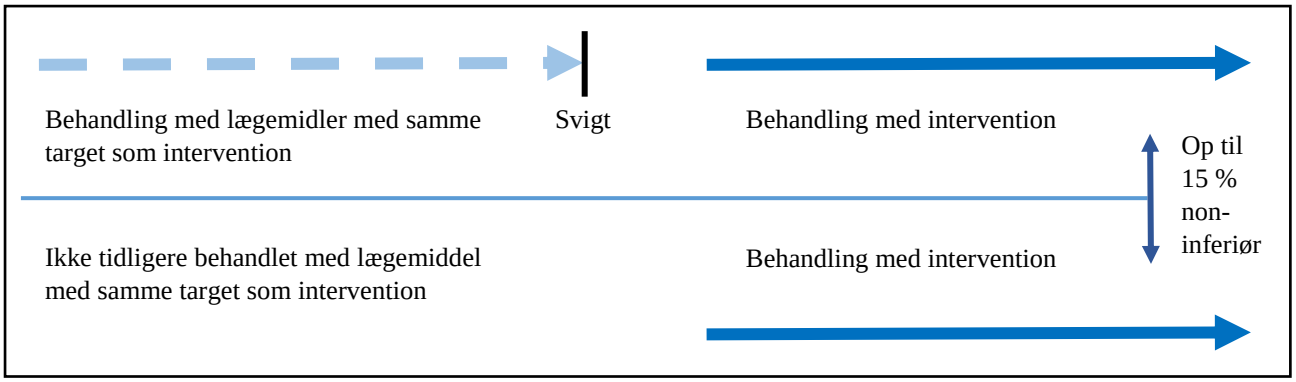
PASI75
PASI75 reflekterer reduktion i PASI-værdi med 75 %. PASI75 er anvendt i RADS-behandlingsvejledningen og ligger til grund for de ligestillede lægemidler. For at kunne sammenligne tildrakizumab med den valgte komparator vurderer fagudvalget, at lægemidlet skal vurderes på samme PASI-grundlag. PASI er et valideret mål for sværhedsgraden af kronisk plaque psoriasis, der kombinerer areal og læsionernes sværhedsgrad på en skala fra 0-72, hvor jo højere score desto sværere grad af psoriasis. Idet PASI-skalaen ikke er lineær, er en ændring i PASI uhensigtsmæssig som måleenhed. Længst mulig opfølgningstid med komparator er valgt som tidsenhed for at afspejle langtidseffekten og vedligeholdelsen af den kliniske effekt. Fagudvalget vurderer, at den mindste klinisk relevante forskel er en absolut forskel i opnået respons (opnået PASI75) mellem interventions- og komparatorgruppe på 15 %.

Alvorlige uønskede hændelser
Alvorlige uønskede hændelser (serious adverse events, SAE) indbefatter enhver alvorlig hændelse eller bivirkning opstået i de kliniske studier ved behandling med lægemidlet. Med tanke på den selekterede studiepopulation i de kliniske studier, og at der rapporteres på korttidsbivirkninger (≤ 1 år), vurderer fagudvalget, at en absolut forskel på 5 % anses for at være klinisk relevant for den samlede forekomst af SAEs.

Vigtige effektmål

PASI90
PASI90 reflekterer reduktion i PASI-værdi med 90 %. Det ideelle langsigtede behandlingsmål for patienter med hudpsoriasis er en fuldstændig eller næsten fuldstændig afglatning af huden, hvorfor fagudvalget også ønsker at se data på PASI90. Ligesom for PASI75 er længst mulig opfølgningstid med komparator valgt som tidsenhed. Fagudvalget vurderer, at en absolut forskel i opnået respons (opnået PASI90) mellem interventions- og komparatorgruppe på 15 % er klinisk relevant.

PASI90 i subpopulationer
For subpopulationerne af patienter med tidligere behandlingssvigt på biologiske lægemidler generelt samt specifikt på lægemidler med hhv. IL-23 og IL-12/23 target, ønsker fagudvalget at vurdere, om behandling med tildrakizumab har den ønskede effekt. En effekt af tildrakizumab hos patienter, hvor andet biologisk lægemiddel herunder IL-23 eller IL-12/23-hæmmende lægemiddel ikke har haft tilstrækkelig effekt, vil kunne betyde flere behandlingsmuligheder. Fagudvalget ønsker dette belyst ved data på PASI90 og med en absolut forskel på op til 15 % (non-inferiør) i forhold til patienter i behandling med tildrakizumab med samme behandlingslængde, som ikke tidligere har haft behandlingssvigt på IL-23 eller IL-12/23-hæmmende lægemiddel (se illustration herunder). Effekten hos patienter med behandlingssvigt på biologiske lægemidler generelt vil vurderes på samme måde (absolut forskel på PASI90 op til 15 %).



DLQI
DLQI reflekterer livskvalitet målt ved dermatologisk life quality index. Spørgeskemaet består af 10 spørgsmål, der berører seks domæner (symptomer og følelsesmæssig påvirkning, påvirkning af dagligdagsaktiviteter, fritid, arbejde og skole, personlige relationer samt gener i forbindelse med behandling), hvor hvert svar graderes på en skala fra 0-3, således at der opnås en scoring på 0-30, hvor 30 repræsenterer størst negativ påvirkning af livskvaliteten. Almindeligvis betragtes en negativ ændring på ≥ 4 point som klinisk relevant [12]. En DLQI-score på 0 eller 1 anses imidlertid af fagudvalget som det ultimative behandlingsmål, hvilket betyder, at patienten ikke oplever påvirkning af livskvaliteten [13]. Eftersom DLQI dog ikke er et psoriasisspecifikt måleinstrument og dermed ikke afspejler den fulde sygdomsbyrde, vægtes effektmålet af fagudvalget som vigtigt. Fagudvalget vurderer, at en absolut forskel i respons (opnået score 0-1) på 15 % er et klinisk patientrelevant mål.

Behandlingsophør
Behandlingsophør reflekterer hvor mange patienter, som afbryder behandlingen i de kliniske studier uanset årsag herunder bivirkninger og skuffende effekt. Effektmålet er medtaget som indikator for behandlingskvalitet og tolerancen ved langtidsbehandling. Fagudvalget finder på denne baggrund, at en absolut forskel på 15 % er klinisk relevant.

4 Litteratursøgning

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

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

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

Søgningen skal som minimum indeholde termer, som er beskrivende for de områder, der er angivet i tabellen herunder. Både indekseret (f.eks. Medical Subject Headings, MeSH) og fritekstsøgning skal anvendes. De anvendte søgetermer, og hvordan de er blevet kombineret, dokumenteres separat for hver af de to databaser.

[Tildrakizumab, Ilumetri] *Udover termer for det generiske navn, handelsnavn og alternative stavemåder og eventuelle MeSH/Supplementary Concepts kombineres med **OR**. AND kan bruges, hvor flere termer skal forekomme samtidigt for at beskrive lægemidlet korrekt, fx ved coformuleringer.*	*Blokkene til venstre og højre kombineres med **AND***	**[psoriasis]** *Termer for indikationen, alternative stavemåder og eventuelle MeSH kombineres med **OR**. AND kan bruges, hvor flere termer skal forekomme samtidigt for at beskrive indikationen korrekt.*
*Ovenstående og nedenstående blokke kombineres med **OR***		
[<generisk navn, handelsnavn på valgte komparator blandt 1. linjelægemidler>] *Udover termer for det generiske navn, handelsnavn, alternative stavemåder og eventuelle MeSH/Supplementary Concepts kombineres med **OR**. AND kan bruges, hvor flere termer skal forekomme samtidigt for at beskrive lægemidlet korrekt, fx ved coformuleringer.*		

Kriterier for udvælgelse af litteratur
Vurderingen af klinisk merværdi baseres i udgangspunktet på data fra publicerede fuldtekstartikler og data fra EMAs EPAR – Public assessment report. Data skal derudover stemme overens med protokollens beskrivelser. Der skal udarbejdes prisma-flowdiagram for udvælgelse af litteratur.

5 Databehandling/analyse

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

Al relevant data skal som udgangspunkt ekstraheres ved brug af Medicinrådets ansøgningsskema. Der skal udføres en komparativ analyse for hvert enkelt effektmål på baggrund af relevant data fra inkluderede studier. For hvert effektmål og studie angives analysepopulation (f.eks. intention-to-treat (ITT), per-protocol) samt metode. Resultater for ITT-populationen skal angives, hvis muligt, hvis komparative analyser ikke i

udgangspunktet er baseret på denne population. Alle ekstraherede data skal krydstjekkes med de resultater, der beskrives i EPAR'en. Findes uoverensstemmelser, gives en mulig grund herfor.

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

Hvis data for et effektmål ikke er 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 (PASI, DLQI, SAE og behandlingsophør), 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 kan afspejle det forventede niveau i Danmark ved behandling med komparator (hvis relativ risiko (RR) = 0,5 og antaget andel med hændelse i komparatorgruppen er 30 %, da er den absolutte risiko reduktion (ARR) = 30 – 30 x 0,5 = 1 %-point). Det antagne niveau for hændelsesraten i komparatorgruppen skal begrundes i den endelige ansøgning.

Hvis der er mere end et sammenlignende studie, foretages en metaanalyse for de effektmål, hvor det er metodemæssigt forsvarligt. Hvis der ikke foreligger sammenlignende studier, kan data eventuelt syntetiseres indirekte (evt. ved brug af Buchers metode), hvis intervention og komparator er sammenlignet med samme alternative komparator i separate studier. Medicinrådet forbeholder sig retten til at foretage sensitivitets- og subgruppeanalyser på baggrund af studiernes validitet og relevans.

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

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

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

***Vigtigt for de narrative sammenligner af psoriasisstudier**:* Det skal tydeligt fremgå, hvilke imputationsmetoder som er anvendt i de inkluderede studier. Patientflowet fra baseline og frem til sidste dataopsamling skal tydeligt fremgå for både tildrakizumab og komparator. For hvert effektmål skal den indirekte analyse suppleres med en tabel, der opgør effekten af tildrakizumab og komparator ved 1 års-behandling eller længst muligt op til.

6 Andre overvejelser

Som udgangspunkt pauseres behandling ikke i den daglige klinik, da psoriasis er en kronisk sygdom, og der ofte ses effekttab ved opstart efter en behandlingspause. Men da behandlingen af psoriasis er langvarig, kan der alligevel opstå behov for midlertidig pausering af behandlingen eksempelvis i tilfælde af rejser, graviditet, kirurgiske indgreb og anden sygdom. Derfor ønsker fagudvalget i deres vurdering at lægge vægt på mulighed for behandlingspauser.

Ligeledes ønsker fagudvalget at se data for vedligeholdelsesdosis, eventuelt serumkoncentrationer og hos velbehandlede patienter mulighed for dosisreduktion eller forlængelse af behandlingsintervaller.

Fagudvalget finder forholdet mellem initialdosis og vedligeholdelsesdosis relevant, idet et inferiørt stof kan fremstå som effektivt ved at give høj initialdosis. Fagudvalget ønsker derfor behovet for den højere initialdosis belyst, med henblik på vurdering af om der kan anvendes samme dosis i hele behandlingsforløbet.

Fagudvalget vil derfor gerne have oplyst følgende forhold for tildrakizumab:

- Mulighed for behandlingspause.
- Mulighed for dosisreduktion/behandlingsintervalforlængelse. Fagudvalget ønsker specifikt en uddybning af 200 mg doseringsgruppen (”patienter med specifikke karakteristika bl.a. høj sygdomsbyrde og kropsvægt ≥ 90 kg”), herunder om der er forskelle i behandlingseffekt i forhold til 100 mg doseringen, og hvad der forstås ved ”høj sygdomsbyrde”. Derudover ønsker fagudvalget en estimering af andelen af patientpopulationen, som forventes at tilhøre gruppen med behov for 200 mg dosering.
- Forhold mellem initialdosis og vedligeholdelsesdosis.
- Vedligeholdelse af effekt mellem doseringer hver 12. uge.

7 Referencer

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8 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende psoriasis og psoriasis med ledgener

Forvaltningslovens § 4, stk. 2 har været anvendt i forbindelse med udpegning af medlemmer til dette fagudvalg.

Formand	***Indstillet af***
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