Medicinrådet

Baggrund for Medicinrådets anbefaling vedrørende dupilumab som mulig standardbehandling til svær astma

Versionsnr.: 1.0

Medicinrådet

Om Medicinrådet

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

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

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

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

Om anbefalingen

Anbefalingen er Medicinrådets vurdering af, om lægemidlets samlede pris er rimelig, når man sammenligner den med lægemidlets værdi for patienterne.

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

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

1 Lægemiddelinformationer

Lægemidlets oplysninger	
Handelsnavn	Dupixent
Generisk navn	Dupilumab
Firma	Sanofi Genzyme
ATC-kode	D11AH05
Virkningsmekanisme	Dupilumab er et monoklonalt antistof rettet mod interleukin 4-receptor underenhed alfa (IL-4Rα). Denne underenhed deles af IL-4 og IL-13 receptorkomplekser, og derfor hæmmer dupilumab signaleringen fra både IL-4 og IL-13. IL-4 er den centrale mediator af naive T-cellers differentiering til Type 2 cytokinproducerende effektorceller, eosinofil trafficking, B-celleaktivering og underliggende øgning af IgE-produktion. IL-13 medierer ydermere remoduleringen af luftvejene ved bægercellehyperplasi, transformation af bronkiale fibroblaster til myofibroblaster, kollagen deposition og proliferation af glatte muskelceller i luftvejene. IL-13 medierer også glat muskelkontraktion samt bronkoepitelial produktion af FeNO.
Administration/dosis	Initial dosis på 400 mg (fordelt på to 200 mg subkutane injektioner), herefter 200 mg subkutan injektion hver anden uge i tillæg til standardbehandling. Patienter som er i vedligeholdelsesbehandling med orale kortikosteroider eller til patienter, som samtidig lider af moderat til svær atopisk eksem: initial dosis på 600 mg (fordelt på to 300 mg subkutane injektioner), herefter 300 mg subkutan injektion hver anden uge i tillæg til standardbehandling.
EMA-indikation	Voksne, unge og børn ≥ 12 år som tillægsvedligeholdelsesbehandling til svær astma med type 2-inflammation karakteriseret ved forhøjet blodeosinofile celler og/eller forhøjet FeNO, som er utilstrækkeligt kontrolleret med højdosis inhalationskortikosteroider og en anden medicinsk vedligeholdelsesbehandling.
Accelerated assessment	Nej
Orphan drug	Nej
Conditional approval	Nej
Øvrige indikationer	Patienter ≥ 12 år med moderat til svær atopisk eksem

2 Medicinrådets anbefaling

- Medicinrådet **anbefaler** dupilumab til patienter ≥ 12 år med svær astma med type 2-inflammation karakteriseret ved eosinofili.

- Medicinrådet **anbefaler** dupilumab til patienter ≥ 12 år med svær astma med type 2-inflammation karakteriseret ved allergi og samtidig eosinofili eller karakteriseret ved allergi og samtidig forhøjet FeNO.

- Medicinrådet **anbefaler ikke** dupilumab til patienter ≥ 12 år med svær astma med type 2-inflammation karakteriseret ved forhøjet FeNO uden samtidig eosinofili og uden samtidig allergi. Effekten af dupilumab i denne population er ikke veldokumenteret.

Medicinrådet anbefaler, at regionerne vælger det lægemiddel, der er forbundet med de laveste omkostninger.

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

1. *Hvilken værdi tilbyder dupilumab sammenlignet med mepolizumab ved behandling af patienter ≥ 12 år med svær astma med type 2-inflammation karakteriseret ved eosinofili?*
2. *Hvilken værdi tilbyder dupilumab sammenlignet med omalizumab ved behandling af patienter ≥ 12 år med svær astma med type 2-inflammation karakteriseret ved allergi og samtidig eosinofili eller karakteriseret ved allergi og samtidig forhøjet FeNO?*
3. *Hvilken værdi tilbyder dupilumab sammenlignet med placebo ved behandling af patienter ≥ 12 år med svær astma med type 2-inflammation karakteriseret ved forhøjet FeNO uden samtidig eosinofili og uden samtidig allergi?*

3 Formål

Formålet med *Baggrund for Medicinrådets anbefaling vedrørende dupilumab som mulig standardbehandling til patienter med svær astma ≥ 12* år er at skabe gennemsigtighed om det materiale, der ligger til grund for Medicinrådets anbefaling.

4 Baggrund

Svær astma defineres som astma, der gennem minimum det sidste år har krævet behandling med højdosis inhalationssteroid samt en eller flere tillægsbehandlinger (typisk langtidsvirkende beta2-agonist, LABA, og/eller som har krævet peroralt steroid i ≥ 50 % af tiden) for at forebygge, at astmaen bliver ukontrolleret eller trods denne behandling forbliver ukontrolleret. Ca. 50 % af patienter med svær astma har type 2-inflammation. Type 2-inflammation er ofte karakteriseret ved forhøjet blodeosinofile celler (eosinofil astma) og/eller forhøjet nitrogenoxid i udåndingsluften (FeNO) (astma med forhøjet FeNO) og/eller allergi (allergisk astma).

4.1 Sagsbehandlingstid og proces for Medicinrådets vurdering

Medicinrådet modtog den foreløbige ansøgning den 28. marts 2019, og protokollen blev sendt til Sanofi den 27. juni 2019. Den endelige ansøgning blev modtaget den 17. september 2019. Udvidet fagligt clock-stop fra den 11. december 2019 til den 22. januar 2020. Beslutning om anbefaling blev truffet den 19. februar 2020.

Sagsbehandlingstiden er dermed 16 uger og 1 dag.

5 Medicinrådets vurdering af samlet værdi

Medicinrådet vurderer at:

- Dupilumab har **ingen dokumenteret merværdi** sammenlignet med mepolizumab til patienter med svær astma med type 2-inflammation karakteriseret ved eosinofili. Evidensens kvalitet vurderes at være **lav**.
- Dupilumab har **ingen dokumenteret merværdi** sammenlignet med omalizumab til patienter med svær astma med type 2-inflammation karakteriseret ved allergi og samtidig eosinofili eller karakteriseret ved allergi og samtidig forhøjet FeNO. Evidensens kvalitet vurderes at være **meget lav**.
- Værdien af dupilumab **kan ikke kategoriseres** sammenlignet med placebo til patienter med svær astma med type 2-inflammation karakteriseret ved forhøjet FeNO uden samtidig eosinofili og uden samtidig allergi. Evidensens kvalitet er ikke vurderet.

6 Høring

Høringsperioden foregik fra den 15.-29. januar 2020. Ansøger havde ikke kommentarer til vurderingen.

7 Resumé af økonomisk beslutningsgrundlag

Medicinrådet har vurderet de gennemsnitlige meromkostninger pr. patient og budgetkonsekvenserne for regionerne ved brug af dupilumab sammenlignet med komparatorerne mepolizumab, omalizumab og placebo. Medicinrådets vurdering af meromkostninger og budgetkonsekvenser er baseret på aftalepris.

Baseret på Medicinrådets hovedanalyse og følsomhedsanalyser vurderes at:

- På nuværende tidspunkt finder Medicinrådet, at der ikke er et rimeligt forhold mellem meromkostninger og lægemidlets værdi sammenlignet med mepolizumab til patienter med svær eosinofil astma. Da dupilumab er ligestillet med andre lægemidler til samme indikation og dermed kan indgå i en kommende lægemiddelrekommandation, vælger Medicinrådet at anbefale dupilumab som mulig standardbehandling. Anbefalingen forventes at øge konkurrencen på området, da regionerne vælger den behandling i lægemiddelrekommandationen, som er forbundet med de laveste omkostninger.

- Der er et rimeligt forhold mellem meromkostninger og lægemidlets værdi sammenlignet med omalizumab til patienter med svær astma med type 2-inflammation karakteriseret ved allergi og samtidig eosinofili eller karakteriseret ved allergi og samtidig forhøjet FeNO.
- Der ikke er et rimeligt forhold mellem meromkostninger og lægemidlets værdi sammenlignet med placebo til patienter med svær astma med type 2-inflammation karakteriseret ved forhøjet FeNO uden samtidig eosinofili og uden samtidig allergi.

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 svær astma

Formand	**Indstillet af**
Bo Chawes Afdelingslæge, seniorforsker, dr.med., ph.d.	Lægevidenskabelige Selskaber og udpeget af Dansk Pædiatrisk Selskab
Medlemmer	**Udpeget af**
Kan ikke opfylde Medicinrådets habilitetskrav	Region Nordjylland
Johannes Martin Schmid Overlæge	Region Midtjylland
Hanne Madsen Afdelingslæge, ph.d.	Region Syddanmark
Udpegning i gang	Region Sjælland
Lars Pedersen Overlæge, ph.d., klinisk lektor	Region Hovedstaden
Pernille Printzlau Klinisk farmaceut	Dansk Selskab for Sygehusapoteksledelse (DSS)
Daniel Pilsgaard Henriksen Læge, ph.d.	Dansk Selskab for Klinisk Farmakologi (DSKF)
To patienter/patientrepræsentanter	Danske Patienter

Medicinrådets sekretariat

Medicinrådet Dampfærgevej 27-29, 3. th. 2100 København Ø + 45 70 10 36 00 medicinraadet@medicinraadet.dk
Sekretariatets arbejdsgruppe: Ehm Andersson Galijatovic (projekt- og metodeansvarlig) Louise Klokker Madsen (projektdeltager) Dorthea Elise Christensen (projektdeltager) Anette Pultera Nielsen (fagudvalgskoordinator) Jan Odgaard-Jensen (biostatistiker) Jesper Skov Neergaard (informationsspecialist) Annemette Anker Nielsen (teamleder)

10 Versionslog

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

11 Bilag

Bilagsliste:

- Bilag 1 - Amgros' forhandlingsnotat for Dupilumab
- Bilag 2 - Medicinrådets sundhedsøkonomiske afrapportering for dupilumab
- Bilag 3 - Medicinrådets vurdering af dupilumab til behandling af svær astma-vers. 1.0
- Bilag 4 - Ansøgers endelige ansøgning vedr. dupilumab
- Bilag 5 - Medicinrådets protokol for vurdering af dupilumab til behandling af svær astma, vers. 1.0

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Forhandlingsnotat

Dato for behandling i Medicinrådet	19.02.2020
Leverandør	Sanofi
Lægemiddel	Dupilumab (Dupixent)
EMA-indikation	Voksne, unge og børn > 12 år som tillægsvedligeholdelsesbehandling til svær astma med type 2-inflammation karakteriseret ved forhøjet blodeosinofile celler og/eller forhøjet FeNO, som er utilstrækkeligt kontrolleret med højdosis inhalationskortikosteroider og en anden medicinsk vedligeholdelsesbehandling.

Forhandlingsresultat

Amgros har opnået følgende pris på dupilumab (Dupixent):

Lægemiddel	Styrke/dosis	Pakningsstørrelse	AIP	Forhandlet SAIP	Rabatprocent ift. AIP
Dupixent	200 mg	2 stk. sprøjte (SC)	9.426,66	[redacted]	[redacted]
Dupixent	300 mg	2 stk. sprøjte (SC)	9.426,66	[redacted]	[redacted]

Aftalen for dupilumab (Dupixent) løber indtil 01.10.2020, hvor det forventes, at aftalerne baseret på det kommende udbud skal starte for alle lægemidlerne i behandlingsvejledningen.

Vurdering af forhandlingsresultatet

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

Patienter med svær astma med type 2 inflammation karakteriseret ved eosinofili

- [redacted]
- [redacted] Dette kan ske fra d. 01.10.2020, når der har været et nyt udbud, og alle leverandørerne har fået mulighed for at give nye priser.

Patienter som også er karakteriseret ved allergi og enten samtidig eosinofili eller samtidig forhøjet FeNO

[redacted]

Konklusion

[redacted]

Relation til markedet

Dupilumab (Dupixent) kan stadig konkurrere med de eksisterende behandlingsalternativer i det kommende udbud, selvom Medicinrådet ikke anbefaler dupilumab (Dupixent) som mulig standardbehandling på dette rådsmøde. Indplacering i lægemiddelrekommandationen forudsætter, at Medicinrådet vælger at revurdere anbefalingen af dupilumab (Dupixent) som mulig standardbehandling, hvis det i denne omgang bliver et nej til standardbehandling.

[redacted]

Medicinrådet

Sundhedsøkonomisk afrapportering

Dupilumab

Svær astma

Version 1.0

Indholdsfortegnelse

Om Medicinrådet

Medicinrådet er et uafhængigt råd, som udarbejder anbefalinger og vejledninger om lægemidler til de fem regioner. Medicinrådet vurderer, om nye lægemidler og nye indikationer kan anbefales som standardbehandling og udarbejder fælles regionale behandlingsvejledninger. Nye lægemidler vurderes i forhold ti l 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.

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Opsummering

Baggrund

Dupilumab er et monoklonalt antistof, indiceret som tillægsbehandling til børn ≥ 12 år og voksne med svær astma med type 2-inflammation, karakteriseret ved forhøjet blodeosinofile celler og/eller forhøjet FeNO, som er utilstrækkeligt kontrolleret med højdosis inhaleret kortikosteroid (ICS) og én anden medicinsk vedligeholdelsesbehandling. Omkring 60 nye patienter kandiderer årligt til behandling af den ansøgte indikation i Danmark. Medicinrådets sekretariats vurdering tager udgangspunkt i dokumentation indsendt af Sanofi Genzyme.

Analyse

I analysen estimeres de inkrementelle omkostninger forbundet med tillægsbehandling med dupilumab af patienter ≥ 12 år med svær astma med type-2-inflammation, sammenlignet med mepolizumab, omalizumab og placebo.

Inkrementelle omkostninger og budgetkonsekvenser

Medicinrådets sekretariat har vurderet de gennemsnitlige inkrementelle omkostninger pr. patient ved brug af dupilumab sammenlignet med mepolizumab, omalizumab og placebo. De inkrementelle omkostninger er angivet i sygehusapotekets indkøbspriser (SAIP).

I det scenarie, Medicinrådets sekretariat finder mest sandsynligt for patienter med svær astma karakteriseret med eosinofili, er de inkrementelle omkostninger for dupilumab sammenlignet med mepolizumab ca. [redacted] DKK over en tidshorisont på 43 år. Hvis analysen udføres med apotekets indkøbspris (AIP) bliver de inkrementelle omkostninger pr. patient til sammenligning ca. 290.000 DKK.

I det scenarie, Medicinrådets sekretariat finder mest sandsynligt for patienter med svær astma karakteriseret ved allergi og samtidig eosinofili eller forhøjet FeNO, er de inkrementelle omkostninger for dupilumab sammenlignet med omalizumab ca. [redacted] DKK over en tidshorisont på 43 år. Hvis analysen udføres med AIP bliver de inkrementelle omkostninger pr. patient til sammenligning ca. 128.000 DKK

I det scenarie, Medicinrådets sekretariat finder mest sandsynligt for patienter med svær astma, karakteriseret ved forhøjet FeNO uden samtidig eosinofili og allergi, er de inkrementelle omkostninger for dupilumab sammenlignet med placebo ca. [redacted] DKK over en tidshorisont på 43 år. Hvis analysen udføres med AIP, bliver de inkrementelle omkostninger pr. patient til sammenligning ca. 2.650.000 DKK.

Hvis omkostningerne opgøres over en tidshorisont på 1 år bliver de gennemsnitlige inkrementelle omkostninger ca. [redacted] DKK i P1, ca. [redacted] DKK i P2 og ca. [redacted] DKK i P3.

Medicinrådets sekretariat vurderer, at budgetkonsekvenserne for regionerne i år 5, ved anbefaling af dupilumab som standardbehandling, vil være ca. [redacted] DKK i P1, ca. [redacted] DKK i P2, og ca. [redacted] DKK i P3. Hvis analysen udføres med AIP, bliver

budgetkonsekvenserne 7 mio. DKK i år 5 i P1, 0,5 mio. DKK i år 5 i P2 og 3 mio. DKK i år 5 i P3.

Konklusion

Behandling med dupilumab er over en tidshorisont på 43 år forbundet med høje inkrementelle omkostninger for P1, meget store besparelser for P2 og meget høje inkrementelle omkostninger for P3. De inkrementelle omkostninger er næsten udelukkende drevet af lægemiddelomkostningerne, og særligt lægemiddelomkostningerne for omalizumab har betydning for analysens resultat for P2.

Dokumentoplysninger	
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Arbejdsgruppe	Emma Munk, Pernille Winther Johansen

Liste over forkortelser

AIP	Apotekets indkøbspris
DKK	Danske kroner
DRG	Diagnoserelaterede grupper
EMA	European Medicines Agency
ICS	Inhalationskortikosteroider
IgE	Immunoglobulin E
SAIP	Sygehusapotekets indkøbspris
LPR	Landspatientregisteret
LABA	Langtidsvirkende betaagonist
RR	Relative risiko

1. Baggrund for den økonomiske analyse

Sanofi Genzyme (herefter omtalt som ansøger) er markedsføringstilladelsesindehaver af dupilumab og har den 17. september 2019 indsendt en ansøgning til Medicinrådet om anbefaling af dupilumab som standardbehandling på danske hospitaler af den nævnte indikation. Som led i denne ansøgning vurderer Medicinrådets sekretariat, på vegne af Medicinrådet, den økonomiske analyse, ansøger har sendt som en del af den samlede ansøgning til Medicinrådet. Denne rapport er Medicinrådets sekretariats vurdering af den fremsendte økonomiske analyse (herefter omtalt som analysen).

1.1 Patientpopulation

Astma er en heterogen sygdom, som oftest skyldes inflammation i luftvejene, hvilket medfører hyperreaktive luftveje med tendens til sammentrækning. Typiske symptomer på astma er hoste, åndenød, pibende vejrtrækning og tendens til lungeinfektioner. Symptomerne kan opstå spontant eller forårsages af en udløsende faktor. Sværhedsgraden bestemmes på baggrund af den behandlingsintensitet, der kræves, for at opnå kontrol over astmaen. Graden af sygdomskontrol bestemmes på baggrund af dags- og natsymptomer samt behovet for anfaldsmedicin, og behandlingen justeres ud fra sygdomskontrollen (1). Det vurderes, at ca. 7-11 % af den danske befolkning har astma, og prævalensen af svær astma er estimeret til ca. 5-15 % blandt alle astmapatienter (2,3).

1.1.1 Subpopulationer

Ca. 50 % af patienterne med svær astma har type-2 inflammation, som er karakteriseret ved cytokinerne IL-4, IL-5 og IL-13, som produceres ved allergenudløst aktivering af det adaptive immunsystem. Type-2 inflammation er desuden karakteriseret ved forhøjet blodeosinofile celler (eosinofil astma) og/eller forhøjet nitrogenoxid i udåndingsluften (astma med forhøjet FeNO) og/eller allergi med IgE-sensibilisering for allergener (allergisk astma) (4). De forskellige karakteristika kan gøre valget af biologisk lægemiddel vanskelig, da nogle patienter kan have flere karakteristika for deres astma (5).

Følgende subpopulationer er specificeret:

P1: Patienter ≥ 12 år med svær astma med type-2-inflammation karakteriseret ved eosinofili.
P2: Patienter ≥ 12 år med svær astma med type-2-inflammation karakteriseret ved allergi og samtidig eosinofili eller samtidig forhøjet FeNO.
P3: Patienter ≥ 12 år med svær astma med type-2-inflammation karakteriseret med forhøjet FeNO uden samtidig eosinofili og allergi.

1.1.2 Komparator

Medicinrådet har defineret mepolizumab, omalizumab og placebo som komparatorer til dupilumab i hhv. P1, P2 og P3, se Tabel 1.

Tabel 1: Definerede populationer og komparatorer.

Population	Komparator
P1: Patienter ≥ 12 år med svær astma med type-2-inflammation karakteriseret ved eosinofili.	Mepolizumab
P2: Patienter ≥ 12 år med svær astma med type-2-inflammation karakteriseret ved allergi og samtidig eosinofili eller samtidig forhøjet FeNO.	Omalizumab
P3: Patienter ≥ 12 år med svær astma med type-2-inflammation karakteriseret med forhøjet FeNO uden samtidig eosinofili og allergi.	Placebo

1.2 Problemstilling

Formålet med analysen er at estimere de gennemsnitlige inkrementelle omkostninger pr. patient og de samlede budgetkonsekvenser for regionerne ved anbefaling af dupilumab som standardbehandling til den nævnte indikation.

Medicinrådet har vurderet værdien af dupilumab som vedligeholdelsesbehandling og specificeret tre kliniske spørgsmål:

Klinisk spørgsmål 1:

Hvilken klinisk merværdi tilbyder dupilumab sammenlignet med mepolizumab ved behandling af patienter ≥ 12 år med svær astma med type-2-inflammation karakteriseret ved eosinofili?

Klinisk spørgsmål 2:

Hvilken klinisk merværdi tilbyder dupilumab sammenlignet med omalizumab ved behandling af patienter ≥ 12 år med svær astma med type-2-inflammation karakteriseret ved allergi og samtidig eosinofili eller karakteriseret ved allergi og samtidig forhøjet FeNO?

Klinisk spørgsmål 3:

Hvilken klinisk merværdi tilbyder dupilumab sammenlignet med placebo ved behandling af patienter ≥ 12 år med svær astma med type-2-inflammation karakteriseret ved forhøjet FeNO uden samtidig eosinofili og uden samtidig allergi?

2. Vurdering af den økonomiske analyse

Ansøger har indsendt tre økonomiske analyser, der estimerer de inkrementelle omkostninger pr. patient for dupilumab sammenlignet med mepolizumab (P1), omalizumab (P2) og placebo (P3). I det nedenstående vil den økonomiske model, som ligger til grund for estimeringen af de inkrementelle omkostninger pr. patient, blive præsenteret.

2.1 Antagelser og forudsætninger for model

De økonomiske modeller har til formål at estimere de inkrementelle omkostninger ved behandling af svær astma med type-2 inflammation med dupilumab.

I analysen er sammenligningen mellem dupilumab og placebo lavet på baggrund af QUEST-studiet (6), mens sammenligningen med mepolizumab og omalizumab er baseret på en indirekte sammenligning af Bergrath et al., 2019 (7).

2.1.1 Modelbeskrivelse

Ansøger har indsendt tre omkostningsanalyser, en for hvert klinisk spørgsmål. Omkostningsanalyserne har til formål at estimere de inkrementelle omkostninger ved tillægsbehandling med dupilumab sammenlignet med mepolizumab (P1), omalizumab (P2) og placebo (P3).

Ansøger har i analyserne estimeret en eksacerbationsrate pr. år ved behandling med hver komparator samt en reduktion i den relative risiko (RR) for eksacerbationer ved behandling med dupilumab, sammenlignet med hver komparator.

I sammenligningen med mepolizumab er den årlige eksacerbationsrate ved behandling med mepolizumab estimeret som et personårsvægtet gennemsnit af tre studier, som kan ses i Tabel 2. Den relative risikoreduktion kommer fra den indirekte sammenligning af Bergrath et al., 2019 (7).

I sammenligningen med omalizumab kommer den årlige eksacerbationsrate ved behandling med omalizumab fra Hanania et al., 2013, og den relative risikoreduktion kommer ligeledes fra den indirekte sammenligning af Bergrath et al., 2019 (7).

I sammenligningen med placebo kommer den årlige eksacerbationsrate ved behandling med placebo samt den relative risikoreduktion fra QUEST-studiet (6).

Tabel 2: Årlige eksacerbationsrater for komparatorerne og reduktion i relative risiko ved behandling med dupilumab sammenlignet med hver komparator.

Komparator	Eksacerbationsrate pr. år	Reduktion i RR for dupilumab	Kilde
Mepolizumab	0,89	0,72	Ortega et al. 2004 Chupp et al. 2014 Pavord et al. 2012
Omalizumab	0,70	0,65	Hanania et al. 2013
Placebo	2,09	0,44	Castro et al. 2018

Medicinrådets sekretariats vurdering

Medicinrådets sekretariat accepterer ansøgers tilgang.

2.1.2 Analyseperspektiv

Ansøgers indsendte omkostningsanalyser har et begrænset samfundsperspektiv. Ansøger har anvendt en livslang tidshorisont, da behandling af svær astma er livslang. Ansøger har estimeret tidshorisonten vha. den gennemsnitlige patientalder i QUEST-studiet (6), den forventede restlevetid og levetidsreduktionen for personer med svær astma, baseret på køn (8). Derved har ansøger beregnet en restlevetid på 43 år. Omkostninger, der ligger efter det første år, er diskonteret med en rate på 4 % i ansøgers hovedanalyse.

Medicinrådets sekretariats vurdering

Det valgte analyseperspektiv og tidshorisonten stemmer overens med Medicinrådets sekretariats metodevejledning. Medicinrådets sekretariat vurderer, at 43 år er tilstrækkeligt til at estimere omkostningerne for et gennemsnitligt livslangt behandlingsforløb med alternativerne. Omkostninger, der ligger efter år 35, skal, jævnfør Finansministeriet, diskonteres med en rate på 3 % (9). Medicinrådets sekretariat har i sin hovedanalyse diskonteret omkostninger i år 1 til år 35 med en rate på 4 %, mens omkostninger i år 36 til år 43 er diskonteret med en rate på 3 %.

Medicinrådets sekretariat accepterer ansøgers antagelser. Dog anvender Medicinrådets sekretariat en diskonteringsrate på 3 % fra år 36 til år 43 i analysen.

2.2 Omkostninger

I det følgende præsenteres ansøgers antagelser for omkostningerne i den økonomiske analyse af dupilumab. De inkluderede omkostninger i ansøgers analyse er lægemiddelomkostninger, hospitalsomkostninger og patientomkostninger. Ansøger har ikke

inkluderet tværsektorielle omkostninger, omkostninger til monitorering eller omkostninger til bivirkninger, da ansøger antager, at disse er ens for alternativerne i analysen. Ansøgers estimering af lægemiddelomkostninger bygger altid på AIP, hvilket i Medicinrådets sekretariats hovedanalyse udskiftes med SAIP.

2.2.1 Lægemiddelomkostninger

Anvendte doser for dupilumab, mepolizumab, omalizumab og prednisolon kommer fra de respektive lægemidlers produktresuméer, se Tabel 3.

I alle populationer gives dupilumab subkutant i en fast dosis af enten 200 mg eller 300 mg hver 2. uge, og ved opstart af behandling gives en initial dosis (loading dose) på enten 400 mg eller 600 mg. Da prisen for 200 mg og 300 mg dupilumab er ens, er der ikke taget højde for, om patienterne modtager den ene eller anden dupilumabdosis.

Mepolizumabdosen er 100 mg subkutant hver 4. uge.

Omalizumabdosen er beregnet på baggrund af en kombination af IgE-niveau og legemsvægt, hvor ansøger har antaget, at patienterne har en gennemsnitsvægt på 70-80 kg og et gennemsnitligt IgE-niveau på 374,3 IU/ml. På baggrund af dette har ansøger estimeret en omalizumabdosis på 600 mg hver 4. uge.

Baseret på udsagn fra to klinikere har ansøger antaget, at patienter selvadministrerer prednisolonbehandling ved eksacerbationer. Ansøger har antaget, at patienterne i gennemsnit behandles med prednisolon i 10 dage med en gennemsnitlig dosis på 37,5 mg.

Tabel 3: Anvendte lægemiddelpriser, SAIP (december 2019).

Lægemiddel	Styrke	dosis	Pakningsstørrelse	Pris [DKK]	Kilde
Dupilumab	200/300 mg	200/300 mg	2 stk.	[redacted]	Amgros
Mepolizumab	100 mg	100 mg	1 stk.	[redacted]	Amgros
Omalizumab	150 mg	600 mg	1 stk.	[redacted]	Amgros
Prednisolon	5 mg	5 mg	100 stk.	[redacted]	Amgros

Medicinrådets sekretariats vurdering

Medicinrådets sekretariat accepterer ansøgers tilgang.

2.2.2 Hospitalsomkostninger

Hospitalsomkostninger er i ansøgers analyse opdelt i administrationsomkostninger og omkostninger til behandling af eksacerbationer. Ansøger har anvendt DRG-2017-takster til at estimere hospitalsomkostningerne forbundet med lægemiddeladministration på

hospitalet samt behandlingsomkostninger ved eksacerbationer og fremskrevet dem til et 2019-niveau. Ansøgers argument for at anvende DRG-2017-takster fremfor DRG-2019-takster er, at DRG-2019-taksterne primært er baseret på stationære patienter. Ansøger har ikke inkluderet hospitalsomkostninger relateret til bivirkninger, da ansøger antager, at bivirkningerne ved behandling med lægemidlerne ikke er behandlingskrævende.

Administrationsomkostninger

Ansøger antager, at alle lægemidler efter oplæring kan administreres af patienten selv i hjemmet. Baseret på udsagn fra klinikere antager ansøger, at de tre første lægemiddeladministrationer af alle alternativer foregår på hospitalet, mens de resterende administrationer foregår i hjemmet. Anvendt DRG-2017-takst og 2019-niveau kan ses i Tabel 4.

Tabel 4: Anvendt DRG-2017-takst og 2019-omkostning.

Anvendte DAGS-takst	Omkostning [DKK]	Kode
Ambulant besøg, patient mindst 7 år	691	BG50A

Den totale administrationsomkostning for alle alternativer bliver da **2.073 DKK**. Ansøger har antaget, at der ikke er nogle administrationsomkostninger ved placebo.

Medicinrådets sekretariats vurdering

Medicinrådets sekretariat accepterer ansøgers tilgang.

Hospitalsomkostninger til behandling af eksacerbationer

Data for antal patienter, der bliver behandlet for eksacerbationer på hospitalet, har ansøger hentet fra landspatientregisteret (LPR) (10). Ansøger har summeret tallene fra perioden 2014-2018 og grupperet LPR-data for akut ambulant besøg og ambulant besøg til at være besøg på akut afsnit. Ansøger antager derudover, at antal udskrivninger svarer til antal indlæggelser.

Ansøger estimerer, at 5.962 patienter med svær astma blev behandlet for en eksacerbation på hospitalet i perioden 2014-2018. Heraf blev 41 % behandlet ambulant, mens 59 % blev behandlet under indlæggelse.

På grund af manglende evidens antager ansøger, på baggrund af udsagn fra klinikere, at 50 % af patienter med svær astma, som får en eksacerbation, vil behandles i hjemmet med telefonisk kontakt til den behandlende afdeling. De resterende 50 %, som antages at blive behandlet på hospitalet, fordeles efter ovenstående LPR-data. Behandlingsfordelingen er præsenteret i Tabel 5.

Tabel 5: Ansøgers antagelser vedrørende behandlingsfordelingen af eksacerbationer.

Behandlingsfordeling af eksacerbationer	Fordeling i procent	Kilde
I hjemmet	50 %	Antagelse
På akutafsnit	20,5 %	Antagelse
Under indlæggelse	29,5 %	Antagelse

Til at estimere hospitalsomkostningen ved ambulant behandling af eksacerbationer har ansøger har anvendt DRG-2017-taksten "Småskader", og for behandling under indlæggelse har ansøger anvendt DRG-2017-taksten "Obstruktive lungesygdomme, patient 0-59 år". Taksterne er fremskrevet til et 2019-niveau, se Tabel 6.

Tabel 6: Anvendte DRG-takster til estimering af hospitalsomkostninger til behandling af eksacerbationer.

DRG-takst	Omkostning [DKK]	Kode
Småskader	497	AA01C
Obstruktiv lungesygdom, pat. 0-59 år	17.870	0425

Medicinrådets sekretariats vurdering

Medicinrådets sekretariat har konsulteret klinikere udpeget af regionerne omkring antagelserne vedr. andelen af eksacerbationer, som behandles hhv. i hjemmet, ambulant og under indlæggelse. På baggrund af deres svar vælger Medicinrådets sekretariat at ændre behandlingsfordelingen, således at 34 % behandles ambulant, 6 % behandles under indlæggelse, og 60 % behandles i hjemmet. Hjemmebehandlingen antages at bestå af telefonisk kontakt med læge eller besøg i almen praksis. Ydermere vælger Medicinrådets sekretariat, efter konsultation med udpegede klinikere, at nedjustere den ambulante behandlingstid fra tre timer til en time i Medicinrådets sekretariats hovedanalyse.

Efter at have konsulteret de kliniske eksperter ændrer Medicinrådets sekretariat behandlingsfordelingen ved eksacerbationer i sin hovedanalyse og anvender en ambulant behandlingstid på en time i stedet for tre timer.

2.2.3 Patientomkostninger

Til at estimere patientomkostninger har ansøger benyttet Medicinrådets sekretariats værdisætning af enhedsomkostninger, se Tabel 7.

Tabel 7: Ansøgers anvendte enhedsomkostninger til estimering af patienttid.

Værdisætning af patienttid	Omkostning [DKK]	Kilde
Transportomkostning pr. hospitalsbesøg	100	Medicinrådets sekretariat
Patientomkostning pr. time	182,72	Medicinrådets sekretariat

Ansøger har baseret patientomkostninger i forbindelse med lægemiddeladministration af de tre første administrationer, som ikke foregår i hjemmet, på Amgros' udvidede sammenligningsgrundlag for biologiske lægemidler til svær eosinofil astma (11). Ansøger har estimeret en samlet patienttid på 1,68 timer, hvilket inkluderer 60 minutter til transport og 41 minutter til behandling og eventuel ventetid på hospitalet.

På baggrund af dette er den totale patientomkostning ved lægemiddeladministration estimeret til **1.221 DKK** for alle lægemidlerne.

Ansøger har også inkluderet patientomkostninger til behandling af eksacerbationer på hospitalet. Ansøgers antagelser om patienttid ved behandling af eksacerbationer er baseret på ekspert udsagn og data fra landspatientregisteret. Baseret på data fra landspatientregisteret finder ansøger, at der i perioden 2014-2018 var 9.787 sengedage med diagnosen status asthmaticus og 3.524 udskrivninger i samme periode. Ansøger har anvendt dette data til at estimere en gennemsnitlig indlæggelsestid på 2,78 dage. Ansøger antager, at patienttiden ved en indlæggelse er et helt døgn (24 timer) og har på den baggrund estimeret en vægtet patientomkostning pr. eksacerbationsbehandling på hospitalet, som kan ses i Tabel 8. Ansøger har antaget, at det tager tre timer at behandle en eksacerbation ambulant.

Tabel 8: Ansøgers estimerede patientomkostninger ved behandling af eksacerbationer på hospitalet.

Patientomkostninger ved behandling af eksacerbationer	Omkostning [DKK]
Behandling på akutafsnit	648
Behandling under indlæggelse	12.279
Vægtet patientomkostning pr. behandling	**3.759**

Medicinrådets sekretariats vurdering

Medicinrådets sekretariat accepterer ansøgers tilgang. Dog ændrer Medicinrådets sekretariat den ambulante behandlingstid fra tre timer til en time efter konsultation med udpegede klinikere.

2.3 Følsomhedsanalyser

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

- Estimering af hospitalsomkostningerne ved lægemiddeladministration med en mikrobaseret tilgang
- Estimering af hospitalsomkostningerne ved lægemiddeladministration med DRG-2019-takster
- 90 % hjemmebehandling af eksacerbationer
- 10 % hjemmebehandling af eksacerbationer
- Lavest mulige dosis af omalizumab (P2)
- Højest mulige dosis af omalizumab (P2)
- Procentvis reduktion i brug af orale kortikosteroider i P3
- Scenarieanalyser med en tidshorisont på et år eller fem år.

Medicinrådets sekretariats vurdering

Inklusionen af følsomhedsanalyser, der undersøger usikkerhederne i ansøgers analyse, er i tråd med Medicinrådets sekretariats metodevejledning. Da lægemiddelomkostningerne er af afgørende betydning for analysens resultat, præsenteres ansøgers følsomhedsanalyse, der ændrer lægemiddelomkostningerne for omalizumab. Scenarieanalyserne med de reducerede tidshorisonter præsenteres også, da Medicinrådets sekretariat vurderer, at det kan være nødvendigt at vise de inkrementelle omkostninger over en kortere tidshorisont.

De resterende følsomhedsanalyser præsenteres ikke, da Medicinrådets sekretariat vurderer, at de har minimal betydning for analysens resultat.

2.4 Opsummering af basisantagelser

I Tabel 9 opsummeres basisantagelserne for ansøgers hovedanalyse og de ændringer, som Medicinråds sekretariatets har foretaget i sin egen hovedanalyse.

Tabel 9: Basisantagelser for ansøgers og Medicinråds sekretariatets hovedanalyse.

Basisantagelser	Ansøger	Medicinrådets sekretariat
Tidshorisont	43 år (livslang)	43 år (livslang)
Diskonteringsrate	4 %	4 % i år 1-35 og 3 % i år 36-43
Omkostninger	Lægemiddelomkostninger Hospitalsomkostninger Patientomkostninger	Lægemiddelomkostninger Hospitalsomkostninger Patientomkostninger
Ambulant behandlingstid	3 timer	1 time
Behandlingsfordeling ved eksacerbationer	Hjemme: 50 % Ambulant: 20,5 % Indlæggelse: 29,5 %	60 % 34,3 % 5,7 %

3. Resultater

3.1 Resultatet af ansøgers hovedanalyse

Ansøger har estimeret de inkrementelle omkostninger ved behandling med dupilumab over en tidshorisont på 43 år for de tre populationer:

P1: Den inkrementelle omkostning pr. patient for dupilumab, sammenlignet med mepolizumab, er ca. [redacted] DKK. Hvis analysen udføres med AIP, bliver den inkrementelle omkostning ca. 243.000 DKK.

P2: Den inkrementelle omkostning pr. patient for dupilumab, sammenlignet med omalizumab, er ca. [redacted] DKK. Udføres analysen med AIP, bliver den inkrementelle omkostning ca. 86.000 DKK.

P3: Den inkrementelle omkostning pr. patient for dupilumab, sammenlignet med placebo, er ca. [redacted] DKK. Udføres analysen med AIP, bliver den inkrementelle omkostning ca. 2.377.000 DKK.

En oversigt over resultaterne fra ansøgers hovedanalyse præsenteres for P1 i Tabel 10, i Tabel 11 for P2 og i Tabel 12 for P3.

Tabel 10: Resultatet af ansøgers hovedanalyse ved sammenligning med mepolizumab, DKK, diskonterede tal. Resultatet er over en tidshorisont på 43 år.

	Dupilumab	Mepolizumab	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	75.189	103.623	-28.434
Patientomkostninger	52.316	72.186	-19.870
Totale omkostninger	[redacted]	[redacted]	[redacted]

Tabel 11: Resultatet af ansøgers hovedanalyse ved sammenligning med omalizumab, DKK, diskonterede tal. Resultatet er over en tidshorisont på 43 år.

	Dupilumab	Omalizumab	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	53.918	81.835	-27.917
Patientomkostninger	37.451	56.960	-19.508
Totale omkostninger	[redacted]	[redacted]	[redacted]

Tabel 12: Resultatet af ansøgers hovedanalyse ved sammenligning med placebo, DKK, diskonterede tal. Resultatet er over en tidshorisont på 43 år.

	Dupilumab	Placebo	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	107.333	238.146	-130.813
Patientomkostninger	74.779	166.419	-91.640
Totale omkostninger	[redacted]	[redacted]	[redacted]

3.1.1 Resultatet af ansøgers følsomhedsanalyser

Ansøger har lavet en følsomhedsanalyse, der ændrer dosis og administrationsfrekvensen for omalizumab, da dosis for omalizumab er afhængig af legemsvægt og IgE-niveau. På baggrund af doseringstabeller i produktresuméet for omalizumab (12) har ansøger i følsomhedsanalysen antaget, at den lavest mulige dosis samt administrationsfrekvens er 150 mg hver 4. uge, samt at den højest mulige omalizumabdosis er 600 mg hver 2. uge (12). Resultatet af følsomhedsanalyserne og de to scenarieanalyser med en reduceret tidshorisont er præsenteret i Tabel 13.

Tabel 13: Resultatet af ansøgers følsomhedsanalyser og scenarieanalyser, inkrementelle omkostninger sammenlignet med dupilumab.

Følsomhedsanalyse	Mepolizumab	Omalizumab	Placebo
Ansøgers hovedanalyse	[redacted]	[redacted]	[redacted]
Minimal dosis omalizumab	[redacted]	[redacted]	[redacted]
Maksimal dosis omalizumab	[redacted]	[redacted]	[redacted]
Tidshorisont på 1 år	[redacted]	[redacted]	[redacted]
Tidshorisont på 5 år	[redacted]	[redacted]	[redacted]

3.2 Resultatet af Medicinrådets sekretariats hovedanalyse

Medicinrådets sekretariat har estimeret de gennemsnitlige inkrementelle omkostninger pr. patient for dupilumab over en tidshorisont på 43 år i de tre populationer:

P1: Den inkrementelle omkostning pr. patient for dupilumab, sammenlignet med mepolizumab, er ca. [redacted] DKK. Hvis analysen udføres med AIP, er lægemiddelomkostningerne for dupilumab ca. 2.700.000 DKK og den inkrementelle omkostning ca. 290.000 DKK.

P2: Den inkrementelle omkostning pr. patient for dupilumab, sammenlignet med omalizumab, er ca. [redacted] DKK. Hvis analysen udføres med AIP, bliver lægemiddelomkostningen for dupilumab ca. 2.700.000 DKK og den inkrementelle omkostning ca. 128.000 DKK.

P3: Den inkrementelle omkostning pr. patient for dupilumab, sammenlignet med placebo, er ca. [redacted] DKK. Hvis analysen udføres med AIP, bliver lægemiddelomkostningen for dupilumab ca. 2.700.000 DKK og den inkrementelle omkostning ca. 2.650.000 DKK.

Resultaterne for Medicinrådets sekretariats hovedanalyse præsenteres for P1 i Tabel 14, for P2 i Tabel 15 og for P3 i Tabel 16.

Tabel 14: Resultatet af Medicinrådets sekretariats hovedanalyse ved sammenligning med mepolizumab, DKK, diskonterede tal. Resultatet er ved en tidshorisont på 43 år.

	Dupilumab	Mepolizumab	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	18.877	25.412	-6.535
Patientomkostninger	12.485	16.865	-4.380
Totale omkostninger	[redacted]	[redacted]	[redacted]

Tabel 15: Resultatet af Medicinrådets sekretariats hovedanalyse ved sammenligning med omalizumab, DKK, diskonterede tal. Resultatet er ved en tidshorisont på 43 år.

	Dupilumab	Omalizumab	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	13.988	20.404	-6.416
Patientomkostninger	9.208	13.509	-4.301
Totale omkostninger	[redacted]	[redacted]	[redacted]

Tabel 16: Resultatet af Medicinrådets sekretariats hovedanalyse ved sammenligning med placebo, DKK, diskonterede tal. Resultatet er ved en tidshorisont på 43 år.

	Dupilumab	Placebo	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	26.265	54.733	-28.468
Patientomkostninger	17.437	36.687	-19.250
Totale omkostninger	[redacted]	[redacted]	[redacted]

3.2.1 Resultatet af Medicinrådets sekretariats følsomhedsanalyser

Grundet usikkerhederne omkring dosis af omalizumab vælger Medicinrådets sekretariat at udføre en følsomhedsanalyse, der nedjusterer og opjusterer det gennemsnitlige IgE-niveau og den gennemsnitlige legemsvægt i Medicinrådets sekretariats hovedanalyse. Formålet med følsomhedsanalysen er at belyse påvirkningen af de inkrementelle omkostninger i sammenligningen med omalizumab, når dosis af omalizumab ændres. I Medicinrådets sekretariats hovedanalyse for sammenligningen med omalizumab er der antaget en dosis for omalizumab på 600 mg hver 4. uge, baseret på et gennemsnitligt IgE-niveau på 374,3 IU/ml og en gennemsnitlig legemsvægt på 74,5 kg.

I produktresuméet for omalizumab ses doseringstabeller, hvori det kan aflæses, at ved et IgE-niveau mellem 200-300 IU/ml og en legemsvægt mellem 60-70 kg gives en omalizumabdosis på 450 mg hver 4. uge. Dette giver en inkrementel omkostning på [redacted] DKK i P2. Hvis der anvendes et IgE-niveau på mellem 400-500 IU/ml og en legemsvægt på mellem 80-90 kg, gives en omalizumabdosis på 375 mg hver 2. uge, hvilket resulterer i en besparelse på [redacted] DKK i P2. Se resultaterne for Medicinrådets sekretariats følsomhedsanalyser i Tabel 17.

Tabel 17: Resultatet af Medicinrådets sekretariats følsomhedsanalyser og scenarieanalyser med reducerede tidshorisonter. Tabellen viser de inkrementelle omkostninger ved behandling med dupilumab sammenlignet med komparatorerne.

Følsomhedsanalyse	Mepolizumab [DKK]	Omalizumab [DKK]	Placebo
Medicinrådets sekretariats hovedanalyse	[redacted]	[redacted]	[redacted]
Omalizumab 375 mg hver 2. uge	[redacted]	[redacted]	[redacted]
Omalizumab 450 mg hver 4. uge	[redacted]	[redacted]	[redacted]
Tidshorisont på 1 år	[redacted]	[redacted]	[redacted]
Tidshorisont på 5 år	[redacted]	[redacted]	[redacted]

4. Budgetkonsekvenser

Budgetkonsekvenserne pr. år er baseret på antagelsen om, at dupilumab vil blive anbefalet som mulig standardbehandling. Man ser derfor på to scenarier:

- Dupilumab bliver anbefalet af Medicinrådets sekretariat som mulig standardbehandling til indikationen, som denne analyse omhandler
- Dupilumab bliver ikke anbefalet af Medicinrådets sekretariat som mulig standardbehandling

Budgetkonsekvenserne bliver differencen mellem budgetkonsekvenserne i de to scenarier.

4.1 Ansøgers budgetkonsekvensanalyse

4.1.1 Ansøgers estimat af patientantal og markedsandel

Ansøger har indsendt budgetkonsekvensanalyser for hver af de tre populationer, hvori ansøger antager, at 100 % af patienterne vil blive behandlet med dupilumab ved en godkendelse, mens 0 % vil blive behandlet, hvis det ikke godkendes. I dette scenarie vil patienterne i stedet modtage komparatoren for populationen.

Ifølge Medicinrådets sekretariats protokol er 500-600 patienter kandidater til biologisk behandling, hvoraf 70 % og 30 % er kandidater til hhv. anti-IL-5-lægemidler og IgE antistoffer, mens 3 % har forhøjet FeNO uden samtidig eosinofili eller allergi. Ifølge protokollen fra Medicinrådets sekretariat kandiderer 60 nye patienter årligt til biologisk behandling.

Ansøger har antaget følgende om patientantallet i sin budgetkonsekvensanalyse:

- P1: 350 patienter i år 1, med en incidens på 42 patienter pr. år i år 2 til år 5
- P2: 150 patienter i år 1, med en incidens på 18 patienter pr. år i år 2 til år 5
- P3: 15 patienter i år 1, med en incidens på 2 patienter pr. år i år 2 til år 5

Tabel 18, Tabel 19 og Tabel 20 viser fordelingen af patienter i hhv. P1, P2 og P3 ved anbefaling af dupilumab som mulig standardbehandling og uden anbefaling.

Tabel 18: Ansøgers estimat af antal nye patienter pr. år for P1.

Anbefales					
	År 1	**År 2**	**År 3**	**År 4**	**År 5**
Dupilumab	350	42	42	42	42
Mepolizumab	0	0	0	0	0
Anbefales ikke					
	År 1	**År 2**	**År 3**	**År 4**	**År 5**
Dupilumab	0	0	0	0	0
Mepolizumab	350	42	42	42	42

Tabel 19: Ansøgers estimat af antal nye patienter pr. år for P2.

Anbefales					
	År 1	**År 2**	**År 3**	**År 4**	**År 5**
Dupilumab	150	18	18	18	18
Omalizumab	0	0	0	0	0
Anbefales ikke					
	År 1	**År 2**	**År 3**	**År 4**	**År 5**
Dupilumab	0	0	0	0	0
Omalizumab	150	18	18	18	18

Tabel 20: Ansøgers estimat af antal nye patienter pr. år for P3.

Anbefales					
	År 1	**År 2**	**År 3**	**År 4**	**År 5**
Dupilumab	15	2	2	2	2
Placebo	0	0	0	0	0
Anbefales ikke					
	År 1	**År 2**	**År 3**	**År 4**	**År 5**
Dupilumab	0	0	0	0	0
Placebo	15	2	2	2	2

Medicinrådets sekretariats vurdering

Ansøgers metode i budgetkonsekvenserne er i tråd med Medicinrådets sekretariats metodevejledning. Medicinrådet har konsulteret klinikere udpeget af regionerne for at få valideret ansøgers antagelser omkring patientantallet i P1, P2 og P3 i budgetkonsekvensanalysen. Flere klinikere er enige i, at estimatet af antal patienter i P2 er højt sat, og derfor reducerer Medicinrådet sekretariat patientantallet i P2 fra 150 til 50 og incidensen fra 18 til 9 i sin hovedanalyse.

Medicinrådets sekretariat ændrer markedsoptaget i sin hovedanalyse af budgetkonsekvenserne for P1 fra 100 % til 20 %, da Medicinrådets sekretariat vurderer, at det er usandsynligt, at dupilumab ved anbefaling vil få mere end 20 % af markedet i P1 med den nuværende pris. Fagudvalget for svær astma har ligestillet dupilumab med de øvrige biologiske behandlingsalternativer i P1. Markedsoptaget i P2 og P3 ændres ikke i Medicinrådets sekretariats budgetkonsekvensanalyse.

Medicinrådets sekretariat udarbejder egen budgetkonsekvensanalyse, hvor patientantallet i P2 er reduceret fra 150 til 50, og hvor den årlige incidens af nye patienter i P2 er reduceret fra 18 til 9. Derudover er markedsoptaget i P1 reduceret fra 100 % til 20 %.

4.1.2 Ansøgers estimat af budgetkonsekvenser

Ansøger har inkluderet de samme omkostninger i sin budgetkonsekvensanalyse som i sin omkostning pr. patient-analyse, men anvendt omkostninger der ikke er diskonterede og ekskluderet patientomkostninger.

Med de indlagte antagelser estimerer ansøger, at anvendelse af dupilumab vil resultere i budgetkonsekvenser i P1 på ca. [redacted] DKK i år 5, ca. [redacted] DKK for P2 i år 5 og ca. [redacted] DKK for P3 i år 5.

Ansøgers estimat af budgetkonsekvenserne for P1 fremgår af Tabel 21, i Tabel 22 for P2 og i Tabel 23 for P3.

Tabel 21: Ansøgers hovedanalyse for totale budgetkonsekvenser for P1, mio. DKK, ikkediskonterede tal.

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

Tabel 22: Ansøgers hovedanalyse for totale budgetkonsekvenser for P2, mio. DKK, ikkediskonterede tal.

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

Tabel 23: Ansøgers hovedanalyse for totale budgetkonsekvenser for P3, mio. DKK, ikkediskonterede tal.

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

Medicinrådets sekretariats vurdering

Medicinrådets sekretariat udarbejder egen budgetkonsekvensanalyse med et reduceret patientantal i P2.

4.2 Medicinrådets sekretariats budgetkonsekvensanalyse

Medicinrådets sekretariats budgetkonsekvensanalyse bygger på Medicinrådets sekretariats hovedanalyse. Som beskrevet under Medicinrådets sekretariats vurdering af ansøgers estimerede patientantal ændrer Medicinrådets sekretariat patientantallet i P2 fra 150 til 50 og den årlige incidens fra 18 til 9 i samme population. Medicinrådets sekretariat ændrer ikke på ansøgers antagelser vedr. markedsoptaget i P2 og P3, men reducerer markedsoptaget i P1 fra 100 % til 20 %.

Med de indlagte antagelser estimerer Medicinrådets sekretariat, at anvendelse af dupilumab vil resultere i budgetkonsekvenser på ca. [redacted]. DKK i år 5 for P1, ca. [redacted] DKK i år 5 for P2 og ca. [redacted] DKK i år 5 for P3.

Hvis analysen udføres med AIP, bliver budgetkonsekvenserne ca. 1,4 mio. DKK i år 5 for P1, ca. 0,5 mio. DKK i år 5 for P2 og ca. 3 mio. DKK i år 5 for P3. Resultaterne for Medicinrådets sekretariats estimat af de totale budgetkonsekvenser, ved anbefaling af dupilumab, er præsenteret for P1 i Tabel 24, i Tabel 25 for P2 og i Tabel 26 for P3.

Tabel 24: Medicinrådets sekretariats analyse af totale budgetkonsekvenser for P1, mio. DKK, ikkediskonterede tal.

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

Tabel 25: Medicinrådets sekretariats analyse af totale budgetkonsekvenser for P2, mio. DKK, ikkediskonterede tal.

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

Tabel 26: Medicinrådets sekretariats analyse af totale budgetkonsekvenser for P3, mio. DKK, ikkediskonterede tal.

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

4.2.1 Medicinrådets sekretariats følsomhedsanalyser for budgetkonsekvensanalysen

Da de biologiske behandlingsalternativer for patienter med svær astma karakteriseret ved eosinofili (P1) er ligestillet af fagudvalget, afhænger ibrugtagningen af alternativerne af prisen på lægemidlerne. Da prisen på dupilumab kan ændre sig i fremtiden, vælger Medicinrådet sekretariat at udarbejde en følsomhedsanalyse, der undersøger budgetkonsekvenserne ved et markedsoptag på 80% i stedet for 20%, som antaget i hovedanalysen for budgetkonsekvenserne.
Derudover udarbejder Medicinrådets sekretariat også en følsomhedsanalyse der undersøger budgetkonsekvenserne ved et halveret markedsoptag i P2. P3 inkluderes ikke i følsomhedsanalyserne, da dupilumab vil være det eneste biologiske behandlingsalternativ til denne population.

Da de udpegede klinikere fandt det vanskeligt at vurdere det faktiske patientantal i P2, vælger Medicinrådets sekretariat at udarbejde en følsomhedsanalyse for budgetkonsekvenserne, hvor det antages, at patientantallet i P2 er 100, og den årlige incidens er 18. Resultatet af analyserne er præsenteret i Tabel 27. Følsomhedsanalyserne bygger på samme antagelser som i Medicinrådets sekretariats hovedanalyse for budgetkonsekvenser. Følsomhedsanalyserne bygger på samme antagelser som i Medicinrådets sekretariats hovedanalyse for budgetkonsekvenser.

Tabel 27: Medicinrådets sekretariats resultat af følsomhedsanalyser for budgetkonsekvenserne.

Følsomhedsanalyse	P1 [DKK]	P2 [DKK]
Medicinrådets sekretariats hovedanalyse	[redacted] **mio. i år 5**	[redacted] **mio. i år 5**
Markedsandel på 80 %	[redacted] mio. i år 5	[redacted]
Markedsandel på 50 %	[redacted]	[redacted] mio. i år 5
Patientantal på 100 i P2	[redacted]	[redacted] mio. i år 5

5. Diskussion

De inkrementelle omkostninger forbundet med behandling med dupilumab afhænger af hvilken population, der behandles. Behandling med dupilumab er forbundet med høje inkrementelle omkostninger sammenlignet med mepolizumab, over en tidshorisont på 43 år og meget høje inkrementelle omkostninger sammenlignet med placebo, over samme tidshorisont. Ved sammenligning med omalizumab er behandling med dupilumab forbundet med meget store besparelser over en tidshorisont på 43 år. De inkrementelle omkostninger skal ses i lyset af, at analysen har en tidshorisont på 43 år, da behandlingen af svær astma er livslang.

5.1 Usikkerheder

Den udarbejdede følsomhedsanalyse i Tabel 17 viser, at der er en usikkerhed forbundet med, hvorvidt dupilumab er forbundet med en besparelse eller en meromkostning sammenlignet med omalizumab. Dette skyldes usikkerheder omkring dosis af omalizumab, hvilket kan ændre den inkrementelle omkostning for dupilumab sammenlignet med omalizumab fra at være en besparelse for en gennemsnitlig patient til at være en meromkostning ved en patient med en lavere legemesvægt eller et lavere IgE-niveau. Ydermere er det usikkert, hvor stort et markedsoptag dupilumab vil få ved en anbefaling, især i sammenligningen med mepolizumab, hvilket i høj grad afhænger af prisen på dupilumab, da de to biologiske lægemidler effektmæssigt er ligestillet.

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Medicinrådet

Medicinrådets vurdering af dupilumab til behandling af svær astma

Versionsnr.: 1.0

Om Medicinrådet

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

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

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

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

Om vurderingen

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

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

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

Dokumentoplysninger	
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Dokumentnummer	69831
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Medicinrådet, Dampfærgevej 27-29, 3. th., 2100 København Ø
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Indhold

1 Lægemiddelinformationer

Lægemidlets oplysninger	
Handelsnavn	Dupixent
Generisk navn	Dupilumab
Firma	Sanofi Genzyme
ATC-kode	D11AH05
Virkningsmekanisme	Dupilumab er et monoklonalt antistof rettet mod interleukin 4-receptor underenhed alfa (IL-4Rα). Denne underenhed deles af IL-4 og IL-13 receptorkomplekser, og derfor hæmmer dupilumab signaleringen fra både IL-4 og IL-13. IL-4 er den centrale mediator af naive T-cellers differentiering til Type 2 cytokinproducerende effektorceller, eosinofil trafficking, B-celleaktivering og underliggende øgning af IgE-produktion. IL-13 medierer ydermere remoduleringen af luftvejene ved bægercellehyperplasi, transformation af bronkiale fibroblaster til myofibroblaster, kollagen deposition og proliferation af glatte muskelceller i luftvejene. IL-13 medierer også glat muskelkontraktion samt bronkoepitelial produktion af FeNO.
Administration/dosis	Initial dosis på 400 mg (fordelt på to 200 mg subkutane injektioner), herefter 200 mg subkutan injektion hver anden uge i tillæg til standardbehandling. Patienter som er i vedligeholdelsesbehandling med orale kortikosteroider eller til patienter, som samtidig lider af moderat til svær atopisk eksem: initial dosis på 600 mg (fordelt på to 300 mg subkutane injektioner), herefter 300 mg subkutan injektion hver anden uge i tillæg til standardbehandling.
EMA-indikation	Voksne, unge og børn > 12 år som tillægsvedligeholdelsesbehandling til svær astma med type 2-inflammation karakteriseret ved forhøjet blodeosinofile celler og/eller forhøjet FeNO, som er utilstrækkeligt kontrolleret med højdosis inhalationskortikosteroider og en anden medicinsk vedligeholdelsesbehandling.

2 Medicinrådets konklusion

Medicinrådet vurderer, at:

- Dupilumab har **ingen dokumenteret merværdi** sammenlignet med mepolizumab til patienter med svær astma karakteriseret ved eosinofili. Evidensens kvalitet vurderes at være **lav**.
- Dupilumab har **ingen dokumenteret merværdi** sammenlignet med omalizumab til patienter med svær astma karakteriseret ved allergi og samtidig eosinofili eller karakteriseret ved allergi og samtidig forhøjet FeNO. Evidensens kvalitet vurderes at være **meget lav**.
- Værdien af dupilumab **kan ikke kategoriseres** sammenlignet med placebo til patienter med forhøjet FeNO uden samtidig eosinofili og uden samtidig allergi. Evidensens kvalitet er ikke vurderet.

Medicinrådet kategoriserer lægemidlers værdi i en af følgende kategorier:

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

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

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

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

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

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

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

3 Forkortelser

ACQ:	*Asthma Control Questionnaire* (astmakontrolspørgeskema)
ACT:	Asthma Control Test
AQLQ:	*Asthma Quality of Life Questionnaire* (astmalivskvalitetspørgeskema)
ATS:	American Thoracic Society
CI:	Konfidensinterval
DLS:	Dansk Lungemedicinsk Selskab
EMA:	*European Medicines Agency*
ERC:	*European Respiratory Society*
FeNO:	Fractional exhaled nitric oxide (fraction af udåndet nitrogenoxid)
FEV_1:	*Forced Expiratory Volume* (forceret ekspirationsvolumen) på 1 sekund
GINA:	*Global Initiative of Asthma*
GRADE:	System til vurdering af evidens (Grading of Recommendations Assessment, Development and Evaluation)
ICS:	Inhaleret kortikosteroid
IL:	Interleukin
LABA:	Long-acting beta2-agonist
LTRA:	Leukotrinreceptorantagonist
MD:	*Mean Difference* (gennemsnitlig forskel)
NO:	Nitrogenoxid
OCS:	Oral kortikosteroid
PICO:	Population, Intervention, *Comparator* (sammenligning) og *Outcome* (effektmål)
RR:	Relativ risiko
SABA:	Short-acting beta2-agonist
SAE's:	*Serious adverse events* (alvorlige uønskede hændelser)
SD:	Standardafvigelse
SMD:	*Standardized Mean Difference* (standardiseret gennemsnitlig forskel)

4 Formål

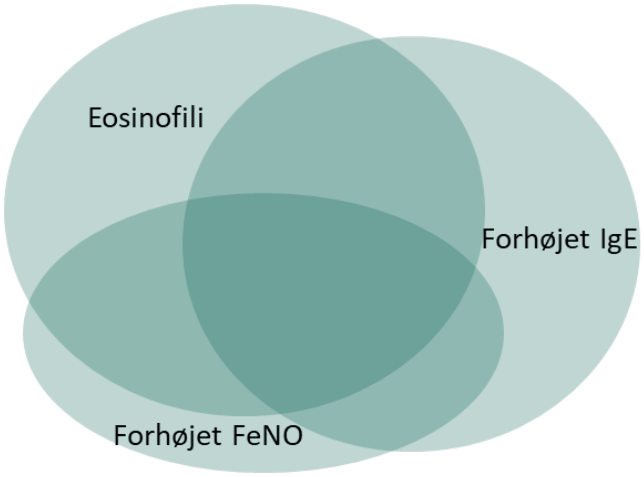
Formålet med Medicinrådets vurdering af dupilumab til patienter med svær astma over 12 år er at vurdere den værdi, lægemidlet har i forhold til et eller flere lægemidler til samme patientgruppe (komparatorer).

Med udgangspunkt i vurderingen og en omkostningsanalyse udarbejdet af Amgros beslutter Medicinrådet, om dupilumab kan anbefales som mulig standardbehandling.

5 Svær astma

Astma er en heterogen sygdom, som oftest skyldes kronisk inflammation i luftvejene, der medfører hyperreaktive luftveje med tendens til sammentrækning. De typiske symptomer på astma er hoste, åndenød og pibende vejrtrækning samt tendens til lungeinfektioner. Symptomerne kan optræde spontant eller være forårsaget af udløsende faktorer som fysisk anstrengelse, luftvejsirritanter (f.eks. tobak) eller luftbårne allergener (f.eks. pollen, dyrehår eller husstøvmider). **Sværhedsgraden** af astma bestemmes retrospektivt på baggrund af den behandlingsintensitet, som kræves for at opnå tilfredsstillende sygdomskontrol. **Graden af sygdomskontrol** vurderes ud fra hyppigheden af dagsymptomer, natsymptomer, begrænsning i aktivitet og behov for anfaldsmedicin, mens den fremtidige risiko for tab af astmakontrol og eksacerbationer (akut forværring) vurderes ud fra bl.a. lungefunktion og evt. tidligere eksacerbationer [1]. Behandlingen justeres ud fra sygdomskontrol. "Manglende kontrol af astma", "ukontrolleret astma" eller "dårligt kontrolleret astma" er synonymer og beskriver alene symptomgennembrud på den aktuelle behandling og siger i sig selv intet om den underliggende astmasværhedsgrad. Det er estimeret, at 7-11 % af den danske population har astma [2]. Prævalensen af **svær astma** er estimeret til at udgøre 5-15 % af alle patienter med astma [3].

Ca. 50 % af patienter med svær astma har **type 2-inflammation**. Type 2 inflammation opstår ved at allergener udløser produktion af cytokinerne IL-4, IL-5 og IL-13 fra det adaptive immunsystem. Type 2-inflammation kan også initieres af virus, bakterier og irritanter, der stimulerer det innate immunsystem via produktion af IL-25, IL-33, og thymic stromal lymfopoitin (TSLP). Type 2-inflammation er ofte karakteriseret ved forhøjet blodeosinofile celler (**eosinofil astma**) og/eller forhøjet nitrogenoxid i udåndingsluften (FeNO) (**astma med forhøjet FeNO**) og/eller allergi (**allergisk astma**). Ved allergisk astma er der IgE-sensibilisering for allergener påvist ved direkte måling af forhøjet specifikt IgE i blodet eller ved hudpriktest med standardiserede allergenekstrakter [4]. Nogle patienter med svær astma med type 2-inflammation er alene karakteriseret ved forhøjede blodeosinofile celler, forhøjet FeNO eller allergi, mens nogle patienter har flere eller alle tre karakteristika, som illustreret i Figur 1. Dette kan gøre valg af biologisk lægemiddel vanskeligt; dvs. anti-IL5, anti-IgE eller anti-IL4R. Ydermere kan op til 50 % af børn, unge og yngre voksne (der har haft astmadebut i barndommen) med svær allergisk astma også have samtidig svær atopisk eksem.



Figur 1: Figur over udvalgte fænotyper indenfor svær astma.
Figuren illustrerer, at der er overlap mellem patientpopulationerne indenfor svær astma i forhold til de tre udvalgte fænotyper: eosinofili ≥ 150 celler pr. mikroliter, FeNO ≥ 25 bpp, og specifik IgE ≥ 0,35 KU/L.

5.1 Nuværende behandling

I Tabel 1 ses en oversigt over behandlingen af astma. Behandlingen er trinvis, hvor der ved manglende astmakontrol øges i dosis eller tillægges yderligere lægemidler. Trin 5 er svær astma som fortsat ikke er tilstrækkelig kontrolleret med inhalationssteroider. For nogle af disse patienter er en mulighed tillæg af biologiske lægemidler. Behandlingsmålet for patienter med svær astma er at undgå eller nedbringe antallet af eksacerbationer, nedbringe forbruget af peroral kortikosteroid samt at opnå astmakontrol og dermed kunne bevare en god livskvalitet og evt. tilknytning til arbejdsmarkedet.

Tabel 1: Behandlingstrin ved astma, oversat fra Global Initiative for Asthma 2017 report [5] **samt pro.medicin.dk**

	Trin 1	**Trin 2**	**Trin 3**	**Trin 4**	**Trin 5 (Specialistopgave)**
Foretrukne forebyggende medicin		Lav dosis ICS	Lav dosis ICS/LABA**	Medium/høj dosis ICS/LABA	Tillæg: Tiotropium[ᵀ], anti-IgE, anti-IL-5(R)*, (anti-IL4R*)
Andre muligheder for forebyggende medicin	Overvej lav dosis ICS	LTRA Lav dosis langsomt absorberbart teofyllin*	Medium/høj dosis ICS Lav dosis ICS + LTRA (eller + langsomt absorberbart teofyllin*)	Tillæg: Tiotropium*[ᵀ] Høj dosis ICS + LTRA (eller + langsomt absorberbart teofyllin*)	Tillæg lav dosis OCS
Anfaldsmedicin		SABA		SABA pn eller lav dosis ICS/formoterol[π]	

***ICS**: Inhaleret kortikosteroid, **LABA**: Long-acting beta2-agonist, **LTRA**: Leukotrinreceptor antagonist, **OCS**: Oral kortikosteroid, **SABA**: Short-acting beta2-agonist.*
** Ikke for børn under 12 år, i Danmark ikke for børn under 18 år.*
*** I trin 3 for børn 6-12 år foretrækkes medium dosis ICS, herefter ICS i lav dosis i kombination med LABA eller LTRA. Høj dosis ICS gives ikke før eventuelt i trin 4.*
**** I trin 4 for børn 6-12 år foretrækkes ICS i medium dosis i kombination med LABA eller/og LTRA, herefter eventuelt ICS i høj dosis.*
[π] *Lav dosis ICS/formoterol er anfaldsmedicin for patienter, der bruger lav dosis ICS (budesonid eller beclometasone/formoterol) som både forebyggende og anfaldsmedicin (altid i fast kombinationspræparat) ikke indiceret til børn og unge under 18 år.*
[ᵀ] *Tiotropium som Respimat er en tillægsbehandling for patienter med en historie med eksacerbationer og er godkendt til behandling af børn over 6 år i Danmark.*

Dansk Lungemedicinsk Selskab (DLS) definerer svær astma i overensstemmelse med ERS (European Respiratory Society)/ATS' (American Thoracic Society) guidelines [3,6]: astma som gennem minimum det sidste år har krævet behandling med høj dosis inhalationssteroid samt en eller flere tillægsbehandlinger (2nd controller (typisk langtidsvirkende beta2-agonist, LABA), og/eller som har krævet peroralt steroid i ≥ 50 % af tiden) for at forebygge, at astmaen bliver ukontrolleret eller trods denne behandling forbliver ukontrolleret. Systematisk udredning af mulig svær astma er afgørende for at sikre diagnosen, og at den manglende sygdomskontrol ikke skyldes forkert diagnose, manglende adhærens med den ordinerede behandling, behandlelige komorbiditeter eller undgåelige triggers [3].

Der vil være en mindre andel af patienter, som ikke opnår tilstrækkelig sygdomskontrol trods ovenstående tiltag. Til patienter med svær eosinofil astma er en yderligere behandlingsmulighed tillægsterapi med mepolizumab, reslizumab eller benralizumab, som er antistoffer rettet mod interleukin 5 (IL-5) eller IL-5-receptoren (IL-5R). Mepolizumab er af EMA godkendt til voksne og børn over 6 år. Det administreres subkutant hver 4. uge i 100 mg fast dosis og kan blive administreret som hjemmebehandling [7]. Reslizumab og benralizumab er godkendt til voksne [8,9]. Reslizumab administreres intravenøst hver 4. uge, og dosis er vægtbaseret. Benralizumab administreres subkutant i fast dosis 30 mg hver 8. uge (de første 3 doser gives hver fjerde uge) og kan blive administreret som hjemmebehandling. IL-5 er et cytokin, som spiller en central rolle i produktion, modning og overlevelse af eosinofile granulocytter, og binding af antistofferne til IL-5 eller IL-5R medfører dermed en reduktion i antallet af eosinofile granulocytter, resulterende i bedre sygdomskontrol.

Til voksne patienter og børn over 6 år med svær allergisk astma, som har en positiv hudpriktest eller in vitro-reaktivitet for et helårs luftbåret allergen, er en behandlingsmulighed desuden tillægsterapi med anti-IgE-behandling i form af omalizumab. Omalizumab er et antistof rettet mod IgE, som hindrer binding af IgE til immunsystemets celler, hvorved allergiske reaktioner reduceres [10]. Omalizumab administreres subkutant hver 2. eller hver 4. uge, og kan blive administreret som hjemmebehandling. Dosis og interval er afhængig af vægt og IgE-niveau.

5.2 Dupilumab

Dupilumab er et monoklonalt antistof rettet mod interleukin 4-receptor underenhed alfa (IL-4Rα). Denne underenhed deles af IL-4- og IL-13-receptorkomplekser, og derfor hæmmer dupilumab signaleringen fra både IL-4 og IL-13. IL-4 er den centrale mediator af naive T-cellers differentiering til type 2-cytokin-producerende effektorceller, eosinofil trafficking, B-celleaktivering og underliggende øgning af IgE-produktion. IL-13 medierer ydermere remoduleringen af luftvejene ved bægercellehyperplasi, transformation af bronkiale fibroblaster til myofibroblaster, kollagendeposition og proliferation af glatte muskelceller i luftvejene. IL-13 medierer også glat muskelkontraktion samt epithelial produktion af FeNO. Dupilumabs virkningsmekanisme er således upstream i signaleringskaskaden for omalizumabs og anti-IL5-lægemidlernes virkningsmekanismer. Dupilumab hæmmer således type 2-inflammation mere bredt. Dupilumab er indiceret som tillæg til vedligeholdelsesbehandling til voksne og unge fra 12 år og derover med svær astma med type 2-inflammation, karakteriseret ved forhøjet eosinofiltal i blodet og/eller forhøjet FeNO, der ikke er tilstrækkeligt kontrolleret med høj dosis inhalationskortikosteroid plus et andet lægemiddel til vedligeholdelsesbehandling.

På baggrund af dupilumabs indikation og virkningsmekanisme kan dupilumabs anvendelse spænde over flere patientpopulationer, hvor der på nuværende tidspunkt er forskellige medicinske alternativer. Fagudvalget vurderer, at der er tale om tre nedenstående populationer:

1) Patienter med svær eosinofil astma hvor dupilumab er et medicinsk alternativ til anti-IL5-lægemidler (mepolizumab, reslizumab, benralizumab).

2) Patienter med svær allergisk astma som samtidig har eosinofili og/eller forhøjet FeNO, hvor dupilumab er et medicinsk alternativ til omalizumab.

3) Patienter med svær astma og som er karakteriseret ved forhøjet FeNO uden samtidig eosinofili og allergi, hvor dupilumab vil være det eneste biologiske lægemiddel.

Udover svær astma er dupilumab godkendt til behandling af atopisk eksem. Dupilumab administreres til patienter med atopisk eksem med en initial dosis på 600 mg (fordelt på to 300 mg subkutane injektioner), herefter gives 300 mg subkutan injektion hver anden uge.

5.2.1 Administration og dosering, svær astma

Dupilumab bliver administreret med forfyldt injektionssprøjte og kan blive administreret som hjemmebehandling. Dupilumab anvendes som langtidsbehandling til svær astma.

- Dupilumab administreres med en initial dosis på 400 mg (fordelt på to 200 mg subkutane injektioner), herefter gives 200 mg subkutan injektion hver anden uge.

Til patienter med svær astma som er i vedligeholdelsesbehandling med orale kortikosteroider eller til patienter med svær astma, som samtidig lider af moderat til svær atopisk eksem:

- Dupilumab administreres med en initial dosis på 600 mg (fordelt på to 300 mg subkutane injektioner), herefter gives 300 mg subkutan injektion hver anden uge.

5.3 Forekomst af svær astma

Fagudvalget estimerer følgende prævalens og incidens:

Der estimeres at være 500-600 patienter med svær astma, som er kandidater til biologisk behandling i Danmark, ca. 50 af disse patienter er børn eller unge under 18 år. Biologisk behandling tilbydes til ca. 60 nye patienter pr. år, hvoraf 5-10 er børn under 18 år.

De fleste patienter under 18 år behandles med omalizumab (ca. 90 %, n = ~45), resten med mepolizumab (n = ~5). Hvis disse ca. 50 pædiatriske patienter skulle behandles med dupilumab, ville ca. 50 % skulle have 200 mg og 50 % have 300 mg pga. samtidig atopisk dermatitis, mens daglig oral kortikosteroid (OCS) vedligeholdelsesbehandling meget sjældent bliver anvendt.

I den voksne patientpopulation behandles ca. 80 % med anti-IL5-lægemidler (n = 400-480) (heraf 80 % mepolizumab) og 15 % (n = 100-120) med omalizumab. De resterende ~5 % (n = 25-30) opfylder ikke indikationen for hverken anti-IL-5-lægemidler eller omalizumab, men kunne opfylde indikationen for dupilumab. Hvis de voksne patienter skulle behandles med dupilumab, ville ca. 20 % opfylde kriterierne for dosering med 300 mg grundet daglig OCS vedligeholdelsesbehandling.

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. protokol som blev godkendt i Medicinrådet den 27. juni 2019.

Ansøgers endelige ansøgning blev modtaget i Medicinrådet den 17. september 2019. I den endelige ansøgning besvarer ansøger de kliniske spørgsmål, som er beskrevet i protokollen. Vurderingen af dupilumab til svær astma er behandlet i Medicinrådets 12-ugersproces for nye lægemidler.

6.1 Klinisk spørgsmål 1

Ansøger har indsendt indirekte sammenlignende analyse mellem dupilumab og mepolizumab via Buchers metode, jf. protokollen. I dupilumabstudierne var eosinofili ikke et inklusionskriterium. Ansøger har lavet analyser for en præspecificeret subgruppe med eosinofili >150 ved baseline. Randomiseringen var stratificeret for eosinofili i DRI12544- og QUEST-studiet, men ikke i VENTURE. Fagudvalget vurderer, at de analyserede subgrupper stemmer overens med inklusionskriterierne i mepolizumabstudier, og derfor at disse subgrupper er passende til den indirekte sammenligning med mepolizumab.

Ansøger har valgt at lave nedenstående tre sammenlignende analyser for effektmål, hvor data er tilgængeligt:

A. eosinofil svær astma for 24-32 uger, 200 mg dupilumab vs. mepolizumab
B. eosinofil svær astma for 52 uger, 200 mg dupilumab vs. mepolizumab
C. OCS-afhængig eosinofil svær astma 24 uger, 300 mg dupilumab vs. mepolizumab

Disse analyser var ikke præspecificerede i protokollen. Ansøger har vurderet, at det ikke er relevant at sammenligne data fra forskellige opfølgningstider, samt at den OCS-behandlede population bør vurderes separat. Fagudvalget er enig i, at det er hensigtsmæssigt at adskille disse tre sammenligninger, da der er tale om forskellig opfølgningstid mellem analyse A og B, og en særlig subpopulation med en anden dosis dupilumab i analyse C.

Fagudvalget accepterer derfor denne opdeling og vil for hvert effektmål tildele foreløbige kategorier for alle tre sammenligninger, hvor dette er relevant og samle disse i en aggregeret kategori pr. effektmål.

6.2 Klinisk spørgsmål 2

Ansøger har indsendt en indirekte sammenlignende analyse mellem dupilumab og omalizumab via Buchers metode, jf. protokollen. Hvor det var muligt, har ansøger foretaget analyser på subgruppen karakteriseret ved allergisk astma. Subgruppen er i dupilumabstudier defineret ved total serum IgE ≥ 30 IU/mL og ≥ 1 positiv helårsallergenspecifik IgE-værdi (≥ 0,35 kU/L) og samtidig blodeosinofili ≥ 150 cells/µL ved baseline, eller samtidig FeNO ≥ 25 ppb ved baseline. Der var ingen krav til eosinofili eller FeNO i omalizumabstudierne, fraset Mukherjee 2019, hvor der var krav om sputum eosinofili > 3 % på trods af højdosis vedligeholdelsesbehandling. Kravet til total serum IgE var 30-700 IU/mL for alle omalizumabstudierne på nær Vignola 2004 og Busse 2013, hvor kravet var 30-1.300 IU/mL og Mukherjee 2019, hvor der var krav om forhøjet IgE, men uden specifikation af niveauet.

Ansøger har lavet sammenlignende analyser, hvor data er tilgængeligt:

A. Allergisk astma, studievarighed 20-32 uger, 200 mg dupilumab hver anden uge vs. omalizumab.
B. Allergisk astma, studievarighed 48-52 uger, 200 mg dupilumab hver anden uge vs. omalizumab.

Disse analyser var ikke præspecificerede i protokollen. Ansøger har vurderet, at det ikke er relevant at sammenligne data fra forskellige opfølgningstider. Fagudvalget er enig i, at det er hensigtsmæssigt med disse to sammenligninger.

Fagudvalget accepterer derfor denne opdeling og vil for hvert effektmål tildele foreløbige kategorier for begge sammenligninger, hvis dette er relevant og samle disse i en aggregeret kategori pr. effektmål.

6.3 Klinisk spørgsmål 3

Det er ikke lykkes ansøger at finde litteratur for populationen, som er defineret i klinisk spørgsmål 3. Derfor har ansøger indsendt data for dupilumab sammenlignet med placebo for patienter med eleveret baseline FeNO ≥ 25bpp, uanset eosinofile granolucytter og allergistatus (QUEST og VENTURE), for effektmålene eksacerbationsrate, peroral vedligeholdelsesbehandling med kortikosteroid og lungefunktion. For øvrige effektmål, hvor subgruppen med forhøjet FeNO ikke var tilgængelig, har ansøger indsendt resultater fra ITT-populationen. I QUEST-studiet opfylder 49 ud af 1.902 patienter (~2,5 %) kriteriet for at indgå i populationen i spørgsmål 3. Ansøger har indsendt data for subpopulationen med forhøjet FeNO svarende til omkring 24 % af populationen i QUEST-studiet eller for hele ITT-populationen. Antallet af patienter, som opfylder den forespurgte population, er ikke opgjort i DRI12544 og VENTURE. Fagudvalget vil vurdere overførbarheden af resultaterne.

Ansøger har valgt at lave nedenstående tre direkte sammenlignende analyser, hvor data er tilgængeligt:

A. Svær astma for 24, 200 mg dupilumab vs. placebo (DRI12544)
B. Svær astma med forhøjet FeNO for 52 uger, 200 mg dupilumab vs. placebo (QUEST)
C. OCS-afhængig svær astma med forhøjet FeNO 24 uger, 300 mg dupilumab vs. placebo (VENTURE)

Disse analyser var ikke præspecificeret i protokollen. Data fra analyse A er kun rapporteret til effektmål relateret til bivirkninger, da det ikke har været muligt at gruppere ud fra FeNO-niveauer i DRI12544.

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

Både den relative og absolutte effekt indgår i kategoriseringen af et lægemiddel. Dette foregår i en trinvis proces. Fagudvalget kategoriserer først den relative foreløbige kategori på baggrund af væsentlighedskriterierne og den absolutte foreløbige kategori på baggrund af de præspecificerede mindste klinisk relevante forskelle. Her er der tale om en ren kvantitativ proces. Herefter fastlægger fagudvalget den aggregerede kategori for hvert effektmål ved at sammenholde de foreløbige kategorier. Her kan fagudvalget inddrage deres kliniske indsigt. Når den samlede kategori for lægemidlets værdi skal fastlægges, sammenvejer fagudvalget alle effektmål. Effektmålenes kategorier kombineres med effektmålenes vægt, og eventuelle kliniske overvejelser inddrages. Den samlede kategorisering af lægemidlets værdi er således delvis en kvantitativ og delvis en kvalitativ proces, hvor der foretages en klinisk vurdering af det foreliggende datagrundlag. Vurdering af evidensens kvalitet foretages med udgangspunkt i GRADE og udtrykker tiltroen til evidensgrundlaget for de enkelte effektstørrelser og den endelige kategori for klinisk værdi. Evidensens kvalitet inddeles i fire niveauer: høj, moderat, lav og meget lav. GRADE-metoden er et internationalt anerkendt redskab til systematisk vurdering af evidens og udarbejdelse af anbefalinger. I denne vurdering er metoden anvendt til at vurdere evidensens kvalitet.

7 Litteratursøgning

Ansøger har gennemført en systematisk søgning efter kliniske studier, der undersøger dupilumabs effekt, sammenlignet med effekten af mepolizumab og omalizumab og placebo, jf. søgestrengen i protokollen. Ansøgers PRISMA-diagram og litteraturgennemgang fremgår af ansøgningen.

Søgningen resulterede i identifikation af 436 hits, hvoraf 33 artikler blev inkluderet, baseret på 23 kliniske studier. Vurderingen af dupilumab foretages på baggrund af de 23 studier.

Ansøger har identificeret 3 studier med dupilumab sammenlignet med placebo, 4 studier med mepolizumab sammenlignet med placebo og 16 studier med omalizumab sammenlignet med placebo eller aktiv komparator. Tre af studierne for omalizumab har en varighed på 16 uger, og ansøger har ikke medtaget disse

i de sammenlignende analyser. Tabel 2 giver en oversigt over inkluderede studier, og hvilke kliniske spørgsmål de besvarer.

Tabel 2: Oversigt over inkluderede studier

	Klinisk spørgsmål 1	Klinisk spørgsmål 2	Klinisk spørgsmål 3
Dupilumab	DRI12544 (Wenzel 2016 , Corren 2019a) [11,12]	DRI12544 (Wenzel 2016 , Corren 2019a) [11,12]	DRI12544 (Wenzel 2016 , Corren 2019a) [11,12]
Dupilumab	QUEST (Castro 2018, Corren 2019b, Castro 2019, submitted) [13,14]	QUEST (Castro 2018, Corren 2019b, Castro 2019, submitted) [13,14]	QUEST (Castro 2018, Corren 2019b, Castro 2019, submitted) [13,14]
Dupilumab	VENTURE (Rabe 2018, Rabe 2019 submitted) [15]	VENTURE (Rabe 2018, Rabe 2019 submitted) [15]	VENTURE (Rabe 2018, Rabe 2019 submitted) [15]
Mepolizumab	DREAM (Pavord 2012) [16]		
Mepolizumab	MENSA (Ortega 2014) [17]		
Mepolizumab	MUSCA (Chupp 2017) [18]		
Mepolizumab	SIRIUS (Bel 2014) [19]		
Omalizumab		Busse 2001 [20], Finn 2003 [21], Lanier 2003 [22]	
Omalizumab		Soler 2001 [23], Buhl 2002a [24], Buhl 2002b [25]	
Omalizumab		Holgate 2004 [26]	
Omalizumab		Vignola 2004 [27]	
Omalizumab		Ayres 2004 [28], Niven 2008 [29]	
Omalizumab		Humbert 2005 [30]	
Omalizumab		Ohta 2009 [31]	
Omalizumab		Chanez 2010 [32]	
Omalizumab		Bousquet 2011 [33], Siergiejko 2011 [34]	
Omalizumab		Hanania 2011 [35]	
Omalizumab		Bardelas 2012 [36]	
Omalizumab		Hoshino 2012 [37]	
Omalizumab		Rubin 2012 [38]	
Omalizumab		Busse 2013 [39]	
Omalizumab		Li 2016 [40]	
Omalizumab		Mukherjee 2019 [41]	

Klinisk spørgsmål 1 er baseret på studier af dupilumab og mepolizumab. Klinisk spørgsmål 2 er baseret på studier af dupilumab og omalizumab. Klinisk spørgsmål 3 er udelukkende baseret på studier af dupilumab.

Ansøger beskriver, at der er overensstemmelse mellem data fra studierne og EMAs EPAR.

Medicinrådet har bedt ansøger opgøre effektestimaterne for 300 mg dupilumab dosis i patienter, som modtager OCS. For de, som ikke modtager behandling med OCS, vil effektestimaterne for 200 mg dupilumab blive opgjort.

7.1 Datagrundlag

De studier, som udgør datagrundlaget for besvarelsen af de kliniske spørgsmål, og som Medicinrådets vurdering baseres på, er beskrevet i bilag 1 og 2. Her fremgår også tabel over studiekarakteristika og baselinekarakteristika. I gennemgang af hvert klinisk spørgsmål vil fagudvalget vurdere datagrundlaget og populationen.

8 Databehandling

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

9 Lægemidlets værdi

9.1 Konklusion klinisk spørgsmål 1

Hvilken værdi tilbyder dupilumab sammenlignet med mepolizumab ved behandling af patienter > 12 år med svær astma med type 2-inflammation karakteriseret ved eosinofili?

Fagudvalget vurderer, at dupilumab giver **ingen dokumenteret merværdi** sammenlignet med mepolizumab ved behandling af patienter > 12 år med svær astma med type 2-inflammation karakteriseret ved eosinofili. Dette betyder, at der ikke er påvist en merværdi af dupilumab i forhold til mepolizumab. Omvendt tyder den tilgængelige evidens heller ikke på, at der er en negativ værdi.

Evidensens kvalitet vurderes at være lav.

Af Tabel 3 fremgår den samlede kategori for lægemidlet og kvaliteten af den samlede evidens. Desuden fremgår de absolutte og relative effektforskelle samt foreløbige og aggregerede værdier.

Tabel 3: Kategorier og resultater for klinisk spørgsmål 1, dupilumab vs. mepolizumab til svær eosinofil astma

Effektmål *A: 24-32 uger* *B: 52 uger* C:OCS-afhængig astma 24 uger	**Måleenhed** **(justeret MKRF)**	**Vigtighed**	**Forskel i absolutte tal**		**Forskel i relative tal**		**Aggregeret værdi pr. effektmål**
			Forskel (95 % CI)	**Foreløbig værdi**	**Forskel (95 % CI)**	**Foreløbig værdi**	
Eksacerbationsrate (Alvorlige symptomer)	Gennemsnitlig reduktion i årlig antal eksacerbationer (0,5 årlig eksacerbation)	Kritisk	B: -0,186 (-0,530; 0,324)	Ingen dokumenteret merværdi	B: 0,850 (0,573; 1,261)	B: kan ikke kategoriseres*	Ingen dokumenteret merværdi
	Andel af patienter som opnår 0 årlige eksacerbationer (5 procentpoint)		B: -10,639 %point [-21,897; 4,544]	B: Kan ikke kategoriseres*	B: 0,804 (0,596; 1,084)	B: Kan ikke kategoriseres*	
Peroral vedligeholdelsesbehandling med kortikosteroid (Alvorlige symptomer)	Gennemsnitlig %-reduktion i daglig dosis (10 %, dog min. 1,25 mg prednisolonækvivalent)	Kritisk	Ingen analyse	Kan ikke kategoriseres	Ingen analyse	Kan ikke kategoriseres	Kan ikke kategoriseres
	Andel af patienter som bliver helt fri for vedligeholdelsesbehandling med peroral kortikosteroid (2,5 procentpoint)		C: -0.501 %point (-9.849; 27.632)	C: Kan ikke kategoriseres*	C: 0.965 (0.312; 2.906)	C: kan ikke kategoriseres*	
	Andel af patienter som opnår ≥ 50 % reduktion af peroral kortikosteroid (5 procentpoint)		C: -1.437 (-21.028; 29.938)	C: Kan ikke kategoriseres*	C: 0.973 (0.608; 1.559)	C: Kan ikke kategoriseres*	
Lungefunktion FEV_1 (Alvorlige symptomer)	Gennemsnitlig ændring i lungefunktion (100 ml for voksne)	Vigtig	A: 0,100 (0,013;0,188) B: 0,189 (0,062;0,316) C: 0.106 (-0.122; 0.334)	A og B: Ingen dokumenteret merværdi C: kan ikke kategoriseres*	Ikke relevant	Ikke relevant	Ingen dokumenteret merværdi
	Andelen af patienter der opnår en forbedring på 200 ml (voksne) (15 procentpoint)		Ingen analyse	Kan ikke kategoriseres	Ingen analyse	Kan ikke kategoriseres	
Astmakontrol (Alvorlige symptomer)	Gennemsnitlig ændring i astmakontrol, målt ved Asthma Control Questionnaire (ACQ) (0,25)	Vigtig	A: -0.017 (-0.218; 0.184) C: 0.050 (-0.413; 0.513)	A: Ingen dokumenteret merværdi C: kan ikke kategoriseres*	Ikke relevant	Ikke relevant	Ingen dokumenteret merværdi
Livskvalitet (Livskvalitet)	Gennemsnitlig ændring i livskvalitet, målt ved	Vigtig	A: -0.129 (-0.319; 0.061)	A: Ingen dokumenteret merværdi	Ikke relevant	Ikke relevant	Ingen dokumenteret merværdi

	Astma Quality of Life Questionnaire (AQLQ) (0,25)		C: -0.006 (-0.411; 0.398)	C: Ingen dokumenteret merværdi			
Serious adverse events (SAE's) (Alvorlige symptomer)	Den samlede forekomst (antal) af SAE's (2,5 procentpoint)	Vigtig	A: 6.478 (-1.596; 27.451) B: 2.010 (-5.669; 17.624) C: 25.969 (1.498; 257.1)	A: Kan ikke kategoriseres* B: Kan ikke kategoriseres* C: Kan ikke kategoriseres*	A: 1.974 (0.760; 5.128) B: 1.153 (0.567; 2.345) C: 19.549 (2.070; 184.6)	A: Kan ikke kategoriseres* B: Kan ikke kategoriseres* C: Negativ merværdi	Kan ikke kategoriseres
	Specifikke undertyper af SAE's, herunder anafylaksi (ingen)		Ingen analyse	Kan ikke kategoriseres	Ingen analyse	Kan ikke kategoriseres	Kan ikke kategoriseres
Frafald af patienter i studier (Ikkealvorlige symptomer og bivirkninger)	Andel af patienter som er frafaldet ved studiets afslutning (5 procentpoint)	Vigtig	1.261 (-2.085; 10.027) B: 1.032 (-6.704; 15.422) C: -1.809 (-4.018; 17.685)	A:Kan ikke kategoriseres* B: Kan ikke kategoriseres* C: Kan ikke kategoriseres*	A: 1.304 (0.498; 3.416) B: 1.066 (0.573: 1.982) C: 0.579 (0.066; 5.113)	A:Kan ikke kategoriseres* B: Kan ikke kategoriseres* C: Kan ikke kategoriseres*	Kan ikke kategoriseres
Sygefravær (Ikke-alvorlige symptomer og bivirkninger)	Gennemsnitligt antal sygedage pr. år (2,5 dage per år)	Vigtig	Ingen analyse	Kan ikke kategoriseres	Ingen analyse	Kan ikke kategoriseres	Kan ikke kategoriseres
Samlet kategori for lægemidlets værdi		**Ingen dokumenteret merværdi**					
Kvalitet af den samlede evidens		**Lav**					

MKRF: mindste klinisk relevante forskel
** De rapporterede forskelle mellem dupilumab og mepolizumab er behæftet med en usikkerhed, som betyder, at de ikke passer i de prædefinerede kategorier for vurdering af merværdi.*
A: analyser baseret på studier med studievarighed på 24 uger. Analysen er foretaget på subgruppen af patienter med eosinofili.
B: analyser baseret på studier med studievarighed på 52 uger. Analysen er foretaget på subgruppen af patienter med eosinofili.
C: analyser baseret på OCS-reduktionsstudier med studievarighed på 24 uger. Analysen er foretaget på subgruppen af patienter med eosinofili.

9.1.1 Gennemgang af studier

Karakteristika

Studiekarakteristika og baselinekarakteristika er beskrevet i bilag 1 og 2.

Karakteristika varierer studierne imellem. Særligt er der forskelle i intensitet af den underliggende astmabehandling og antal tidligere eksacerbationer. En del af patienterne, ~50 % i dupilumabstudierne, DRI12544 og QUEST, får ikke den definerede standardbehandling for svær astma, da inklusionskriteriet i disse studier er moderat dosis ICS plus 2nd controller. I mepolizumabstudierne opfylder alle kravet om svær astma svarende til højdosis ICS plus 2nd controller. Fagudvalget vurderer, at dette kan have betydning for resultaterne, men det er ikke entydigt, hvilken retning denne forskel evt. ville kunne trække. I dupilumabstudierne er kravet minimum 1 årlig eksacerbation, mens det er 2 i mepolizumabstudierne. Fagudvalget vurderer, at mepolizumabstudierne bedst svarer til svær astma i dansk klinisk praksis. Fagudvalget finder ikke grund til at bemærke andet ved studie- og baselinekarakteristik.

9.1.2 Resultater og vurdering

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

Hvilken værdi tilbyder dupilumab sammenlignet med mepolizumab ved behandling af patienter > 12 år med svær astma med type 2-inflammation karakteriseret ved eosinofili?

Eksacerbationsrate (kritisk)

Eksacerbationsraten ønskes undersøgt ved den årlige rate og ved andel, der opnår 0 eksacerbationer efter 1 år.

Kun studier med 1 års opfølgning inkluderes i vurderingen af eksacerbationsraten. Datagrundlaget er derfor ét studie på dupilumab (QUEST) og ét studie på mepolizumab (DREAM).

Baseret på de absolutte effektforskelle har dupilumab foreløbigt *ingen dokumenteret merværdi* vedr. antallet af årlige eksacerbationer, som er 0,19 til fordel for dupilumab. Forskellen i andelen af patienter, som ikke oplever eksacerbationer i løbet af et år *kan ikke kategoriseres*, og er 10,6 % procentpoint til fordel for mepolizumab. Forskellen er ikke klinisk relevant eller statistisk signifikant.

Baseret på de relative effektforskelle kan værdien af dupilumab *ikke kategoriseres* vedr. antal årlige eksacerbationer og for andelen, der ikke oplever eksacerbationer i løbet af et år. Det skyldes usikkerhed om forskellene, hvilket betyder, at effekten af dupilumab kan være både bedre og dårligere end mepolizumab. Forskellene er ikke statistisk signifikante og heller ikke klinisk relevante.

På aggregeret niveau vurderer fagudvalget, at dupilumab har *ingen dokumenteret merværdi* vedr. eksacerbationsrate (lav evidenskvalitet). Fagudvalget vægter, at forskellen på den absolutte skala for årlig eksacerbationsrate er marginal, og at ingen øvrige forskelle er klinisk relevante. For alle de foreløbige værdier, som ikke kan kategoriseres, vurderer fagudvalget, at der ikke er grund til at tro, at dupilumab hverken er dårligere eller bedre end mepolizumab.

Peroral vedligeholdelselsbehandling med kortikosteroid (kritisk)

Peroral vedligeholdelsesbehandling med kortikosteroid er undersøgt ved gennemsnitlig reduktion i daglig dosis, andel der bliver helt fri for vedligeholdelsesbehandling med peroral kortikosteroid og andel af patienter, som opnår 50 % reduktion i peroral kortikosteroid.

Datagrundlaget er ét studie på dupilumab (VENTURE) og ét studie på mepolizumab (SIRIUS).

Der er ikke leveret en analyse på den gennemsnitlige reduktion i daglig dosis, da mepolizumabstudier ikke opgiver denne analyse. Denne kan derfor *ikke kategoriseres*.

Baseret på de relative og absolutte effektforskelle for andel af patienter, der bliver helt fri for vedligeholdelsesbehandling med kortikosteroid og andel af patienter, som opnår 50 % reduktion i peroral kortikosteroid, kan værdien af dupilumab *ikke kategoriseres*. Det skyldes usikkerhed om forskellen, hvilket betyder, at effekten af dupilumab kan være både bedre og dårligere end mepolizumab. Forskellene er ikke statistisk signifikante og punktestimaterne er tæt på nul (0,5-1,4 %-point til fordel for dupilumab).

På aggregeret niveau vurderer fagudvalget, at dupilumab *ikke kan kategoriseres* vedr. peroral vedligeholdelsesbehandling med kortikosteroid (lav evidenskvalitet). De observerede forskelle er hverken statistisk signifikante eller klinisk relevante, og punktestimaterne ligger tæt op ad ingen forskel, både på de relative og absolutte skalaer. Fagudvalget vurderer derfor, at der ikke er grund til at tro, at der er forskel på de to lægemidler for dette effektmål.

Lungefunktion FEV_1 (vigtigt)

Lungefunktion er undersøgt ved den gennemsnitlige ændring og andel, der opnår forbedring på 200 ml.

Datagrundlaget er 3 studier på dupilumab (DRI12544, QUEST og VENTURE) og 4 studier på mepolizumab, (DREAM, MENSA, SIRIUS og MUSCA).

Der er ikke leveret en analyse på andel, der opnår forbedring på 200 ml, da mepolizumabstudier ikke opgiver denne analyse. Denne kan derfor *ikke kategoriseres*.

Ansøger har leveret 3 analyser A: 24 uger, B: 52 uger og C: 24 uger (OCS-afhængig svær astma).

Baseret på den absolutte effektforskel har dupilumab foreløbig *ingen dokumenteret merværdi* vedr. lungefunktion i analyse A og B. Dupilumab giver en statistisk signifikant forbedring i lungefunktion, men effekten er ikke klinisk relevant. Punktestimaterne ligger mellem 100-189 ml til fordel for dupilumab.

For C kan forskellen *ikke kategoriseres*, hvilket skyldes usikkerhed om forskellen, og det betyder, at effekten af dupilumab kan være både bedre og dårligere end mepolizumab. Punktestimatet tilsiger 106 ml forbedring til fordel for dupilumab, og forskellen er ikke statistisk signifikant.

På aggregeret niveau vurderer fagudvalget, at dupilumab har *ingen dokumenteret merværdi* vedr. lungefunktion (moderat evidenskvalitet). Fagudvalget lægger vægt på, at der ingen dokumenteret merværdi er i QUEST, som er det største studie med længst mulig opfølgningstid. I VENTURE er forskellen ikke klinisk relevant og ej heller statistisk relevant, hvilket bakker op om kategorien *ingen dokumenteret merværdi.*

Astmakontrol (vigtigt)

Astmakontrol er undersøgt ved den gennemsnitlige ændring i ACQ-score.

Datagrundlaget er 3 studier på dupilumab (DRI12544, QUEST og VENTURE) og 4 studier på mepolizumab (DREAM, MENSA, SIRIUS og MUSCA).

Ansøger har leveret to analyser A: 24 uger og C: 24 uger (OCS-afhængig svær astma).

Baseret på den absolutte effektforskel har dupilumab foreløbig *ingen dokumenteret merværdi* vedr. astmakontrol i analyse A. Forskellen er ikke klinisk relevant og heller ikke statistisk signifikant. For C kan forskellen *ikke kategoriseres*, hvilket skyldes usikkerhed om forskellen, og det betyder, at effekten af dupilumab kan være både bedre og dårligere end mepolizumab. Forskellen er ikke statistisk signifikant.

På aggregeret niveau vurderer fagudvalget, at dupilumab har *ingen dokumenteret merværdi* vedr. astmakontrol (moderat evidenskvalitet). Fagudvalget lægger vægt på, at der *ingen dokumenteret merværdi* er i den ene analyse, mens der heller ikke er klinisk relevant forskel og ej heller statistisk signifikant forskel i den anden analyse, hvilket bakker op om kategorien *ingen dokumenteret merværdi.*

Livskvalitet (vigtigt)

Livskvalitet er undersøgt ved den gennemsnitlige ændring i AQLQ.

Datagrundlaget er 3 studier på dupilumab (DRI12544, QUEST og VENTURE) og 4 studier på mepolizumab (DREAM, MENSA, SIRIUS og MUSCA).

Ansøger har leveret to analyser A: 24 uger og C: 24 uger (OCS-afhængig svær astma).

Baseret på den absolutte effektforskel har dupilumab foreløbig *ingen dokumenteret merværdi* vedr. livskvalitet i analyse A og C. Forskellene er hverken klinisk relevante eller statistisk signifikante.

På aggregeret niveau vurderer fagudvalget, at dupilumab har *ingen dokumenteret merværdi* vedr. livskvalitet (moderat evidenskvalitet).

Serious adverse events (vigtigt)

SAE's er opgjort som:

- Andel der får en eller flere SAE's
    - Ansøger har leveret 3 analyser A: 24 uger, B: 52 uger og C: 24 uger patienter med behov for daglig OCS.
- Specifikke undertyper af SAE's, herunder anafylaksi
    - Ansøger har angivet forekomsten af anafylaksi, som for dupilumab er meget sjælden (< 1/10.000), og for omalizumab er sjælden (< 1/1.000). Da forskellen ikke er opgjort, kan værdien af dupilumab *ikke kategoriseres* foreløbig vedr. forekomsten af anafylaksi.

Datagrundlaget er 3 studier på dupilumab (DRI12544, QUEST og VENTURE) og 4 studier på mepolizumab, (DREAM, MENSA, SIRIUS og MUSCA).

Baseret på de absolutte effektforskelle kan dupilumab foreløbig *ikke kategoriseres* vedr. SAE's. Det skyldes usikkerhed om forskellen, hvilket betyder, at effekten af dupilumab kan være både bedre og dårligere end mepolizumab. Forskellen i andelen af patienter, som oplever SAE's, er mellem 2-25 %-point til fordel for mepolizumab i de 3 analyser. Forskellene er ikke statistisk signifikante i A og B, men i C er der statistisk signifikant forskel.

Baseret på de relative effektforskelle kan værdien af dupilumab *ikke kategoriseres* vedr. SAE's for A og B. Det skyldes usikkerhed om forskellen, hvilket betyder, at effekten af dupilumab kan være både bedre og dårligere end mepolizumab. Forskellen er ikke statistisk signifikant.

I analyse C er den relative risiko 19,5 til fordel for mepolizumab, og dupilumab har derfor en *negativ merværdi*. Denne forskel er drevet af en lav eventrate (1/69) i mepolizumabarmen i SIRIUS-studiet. I dupilumabstudier er der ikke en højere SAE-rate sammenlignet med placebo.

På aggregeret niveau vurderer fagudvalget, at dupilumab *ikke kan kategoriseres* vedr. SAE's (moderat evidenskvalitet). I de to største studier er forskellene hverken statistisk signifikante eller klinisk relevante, og fagudvalget vurderer derfor, at der ikke er grund til at tro, at der er forskel på de to lægemidler vedr. SAE's. Fagudvalget tillægger ikke den negative merværdi i den ene analyse betydning, idet dupilumab i egne studier sammenlignet med placebo ikke har vist sig at være relateret til en øget forekomst af SAE's. Fagudvalget vurderer, at den observerede forskel sandsynligt kan skyldes tilfældigheder, når der er meget få events i en

lille sample size. Fagudvalget vurderer derfor, at der ikke er grund til at tro, at der er forskel på de to lægemidler vedr. SAE's.

Bivirkninger – kvalitativ vurdering

Fagudvalget vurderer, at både dupilumab og mepolizumab generelt er veltolererede behandlinger med få bivirkninger. Anafylaktisk chok er yderst sjælden rapporteret. Injektionsreaktioner forekommer ved alle de biologiske lægemidler, der administreres ved injektion og kan være generende for patienterne. Da dupilumab gives hyppigere end de øvrige lægemidler, vil det potentielt være til større gene for patienterne. Fagudvalget vurderer, at dette er et mindre problem, som ikke bør have betydning for behandlingsvalg.

Fagudvalget bemærker, at der ikke er øget forekomst af svær conjunctivitis (øjenbetændelse) ved behandling med dupilumab til svær astma, hvilket er set ved behandling med dupilumab 300 mg til atopisk eksem [42]. Derfor bør der være opmærksomhed på denne bivirkning hos patienter med svær astma, som samtidig har atopisk eksem.

Frafald af patienter i studier (vigtigt)

Frafald er undersøgt ved andel af patienter der falder fra i studier.

Datagrundlaget er 3 studier på dupilumab (DRI12544, QUEST og VENTURE) og 4 studier på mepolizumab (DREAM, MENSA, SIRIUS og MUSCA).

Ansøger har leveret 3 analyser A: 24 uger, B: 52 uger og C: 24 uger (OCS-afhængig svær astma).

Baseret på de absolutte effektforskelle kan dupilumab foreløbig ikke kategoriseres vedr. frafald af patienter i studier. Det skyldes usikkerhed om forskellen, hvilket betyder, at effekten af dupilumab kan være både bedre og dårligere end mepolizumab. Forskellen i andelen af patienter, som frafalder, er mellem -1,8-1,2 %-point i de tre analyser, hvilket betyder, at punktestimatet ligger tæt på 0, som er ingen forskel. Forskellene er ikke klinisk relevante eller statistisk signifikante i alle 3 analyser.

Baseret på de relative effektforskelle kan værdien af dupilumab *ikke kategoriseres* vedr. frafald af patienter i studier. Det skyldes usikkerhed om forskellen, hvilket betyder, at effekten af dupilumab kan være både bedre og dårligere end mepolizumab. Forskellen er ikke statistisk signifikant.

På aggregeret niveau vurderer fagudvalget, at dupilumab *ikke kan kategoriseres* vedr. frafald af patienter i studier (moderat evidenskvalitet). Forskellene i alle analyser er hverken statistisk signifikante eller klinisk relevante, og punktestimaterne ligger tæt op ad 0, dvs. ingen forskel. Fagudvalget vurderer derfor, at der ikke er grund til at tro, at der er forskel på de to lægemidler vedr. frafald af patienter i studier.

Sygefravær (vigtigt)

Der er ikke lavet en sammenlignende analyse for sygefravær, da dette effektmål kun er rapporteret i dupilumabstudierne. Effektmålet kan derfor *ikke kategoriseres.*

9.1.3 Evidensens kvalitet

Evidensens kvalitet for klinisk spørgsmål 1 er samlet set vurderet som værende **lav**. Overvejelser vedrørende evidensens kvalitet kan ses i bilag 3.

Fagudvalget vurderer, at evidensen er indirekte i forhold til patientpopulationen og den underliggende standardbehandling i dupilumabstudierne, som ikke er direkte overførbar til danske forhold. Dette skyldes især inklusion af patienter med moderat sygdom og den manglende systematiske udredning i alle studier, hvilket ikke afspejler dansk standard. Derfor er der nedgraderet ét niveau for indirekthed for alle effektmål.

9.1.4 Fagudvalgets vurdering af samlet værdi, klinisk spørgsmål 1

Fagudvalget vurderer, at dupilumab til patienter > 12 år med svær astma med type 2-inflammation karakteriseret ved eosinofili giver **ingen dokumenteret merværdi** sammenlignet med mepolizumab. Det betyder, at der ikke er påvist en merværdi af dupilumab i forhold til mepolizumab. Omvendt tyder den tilgængelige evidens heller ikke på, at der er en negativ værdi.

Evidensens kvalitet vurderes at være lav.

Fagudvalget lægger vægt på, at der *ingen dokumenteret merværdi* er for eksacerbationsraten, som er et kritisk effektmål. For det andet kritiske effektmål, som er peroral vedligeholdelsesbehandling med kortikosteroid, kan effekten af dupilumab vs. mepolizumab *ikke kategoriseres* grundet usikkerheden om forskellen. De observerede forskelle er dog hverken statistisk signifikante eller klinisk relevante, og punktestimaterne ligger tæt op ad ingen forskel både på de relative og absolutte skalaer. Fagudvalget vurderer derfor, at der ikke er grund til at tro, at der er forskel på de to lægemidler vedr. peroral vedligeholdelsesbehandling med kortikosteroider.

For de vigtige effektmål lungefunktion, astmakontrol og livskvalitet er der ligeledes *ingen dokumenteret merværdi*, hvilket underbygger konklusionen på de kritiske effektmål.

For de vigtige effektmål SAE's, frafald af patienter i studier og sygefravær kan effekten *ikke kategoriseres* pga. usikkerhed omkring effektforskellene eller manglende data. Fagudvalget vurderer ikke, at dette påvirker kategoriseringen hverken i negativ eller positiv retning for klinisk spørgsmål 1.

9.2 Konklusion klinisk spørgsmål 2

Hvilken værdi tilbyder dupilumab sammenlignet med omalizumab ved behandling af patienter > 12 år med svær astma med type 2-inflammation karakteriseret ved allergi og samtidig eosinofili eller karakteriseret ved allergi og samtidig forhøjet FeNO?

Fagudvalget vurderer, at til patienter med svær astma med type 2-inflammation karakteriseret ved allergi + eosinofili eller allergi + forhøjet FeNO giver dupilumab **ingen dokumenteret merværdi** sammenlignet med omalizumab. Det betyder, at der ikke er påvist en merværdi af dupilumab i forhold til omalizumab. Omvendt tyder den tilgængelige evidens heller ikke på, at der er en negativ værdi.

Evidensens kvalitet vurderes at være meget lav.

Af Tabel 4 fremgår den samlede kategori for lægemidlet og kvaliteten af en samlede evidens. Desuden fremgår de absolutte og relative effektforskelle samt foreløbige og aggregerede værdier.

Tabel 4: Kategorier og resultater for klinisk spørgsmål 2, ***dupilumab vs. omalizumab til svær astma karakteriseret ved allergi + eosinofili eller allergi + forhøjet FeNO***

Effektmål (gruppe)	**Måleenhed** (justeret MKRF)	**Vigtighed**	**Forskel i absolutte tal**		**Forskel i relative tal**		**Aggregeret værdi pr. effektmål**
			Forskel [95 % CI]	**Foreløbig værdi**	**Forskel [95 % CI]**	**Foreløbig værdi**	
Eksacerbationsrate (Alvorlige symptomer)	Gennemsnitlig reduktion i årlig antal eksacerbationer (minimum reduceret med 0,5 årlig eksacerbation)	Kritisk	-0,107 [-0,268; 0,114]	Ingen dokumenteret merværdi	RR 0,845 [0,612; 1,165]	Kan ikke kategoriseres*	Ingen dokumenteret merværdi
	Andel af patienter som opnår 0 årlige eksacerbationer (5 procentpoint)		2,6 % [-5,6; 12,2]	Kan ikke kategoriseres*	RR 1,046 [0,902; 1,214]	Kan ikke kategoriseres*	
Peroral vedligeholdelsebehandling med kortikosteroid (Alvorlige symptomer)	-	Kritisk	Ingen analyse	Kan ikke kategoriseres	Ingen analyse	Kan ikke kategoriseres	Kan ikke kategoriseres
Lungefunktion FEV_1 (Alvorlige symptomer)	Gennemsnitlig ændring i lungefunktion (100 ml for voksne)	Vigtig	96 ml [11; 182]	Ingen dokumenteret merværdi	Ikke relevant	Ikke relevant	Ingen dokumenteret merværdi
	Andel af patienter der opnår en forbedring på 200 ml (7,5 procentpoint)		Ingen analyse	Kan ikke kategoriseres	Ingen analyse	Kan ikke kategoriseres	
Astmakontrol (Alvorlige symptomer)	Gennemsnitlig ændring i astmakontrol målt ved Asthma Control Questionnaire (ACQ) (0,25)	Vigtig	-0,111 [-0,417; 0,195]	Ingen dokumenteret merværdi	Ikke relevant	Ikke relevant	Ingen dokumenteret merværdi
Livskvalitet (Livskvalitet)	Gennemsnitlig ændring i livskvalitet, målt ved Astma Quality of Life Questionnaire (AQLQ) (0,25)	Vigtig	-0,077 [-0,304; 0,151]	Kan ikke kategoriseres*	Ikke relevant	Ikke relevant	Kan ikke kategoriseres
Serious adverse events (SAE's) (Alvorlige symptomer)	Den samlede forekomst (antal) af SAE's (2,5 procentpoint)	Vigtig	Studievarighed 20-32 uger: 3 procentpoint [-1,8; 14,9] Studievarighed 48-52 uger: 0,2 procentpoint [-2,7; 5,3]	Kan ikke kategoriseres*	Studievarighed 20-32 uger: RR 1,610 [0,641; 4,048] Studievarighed 48-52 uger: RR 1,036 [0,596; 1,802]	Kan ikke kategoriseres*	Kan ikke kategoriseres

	Specifikke undertyper af SAE's, herunder anafylaksi. (ingen)		Ikke rapporteret	Kan ikke kategoriseres	Ikke rapporteret	Kan ikke kategoriseres	
Frafald af patienter i studier (Ikke-alvorlige symptomer og bivirkninger)	Andel af patienter som er frafaldet ved studiets afslutning (5 procentpoint)	Vigtig	Studievarighed 20-32 uger: -0,5 procentpoint [-6,2; 12,5] Studievarighed 48-52 uger: 4,3 procentpoint [-2,0; 13,7]	Kan ikke kategoriseres*	Studievarighed 20-32 uger: RR 0,948 [0,413;2,180] Studievarighed 48-52 uger: RR 1,206 [0,859; 1,988]	Kan ikke kategoriseres*	Kan ikke kategoriseres
Sygefravær (Ikke-alvorlige symptomer og bivirkninger)	Gennemsnitligt antal sygedage pr. år (2,5 dage per år)	Vigtig	Ikke rapporteret	Kan ikke kategoriseres	Ikke relevant	Ikke relevant	Kan ikke kategoriseres
Samlet kategori for lægemidlets værdi		Ingen dokumenteret merværdi					
Kvalitet af den samlede evidens		Meget lav					

** De rapporterede forskelle mellem dupilumab og omalizumab er behæftet med en usikkerhed, som betyder, at de ikke passer i de prædefinerede kategorier for vurdering af merværdi.*

9.2.1 Gennemgang af studier

Til besvarelse af klinisk spørgsmål 2 har ansøger anvendt data fra ét studie for dupilumab (QUEST) og 16 studier for omalizumab (se Tabel 2 i afsnit 7).

Karakteristika

Studiekarakteristika og baselinekarakteristika er beskrevet i bilag 1 og 2.

Der er væsentlige forskelle mellem subgruppen med allergi fra dupilumab studiet (QUEST) og populationerne i omalizumabstudierne i forhold til nogle af inklusionskriterierne og baseline karakteristika:

- Antallet af eksacerbationer inden for et år var ca. 2 i dupilumabstudiet og i nogle af omalizumabstudierne. De fleste af omalizumabstudierne angav imidlertid ikke antallet af tidligere eksacerbationer, og i andre var antallet højere end 2: 4-4,7 (Chanez 2010), 2,7-3,3 (OCS subgruppen i Bousquet 2011).
- Hvor FEV_1 var angivet i omalizumabstudierne, var lungefunktionen bedre (FEV_1 på 2,3-2,8 L) sammenlignet med subgruppen med allergi i dupilumabstudiet (FEV_1 på 1,8 L).
- I dupilumabstudiet var medium-højdosis ICS et inklusionskriterie. I de fleste af omalizumabstudierne var højdosis ICS et inklusionskriterie, men ikke rapporteret i alle studierne.
- Brug af OCS var ikke rapporteret i dupilumabstudiet og var enten ikke tilladt eller blev ikke anvendt blandt 7-80 % af patienterne i omalizumabstudierne.
- I dupilumabstudiet var brug af LABA eller anden 2nd controller et inklusionskriterie, mens det var tilladt i nogle af omalizumabstudierne og ikke i andre.
- I protokollen blev allergi defineret som påvist sensibilisering for et periannal allergen ved hudpriktest og/eller måling af forhøjet specifik IgE antistof (> 0,35 kU/L) og symptomer for relevant allergenpåvirkning. Ingen af studierne rapporterede sidstnævnte; dvs. kongruens mellem relevant sensibilisering og symptomer ved eksposition for allergenet. I dupilumabstudiet angav over 90 % af populationen selvrapporteret vedvarende allergisk/atopisk lidelse. Det gennemsnitlige IgE-niveau var lidt højere i subgruppen med allergi fra dupilumabstudiet (304-337 IU/mL) end i de fleste omalizumabstudier (167-281 IU/mL i alle studier undtaget Mukherjee 2019).

Fagudvalget vurderer, at disse forskelle gør de indirekte sammenligninger mindre robuste. Det er ikke entydigt, om disse forskelle studierne imellem vil føre til, at man evt. ville kunne komme til at overestimere eller underestimere en eventuel effekt af det ene lægemiddel overfor det andet.

9.2.2 Resultater og vurdering

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

Datagrundlaget er, med mindre andet er angivet: ét studie (QUEST) med 1 års opfølgningstid for dupilumab og tre studier med 1 års opfølgningstid (Busse 2001, Soler 2001 og Ayres 2004) samt ét studie med 48 ugers opfølgningstid (Hanania 2011) for omalizumab.

Eksacerbationsrate (kritisk)

Eksacerbationsrate er opgjort som:

- Reduktion i årligt antal eksacerbationer.
- Andel der opnår 0 årlige eksacerbationer. Datagrundlaget for omalizumab er to studier (Ayres 2004 og Hanania 2011) med 48-52 ugers opfølgningstid.

Baseret på de absolutte effektforskelle har dupilumab foreløbig *ingen dokumenteret merværdi* vedr. eksacerbationsrate. Forskellen i antallet af årlige eksacerbationer er 0, til fordel for dupilumab og dermed ikke klinisk relevant. Forskellen i andelen af patienter, som ikke oplever eksacerbationer i løbet af et år, *kan ikke kategoriseres* på grund af usikkerheden på forskellen. Forskellen er 2,6 procentpoint til fordel for dupilumab. Denne forskel er ikke klinisk relevant og ej heller statistisk signifikant.

Baseret på de relative effektforskelle kan den foreløbige værdi af dupilumab *ikke kategoriseres* vedr. eksacerbationsrate. Det skyldes usikkerhed om forskellen, hvilket betyder, at effekten af dupilumab kan være både bedre og dårligere end omalizumab.

På aggregeret niveau vurderer fagudvalget, at dupilumab har *ingen dokumenteret merværdi* vedr. eksacerbationsrate (lav evidenskvalitet). Fagudvalget lægger vægt på, at den absolutte forskel i antal årlige eksacerbationer er marginal, og at ingen øvrige forskelle er kliniske relevante. Selvom der er usikkerhed omkring øvrige forskelle, der ikke kan kategoriseres, vurderer fagudvalget, at der ikke er grund til at tro, at dupilumab hverken er dårligere eller bedre end omalizumab vedr. eksacerbationsrate.

Peroral vedligeholdelselsbehandling med kortikosteroid (kritisk)

Der er ikke rapporteret data for dette effektmål, som var vurderet at være kritisk. Derfor kan den foreløbige værdi af dupilumab *ikke kategoriseres* vedr. peroral vedligeholdelsesbehandling med kortikosteroid.

Lungefunktion FEV_1 (vigtigt)

Lungefunktion er opgjort som:

- Absolut forskel i gennemsnitlig ændring i FEV_1.
- Fagudvalget havde i protokollen også efterspurgt forskelle i andelen af patienter, der opnår en forbedring i lungefunktion på 200 ml. Det var ikke muligt for ansøger at angive dette, idet data for dette effektmål kun er rapporteret i dupilumabstudierne. Derfor kan værdien ikke kategoriseres for andelen af patienter, der opnår en forbedring på 200 ml.

Baseret på den absolutte effektforskel har dupilumab foreløbig *ingen dokumenteret merværdi* vedr. lungefunktion. Forskellen i gennemsnitlig ændring i FEV_1 er 96 ml (til fordel for dupilumab) og er dermed ikke klinisk relevant.

På aggregeret niveau vurderer fagudvalget, at værdien af dupilumab har *ingen dokumenteret merværdi* vedr. lungefunktion (meget lav evidenskvalitet). Den observerede forskel er statistisk signifikant, men ikke klinisk relevant.

Astmakontrol (vigtigt)

Astmakontrol er opgjort som en absolut forskel i den gennemsnitlige ændring, målt ved spørgeskemaet ACQ (Asthma Control Questionnaire). Datagrundlaget for omalizumab er ét studie (Li 2016) med 24 ugers opfølgningstid.

Baseret på den absolutte effektforskel har dupilumab foreløbig *ingen dokumenteret merværdi* vedr. astmakontrol. Forskellen i den gennemsnitlige ændring af ACQ-score er 0,1 og er ikke klinisk relevant.

På aggregeret niveau vurderer fagudvalget, at dupilumab har *ingen dokumenteret merværdi* vedr. astmakontrol (meget lav evidenskvalitet).

Livskvalitet (vigtigt)

Astmakontrol er opgjort som en absolut forskel i den gennemsnitlige ændring, målt ved spørgeskemaet Astma Quality of Life Questionnaire (AQLQ). Datagrundlaget for omalizumab er to studier (Li 2016 og Vignola 2004) med henholdsvis 24 og 28 ugers opfølgningstid.

Baseret på den absolutte effektforskel kan den foreløbige værdi af dupilumab *ikke kategoriseres* vedr. livskvalitet, på grund af usikkerhed omkring effekten. Forskellen i den gennemsnitlige ændring af AQLQ-score er 0,08 og dermed tæt på 0 og ikke klinisk relevant, ej heller statistisk signifikant.

På aggregeret niveau vurderer fagudvalget, at værdien af dupilumab *ikke kan kategoriseres* vedr. livskvalitet (lav evidenskvalitet). Forskellen er hverken statistisk signifikant eller klinisk relevant. Selvom der er usikkerhed omkring effekten, vurderer fagudvalget, at der ikke er grundlag for at tro, at dupilumab hverken er dårligere eller bedre end omalizumab vedr. livskvalitet.

Serious adverse events (SAE's) (vigtigt)

Serious adverse events er opgjort som:

- Den samlede forekomst af SAE's ved 20-32 uger. Datagrundlaget for dupilumab er ét studie (DRI12544) og for omalizumab 7 studier (Holgate 2004, Vignola 2004, Humbert 2005, Bousquet 2011, Chanez 2010, Busse 2013 og Li 2016).
- Den samlede forekomst af SAE's ved 48-52 uger. Datagrundlaget for dupilumab er ét studie (QUEST) og for omalizumab 3 studier (Busse 2001, Soler 2001 og Hanania 2011).
- Fagudvalget havde i protokollen også efterspurgt specifikke undertyper af SAE's, herunder anafylaksi. Ansøger har angivet forekomsten af anafylaksi, som for dupilumab er meget sjælden (< 1/10.000) og for omalizumab er sjælden (< 1/1.000). Da forskellen ikke er opgjort, kan den foreløbige værdi af dupilumab ikke kategoriseres foreløbig vedr. forekomsten af anafylaksi.

Baseret på den absolutte effektforskel kan den foreløbige værdi af dupilumab *ikke kategoriseres* vedr. den samlede forekomst af SAE's. Der er 3 procentpoints forskel efter studievarighed på 20-32 uger og 0,2 procentpoints forskel efter 48-52 uger. På grund af usikkerheden omkring effektforskellene kan værdien ikke kategoriseres.

Baseret på den relative effektforskel kan den foreløbige værdi af dupilumab *ikke kategoriseres* vedr. den samlede forekomst af SAE's på grund af usikkerheden på forskellen for alle studievarigheder.

På aggregeret niveau vurderer fagudvalget, at værdien af dupilumab *ikke kan kategoriseres* vedr. SAE's (lav evidenskvalitet), idet usikkerheden på forskellen er for stor til at vurdere, om der reelt er en forskel. Forskellene i alle analyser er hverken statistisk signifikante eller klinisk relevante, og punktestimaterne ligger tæt op ad 0, dvs. ingen forskel. Fagudvalget vurderer derfor, at der ikke er grund til at tro, at der er forskel på de to lægemidler vedr. SAE's.

Bivirkninger – narrativ vurdering

Fagudvalget vurderer, at både dupilumab og omalizumab generelt er veltolererede behandlinger med få bivirkninger. Anafylaktisk chok er yderst sjælden rapporteret. Injektionsreaktioner forekommer ved alle de biologiske lægemidler, der administreres ved injektion og kan være generende for patienterne. Da dupilumab gives hyppigere end de øvrige lægemidler, vil det potentielt være til større gene for patienterne; der er dog en andel af omalizumabpatienter, der får injektioner hver 2. uge ligesom dupilumab. Fagudvalget vurderer, at dette er et mindre problem, som ikke bør have betydning for behandlingsvalg.

Frafald af patienter i studier (vigtigt)

Frafald af patienter i studier er opgjort som:

- Andelen af patienter som er frafaldet ved 20-32 uger. Datagrundlaget for dupilumab er ét studie (DRI12544) og for omalizumab 7 studier (Holgate 2004, Vignola 2004, Humbert 2005, Bardelas 2012, Busse 2013, Li 2016 og Mukherjee 2019).
- Andelen af patienter som er frafaldet ved 48-52 uger. Datagrundlaget for dupilumab er ét studie (QUEST) og for omalizumab 3 studier (Busse 2001, Soler 2001 og Hanania 2011).

Baseret på den absolutte effektforskel kan værdien af dupilumab *ikke kategoriseres* foreløbig vedr. frafald af patienter i studiet. Der er 0,5 procentpoints forskel efter studievarighed på 20-32 uger og 4,3 procentpoints forskel efter 48-52 uger. På grund af usikkerheden omkring effektforholdene kan værdien ikke kategoriseres.

Baseret på den relative effektforskel kan den foreløbige værdi af dupilumab *ikke kategoriseres* vedr. frafald af patienter i studiet på grund af usikkerheden på forskellen for alle studievarigheder.

På aggregeret niveau vurderer fagudvalget, at værdien af dupilumab *ikke kan kategoriseres* vedr. frafald af patienter i studiet (meget lav evidenskvalitet). Forskellene i alle analyser er hverken statistisk signifikante eller klinisk relevante. Fagudvalget vurderer derfor, at der ikke er grund til at tro, at der er forskel på de to lægemidler vedr. SAE's.

Sygefravær (vigtigt)
Sygefravær er rapporteret forskelligt i studierne, og derfor har ansøger ikke angivet forskelle. For dupilumab viser data fra ét studie (QUEST) en årlig rate på 0,613 sygedage pr. år vs. 2,238 i placebogruppen. For omalizumab viser data fra ét studie (Niven 2008) en median i antal af sygedage på 15,5 vs. 46 i placebogruppen. Fagudvalget vurderer, at disse data ikke kan sammenlignes, da der ikke er opgjort et gennemsnit i omalizumabstudierne. Effektmålet kan derfor *ikke kategoriseres.*

9.2.3 Evidensens kvalitet
Evidensens kvalitet for klinisk spørgsmål 2 er samlet set vurderet som værende **meget lav**. Overvejelser vedrørende evidensens kvalitet kan ses i bilag 3.

Fagudvalget vurderer, at evidensen er indirekte i forhold til patientpopulationen og den underliggende standardbehandling, som ikke er direkte overførbar til danske forhold. Dette skyldes især inklusion af patienter med moderat sygdom og den manglende systematiske udredning i alle studier, hvilket ikke afspejler dansk standard. Der er især en mangelfuld beskrivelse af udredning i de ældre omalizumabstudier. Desuden er analyserne indirekte sammenligninger af studier, hvor fagudvalget vurderer at der er væsentlige forskelle på studiekarakteristika, hvilket yderligere bidrager til indirekte evidens.

9.2.4 Fagudvalgets vurdering af samlet værdi, klinisk spørgsmål 2
Fagudvalget vurderer, at til patienter med svær astma med type 2-inflammation karakteriseret ved allergi + eosinofili eller allergi + forhøjet FeNO giver dupilumab *ingen dokumenteret merværdi* sammenlignet med omalizumab. Det betyder, at der ikke er påvist en merværdi af dupilumab i forhold til omalizumab. Omvendt tyder den tilgængelige evidens heller ikke på, at der er en negativ værdi.

Evidensens kvalitet vurderes at være meget lav.

Fagudvalget lægger vægt på, at der for det kritiske effektmål eksacerbationsrate ikke er påvist en klinisk relevant forskel i effekten af dupilumab og omalizumab (ingen dokumenteret merværdi). For de vigtige effektmål lungefunktion og astmakontrol er der ligeledes ingen dokumenteret merværdi, hvilket underbygger resultatet på eksacerbationsraten.

Analyserne for de øvrige effektmålene giver resultater, som hverken er klinisk relevante eller statistisk signifikante. De er dog forbundet med en usikkerhed, som gør, at de ikke kan placeres i Medicinrådets kategorier for merværdi, hvilket betyder, at de ikke kan kategoriseres. På trods af denne usikkerhed om forskellene vurderer fagudvalget, at der formentlig ikke er forskel i effekten. Fagudvalget vurderer derfor, at det ikke påvirker kategoriseringen hverken i negativ eller positiv retning. Der var ikke mulighed for at lave sammenlignende analyser for peroral vedligeholdelsesbehandling med kortikosteroid. Da perorale steroider gives for at undgå eksacerbationer og bevare astmakontrol, finder fagudvalget ikke anledning til, at den manglende analyse for dette effektmål skal rykke ved kategoriseringen.

9.3 Konklusion klinisk spørgsmål 3

Hvilken værdi tilbyder dupilumab sammenlignet med placebo ved behandling af patienter > 12 år med svær astma med type 2-inflammation karakteriseret ved forhøjet FeNO uden samtidig eosinofili og uden samtidig allergi?

Fagudvalget vurderer, at dupilumab til patienter med svær astma med type 2-inflammation karakteriseret ved forhøjet FeNO uden samtidig eosinofili og uden samtidig allergi **ikke kan kategoriseres** sammenlignet med placebo.

Studier på dupilumab vs. placebo viser klinisk relevante effekter på eksacerbationsrate, peroral vedligeholdelsesbehandling med OCS og lungefunktion på tværs af forskellige subpopulationer af svær astma med type 2-inflammation, herunder også den samlede subpopulation med forhøjet FeNO uanset eosinofili- og allergistatus. Der er et betragteligt overlap mellem de forskellige subpopulationer. Der er generelt forholdsvis få og tolerable bivirkninger forbundet med anvendelse af dupilumab.

9.3.1 Gennemgang af studier

Populationen for dette kliniske spørgsmål var defineret som patienter med forhøjet FeNO uden samtidig eosinofili og allergi. Det er ikke lykkes ansøger at finde litteratur for populationen, som udgøres af klinisk spørgsmål 3. Derfor har ansøger indsendt data for dupilumab sammenlignet med placebo for patienter med eleveret baseline FeNO ≥ 25 bpp, uanset eosinofile granolucytter og allergistatus (QUEST og VENTURE). I QUEST-studiet opfylder 49 ud af 1.902 patienter (~ 2,5 %) kriteriet for at indgå i populationen i spørgsmål 3. Ansøger har indsendt data for populationen med forhøjet FeNO svarende til omkring 24 % af populationen i QUEST-studiet. Antallet af patienter, som opfylder den forespurgte population, er ikke opgjort i DRI12544 og VENTURE.

Ansøger har for hvert effektmål foretaget tre analyser:

- A: analyser baseret på DRI12455 med studievarighed 24 uger. Analysen er foretaget på ITT-populationen. Denne analyse er kun lavet for effektmål relateret til "safety".
- B: analyser baseret på QUEST-studiet med studievarighed på 52 uger. Analysen er foretaget på subgruppen af patienter med forhøjet FeNO, hvor dette er muligt.
- C: analyser baseret på VENTURE-studiet med studievarighed på 24 uger (OCS-afhængig astma). Analysen er foretaget på subgruppen af patienter med forhøjet FeNO, hvor dette er muligt.

Karakteristika

Studiekarakteristika og baselinekarakteristika er beskrevet i bilag 1 og 2.

En del af patienterne, ~50 % i dupilumabstudierne, DRI12544 og QUEST, får ikke den danske definerede standardbehandling for svær astma, da inklusionskriteriet i disse studier er moderat dosis ICS plus 2nd controller. Herudover er kravet minimum 1 årlig eksacerbation, mens det er 2 i dansk klinisk praksis. Fagudvalget vurderer, at dupilumabstudierne ikke helt svarer til svær astma i dansk klinisk praksis. Det er ikke entydigt, om disse forhold kan føre til generel over- eller underestimereting af en evt. effekt. Fagudvalget finder ikke grund til at bemærke andet ved studie- og baselinekarakteristik.

9.3.2 Resultater og vurdering

Fagudvalget vurderer, at det indsendte data på den samlede gruppe af patienter med forhøjet FeNO eller ITT-populationen ikke stemmer tilstrækkelig overens med det efterspurgte data for klinisk spørgsmål 3 i protokollen. For størstedelen af patienter i det indsendte data vil placebo ikke være den rette komparator.

Fagudvalget mener ikke, at datagrundlaget er tilstrækkeligt til at lave en evidensbaseret og dermed præcis kategorisering af dupilumab til patienter med svær astma med forhøjet FeNO uden eosinofili og uden allergi. Fagudvalget vurderer, at man ikke kan vide, om det er grupperne, der også har allergi eller eosinofili, der driver effekten, som observeres i den samlede gruppe af patienter med forhøjet FeNO.

På baggrund af det utilstrækkelige datagrundlag er det ikke muligt at kategorisere de enkelte effektmål i resultatafsnittet.

Af Tabel 5 fremgår en opgørelse og beskrivelse af resultaterne indsendt af ansøger.

Tabel 5: Resultater for dupilumab vs. placebo til svær astma karakteriseret ved forhøjet FeNO

Effektmål (Gruppe)	**Måleenhed** (Justeret MKRF)	**Vigtighed**	**Forskel i absolutte tal [95 % CI]**	**Forskel i relative tal [95 % CI]**
Eksacerbationsrate (Alvorlige symptomer)	Gennemsnitlig reduktion i årlig antal eksacerbationer (minimum reduceret med 0,5 årlig eksacerbation)	Kritisk	B: -0,65 [-0,750; -0,500]	B: 0,35 [0,25; 0,50]
	Andel af patienter som opnår 0 årlige eksacerbationer (5 procentpoint)		B: 20,75 % [11,74; 29,76]	B: 1,37 [1,179; 1,590]
Peroral vedligeholdelsebehandling med kortikosteroid (Alvorlige symptomer)	Gennemsnitlig %-reduktion i daglig dosis (10 %, dog min. 1,25 mg prednisolon ækvivalent)	Kritisk	34,75 % [18,66; 54,05]	Ikke relevant
	Andel af patienter som bliver helt fri for vedligeholdelsesbehandling med peroral kortikosteroid (2,5 procentpoint)		23,46 % [10,54; 36,37]	1,810 [1,276; 2,566]
	Andel af patienter som opnår ≥ 50 % reduktion af peroral kortikosteroid (5 procentpoint)		26,34 % [14,10; 38,58]	1,494 [1,220; 1,830)
Lungefunktion FEV_1 (Alvorlige symptomer)	Gennemsnitlig ændring i lungefunktion (100 ml for voksne)	Vigtig	B: 300 ml [220; 390] C: 250 [40; 450]	Ikke relevant
	Andelen af patienter der opnår en forbedring på 200 ml (voksne) (7,5 procentpoint)		B: 23,78 [13,10; 34,45] C: 19,19 [0,83; 37,56]	B: 1,556 [1,244; 1,947] C: 1,528 [1,001; 2,333]
Astmakontrol (Alvorlige symptomer)	Gennemsnitlig ændring i astmakontrol, målt ved Asthma Control Questionnaire (ACQ) (0,25)	Vigtig	B: -0,39 [-0,53; -0,25] C: -0,47 [-0,76; -0,18]	Ikke relevant
Livskvalitet (Livskvalitet)	Gennemsnitlig ændring i livskvalitet, målt ved Astma Quality of Life Questionnaire (AQLQ) (0,25)	Vigtig	B: 0,29 [0,15; 0,44] C: 0,35 [0,073; 0,627]	Ikke relevant
Serious adverse events (SAE's) (Alvorlige symptomer)	Den samlede forekomst (antal) af SAE's (2,5 procentpoint)	Vigtig	A: 1,06 [-4,36;6,48] B: -0,54 % [-4,24; 3,16] C: 3,13 % [-3,85; 10,11)	A: 1,19 [0,50;2,84] B: 0,935 [0,593; 1,475] C: 1,558 [0,575; 4,223]
	Specifikke undertyper af SAE's, herunder anafylaksi (ingen)		-	-
Frafald af patienter i studier (Ikkealvorlige symptomer og bivirkninger)	Andel af patienter som er frafaldet ved studiets afslutning (5 procentpoint)	Vigtig	A:-0,16 [-6,07; 5,57] B: -0,89 % [-5,23; 3,44] C: -2,73 % [-7,54; 2,07]	A: 0,98 [0,45;2,15] B: 0,925 [0,638; 1,341] C: 0,416 [0,082; 2,094]
Sygefravær (Ikkealvorlige symptomer og bivirkninger)	Gennemsnitligt antal sygedage pr. år (2,5 dage per år)	Vigtig	Ikke rapporteret	Ikke rapporteret

MKRF: mindste klinisk relevante forskel
A: analyser baseret på DRI12544-studiet med studievarighed på 24 uger. Studiet er kun anvendt til SAE's og frafald af patienter og analyserne er baseret på ITT-populationen. B: analyser baseret på QUEST-studiet med studievarighed på 52 uger. Analysen er foretaget på subgruppen af patienter med ukontrolleret astma + forhøjet FeNO. Dog baseret på ITT-populationen i QUEST for effektmålene: astmakontrol, livskvalitet, serious adverse events, frafald af patienter i studier. C: analyser baseret på VENTURE-studiet med studievarighed på 24 uger. Analysen er foretaget på subgruppen af patienter med OCS-afhængig astma + forhøjet FeNO. Dog baseret på ITT-populationen i VENTURE for effektmålene: astmakontrol, livskvalitet, serious adverse events, frafald af patienter i studier.

Effekt

I de af ansøger indsendte analyser af subgruppen med forhøjet FeNO uanset eosinofile granolucytter og allergistatus viser dupilumab en klinisk relevant effekt over placebo for eksacerbationsraten, reduktion i daglig OCS og lungefunktion (Tabel 5).

For astmakontrol, livskvalitet og SAE's, frafald er resultaterne kun opgjort for ITT-populationen, dvs. populationen inkluderer også patienter, som ikke har forhøjet FeNO. For disse effektmål kan der i ITT-populationen ikke påvises en klinisk relevant effekt for dupilumab overfor placebo. For astmakontrol og livskvalitet ses en statistisk forskel til fordel for dupilumab, mens der ikke ses nogle forskelle i SAE's og frafald. Sygefravær er ikke rapporteret (Tabel 5).

Bivirkninger

Fagudvalget vurderer, at dupilumab er et veltolereret lægemiddel med få og håndterbare bivirkninger. Anafylaktisk chok er yderst sjælden rapporteret. Injektionsreaktioner forekommer ved alle biologiske lægemidler, der administreres ved injektion og kan være generende for patienterne.

9.3.3 Evidensens kvalitet

Evidensens kvalitet vurderes ikke for klinisk spørgsmål 3.

9.3.4 Fagudvalgets vurdering af samlet værdi, klinisk spørgsmål 3

Fagudvalget vurderer, at dupilumab til patienter med svær astma med type 2-inflammation karakteriseret ved forhøjet FeNO uden samtidig eosinofili og allergi *ikke kan kategoriseres*, Jf. Medicinrådets metoder (evidens kan ikke vurderes). Fagudvalget, at effekten ikke kan præciseres yderligere.

Studier på dupilumab vs. placebo viser klinisk relevante effekter på eksacerbationsrate, peroral vedligeholdelsesbehandling med OCS og lungefunktion på tværs af forskellige subpopulationer af svær astma med type 2-inflammation, herunder også den samlede subpopulation med forhøjet FeNO uanset eosinofili- og allergistatus. Der er et betragteligt overlap mellem de forskellige subpopulationer. Der er generelt forholdsvis få og tolerable bivirkninger forbundet med anvendelse af dupilumab. Fagudvalget vurderer derfor, at dupilumab vil være et relevant behandlingsvalg til patientgruppen med svær astma og forhøjet FeNO uden allergi og eosinofili, som opfylder krav for opstart på biologisk behandling, samt at der ikke findes andre biologiske alternativer til disse patienter. Fagudvalget vurderer, at denne patientgruppe er lille og udgør ~2-5 % af de patienter, der er kandidater til biologisk behandling.

10 Andre overvejelser

Fagudvalget bemærker, at de fleste patienter er glade for muligheden for hjemmebehandling, men udtrykker samtidig at der bør være særlig opmærksomhed på, om patienten fortsat tager den øvrige astmamedicin, der er udskrevet, især inhalationsmedicin. Fagudvalget vurderer, at muligheden for hjemmebehandling ikke adskiller sig mellem dupilumab, mepolizumab og omalizumab.

Der ses forhøjet eosinofili ved behandling med dupilumab. Fagudvalget mener, at der bør være opmærksomhed på at følge patientens niveau af eosinofili efter opstart af behandling.

11 Fagudvalgets vurdering af samlet værdi og samlet evidensniveau

Fagudvalget vurderer, at:

- Dupilumab har **ingen dokumenteret merværdi** sammenlignet med mepolizumab til patienter med svær astma karakteriseret ved eosinofili. Evidensens kvalitet vurderes at være **lav**.
- Dupilumab har **ingen dokumenteret merværdi** sammenlignet med omalizumab til patienter med svær astma karakteriseret ved allergi og samtidig eosinofili eller karakteriseret ved allergi og samtidig forhøjet FeNO. Evidensens kvalitet vurderes at være **meget lav**.
- Værdien af dupilumab **kan ikke kategoriseres** sammenlignet med placebo til patienter med forhøjet FeNO uden samtidig eosinofili og uden samtidig allergi. Evidensens kvalitet er ikke vurderet.

12 Rådets vurdering af samlet værdi og samlet evidensniveau

Medicinrådet vurderer, at:

- Dupilumab har **ingen dokumenteret merværdi** sammenlignet med mepolizumab til patienter med svær astma karakteriseret ved eosinofili. Evidensens kvalitet vurderes at være **lav**.
- Dupilumab har **ingen dokumenteret merværdi** sammenlignet med omalizumab til patienter med svær astma karakteriseret ved allergi og samtidig eosinofili eller karakteriseret ved allergi og samtidig forhøjet FeNO. Evidensens kvalitet vurderes at være **meget lav**.
- Værdien af dupilumab **kan ikke kategoriseres** sammenlignet med placebo til patienter med forhøjet FeNO uden samtidig eosinofili og uden samtidig allergi. Evidensens kvalitet er ikke vurderet.

13 Relation til eksisterende behandlingsvejledning

Nærværende vurderingsrapport for dupilumab til svær astma relaterer sig til Medicinrådets behandlingsvejledning for biologiske lægemidler til svær astma [43].

Klinisk spørgsmål 1

Medicinrådets behandlingsvejledning for biologiske lægemidler til svær astma indeholder følgende anbefaling: ”*Mepolizumab, reslizumab og benralizumab er klinisk ligeværdige, og kan ligestilles som tillægsbehandling til patienter med svær eosinofil astma. De ligestilles til 80 % af populationen.”* Med den nuværende viden vurderer fagudvalget, at dupilumab er klinisk ligeværdig med benralizumab, mepolizumab og reslizumab og kan ligestilles som tillægsbehandling til patienter med svær, eosinofil astma. For dupilumab gælder de samme kriterier vedrørende opstart, monitorering, seponering og skift, som er angivet for benralizumab, mepolizumab og reslizumab i behandlingsvejledningen for biologiske lægemidler til svær astma.

Dupilumab har en virkningsmekanisme, der er rettet mod et tidligere led i den inflammatoriske proces i forhold til virkningsmekanismen for anti-IL5-lægemidler. Det kan ikke vurderes, om dupilumab kan anvendes ved manglende effekt af anti-IL5-behandling, da der ikke foreligger data for behandling med dupilumab efter behandling med anti-IL5-lægemidler.

Klinisk spørgsmål 2

I Medicinrådets behandlingsvejledning for biologiske lægemidler til svær astma er omalizumab anbefalet som tillægsbehandling til patienter med svær allergisk astma > 6 år. Med den nuværende viden vurderer fagudvalget, at dupilumab er klinisk ligeværdig med omalizumab og kan ligestilles som tillægsbehandling til patienter med svær, allergisk astma > 12 år, som opfylder indikationskriterierne for både dupilumab og omalizumab. For dupilumab gælder de samme kriterier vedrørende opstart, monitorering, seponering og skift, som er angivet for omalizumab i behandlingsvejledningen for biologiske lægemidler til svær astma.

Dupilumab har en virkningsmekanisme, der er rettet mod et tidligere led i den inflammatoriske proces i forhold til virkningsmekanismen for omalizumab. Det kan ikke vurderes, om dupilumab kan anvendes ved manglende effekt af omalizumabbehandling, da der ikke foreligger data for behandling med dupilumab efter behandling med omalizumab.

Klinisk spørgsmål 3

Medicinrådets behandlingsvejledning for biologiske lægemidler til svær astma omfatter ikke gruppen af patienter med forhøjet FeNO uden samtidig eosinofili og allergi.

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15 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende svær astma

Formand	**Indstillet af**
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16 Versionslog

Version	Dato	Ændring
1.0	22. januar 2020	Godkendt af Medicinrådet.

17 Bilag 1: Studiekarakteristika

I det følgende beskrives karakteristika for de studier, der udgør datagrundlaget for vurderingen af dupilumab, herunder en tabel over studiekarakteristika.

Studiedesign

Dupilumab: alle studier er randomiserede, blindede og placebo kontrollerede. Rabe 2018 (VENTURE) er et glukokortikoidreduktionsstudie, hvor OCS nedtrappes, mens øvrig astmabehandling fastholdes. I de øvrige inkluderede studier fastholdes underliggende astma behandling, herunder evt. OCS, igennem studiet.

Mepolizumab: alle studier er randomiserede, blindede og placebo kontrollerede. Bel 2014 (SIRIUS) er et glukokortikoidreduktionsstudie, hvor OCS nedtrappes, mens øvrig astmabehandling fastholdes. I de øvrige inkluderede studier fastholdes underliggende astma behandling, herunder evt. OCS, igennem studiet.

Omalizumab: alle studier er randomiserede. Tolv studier er dobbeltblindede og placebokontrollerede, de resterende fire studier er ublindede med en aktiv komparator.

Opfølgningstid

Studiernes varighed ligger mellem 16 og 52 uger. Resultater fra studier med opfølgning under 1 år inkluderes ikke for effektmålet eksacerbationsrate. For øvrige effektmål indgår alle studier med tilgængelige data.

Behandlingsintensitet svarende til svær astma

Fagudvalget definerer svær astma i henhold til ERS/ATS' guidelines [8].

Dupilumab: DRI12544 og QUEST har behandlingsintensitet svarende til moderat til svær astma. Studier har som inklusionskriterium minimum en moderat dosis ICS. Omkring 50% af patienter i begge studier får højdosis ICS. Brug af 2nd controller er et inklusionskriterium. Rabe 2018 (VENTURE) har behandlingsintensitet svarende til svær astma og har daglig OCS som et krav grundet design, gennemsnitsdosis på 11,3 mg ved studiestart.

Mepolizumab: Alle studier har behandlingsintensitet svarende til svær astma. Inklusionskriterium er højdosis ICS og brug af en 2nd controller, dosis er ikke angivet. Bel 2014 har daglig OCS som et krav grundet design, gennemsnitsdosis på 12,5-15 mg ved screening. Daglig OCS er tilladt uden at være et krav i øvrige studier. Her får 23-30 % af patienter OCS, med en gennemsnitsdosis på 10-15 mg.

Omalizumab: de fleste studier har krav om højdosis ICS, dog tillades der i 6 studier medium dosis. Øvrig behandling (2nd controller og OCS) varierer.

Systematisk udredning af patienter med mulig svær astma og differentialdiagnoser

Ifølge fagudvalget er det dansk guldstandard systematisk at udrede patienter med mulig svær astma i henhold til DLS' vejledning [1].

I korte træk indebærer det følgende trin:

- bekræftelse af astmadiagnose og hvis relevant udelukkelse af differentialdiagnoser
- tjek af behandlingsbarrierer; sygdomsforståelse, medicinadhærens og korrekt inhalationsteknik
- eliminering af triggers og behandling af forværrende faktorer (komorbiditeter).

Generelt er der i studierne ikke gjort tydeligt og grundigt rede for, hvorvidt der er foretaget systematisk udredning af patienterne forud for inklusion.

Dupilumab: Alle studier ekskluderer nuværende rygere og patienter med mere end 10 pakkeår i anamnesen. I Rabe 2018 er der en optimeringsfase, som mest er beskrevet med henblik på optimering af daglig OCS.

Mepolizumab: Alle studier ekskluderer patienter, der er kendt med dårlig medicinadhærens. Alle studier ekskluderer nuværende rygere og patienter med mere end 10 pakkeår i anamnesen. I Bel 2014 er der en optimeringsfase, som mest er beskrevet med henblik på optimering af daglig OCS.

Omalizumab: En del studier har en run-in med ICS-optimering. De fleste studier ekskluderer rygere eller tidliger rygerer med mere end 10-20 pakkeår i anamnesen.

Graden af astmakontrol - eksacerbationer og ACQ

Dupilumab: Castro 2018 (QUEST) og DRI12544 kræver minimum 1 eksacerbation i det foregående år, og gennemsnittet er på 2,1-2,2. Begge studier har som inklusionskriterium ACQ > 1.5. I VENTURE var der ikke krav til tidligere eksacerbationer men gennesnittet var 2,1. ACQ var ikke et inklusionskriterium.

Mepolizumab: Pavord 2012, Ortega 2014, og Chupp 2017 kræver minimum 2 eksacerbationer i det foregående år og har en gennemsnitlig eksacerbationsrate ved inklusion på mellem 2,7-3,7. Bel har intet krav til tidligere eksacerbationer, men gennemsnittet er 2,9-3,3 i det foregående år. Ingen af studierne har krav til ACQ > 1.5.

Omalizumab: studierne har variende krav til astma kontrol. Nogle studier kræver minimum 2 eller 1 eksacerbation om året, mens andre benytter forskellige mål for astma kontrol og symptomer som inklusionskriterier.

Eosinofili

Dupilumab: eosinofili var ikke et inklusionskriterium. Subgruppe analyser på blod eosinofile celler >150 ved baseline er anvendt i klinisk spørgsmål 1

Mepolizumab: Ortega 2014, Bel 2014 og Chupp 2017 har som inklusionskriterium ≥ 300 eosinofile celler per mikroliter i blodet det foregående år ELLER ≥ 150 celler per mikroliter i blodet ved screening. Pavord har som inklusionskriterium ≥ 300 eosinofile celler per mikroliter i blodet det foregående år ELLER sputum eosinofili ≥ 3 % ELLER FeNo i udåndingsluft ≥ 50 pbb ved screening ELLER dokumenteret øjeblikkelig forværring af astmakontrol ved 25 % reduktion i daglig ICS eller OCS-behandling.

Omalizumab: Ansøger har ikke angivet værdier for eosinofili i omalizumab studierne.

Allergi

Dupilumab: subgruppen med allergisk allergi fra QUEST studiet har total serum IgE ≥ 30 IU/mL og ≥ 1 positiv helårsallergen-specifik IgE ≥ 0,35 kU/L. For alle patienter der var inkluderet i QUEST studiet var den gennemsnitlige IgE på 432 IU/mL ved baseline.

Mepolizumab: allergi er ikke opgjort

Omalizumab: For de fleste omalizumabstudier er niveauet af IgE angivet (ikke angivet i Vignola 2004, Niven 2008 og Rubin 2012). Generelt havde de patienter, der fik omalizumab i studierne, et gennemsnitligt IgE niveau på 173-272 IU/mL ved baseline. Kontrolgrupperne havde lignende niveauer. Dog havde patienterne i Mukherjee studiet fra 2019 et IgE niveau på 965 IU/mL og mens kontrolgruppen havde 482 UI/mL.

Interventioner

Dupilumab: alle fast dosis subkutan administration hver 2. uge, dosis er 200 mg eller 300 mg ved dagligt behov for OCS eller samtidig atopisk eksem.

Mepolizumab: alle: fast dosis hver 4. uge. Ortega 2104, Bel 2014 og Chupp 2017 benytter 100 mg s.c., mens der i Pavord 2012 og Ortega 2014 benyttes 75 mg i.v. administration.

Omalizumab: Omalizumab blev i studierne generelt administreret subkutant med dosis på ≥ 0,016 mg/kg IgE (IU/mL) hver anden eller fjerde uge, baseret på kropsvægt og total serum IgE niveau ved baseline. I ét studie (Mukherjee 2019) var dosis ikke specificeret.

Komparatorer

Dupilumab og mepolizumab: I alle studierne benyttes placebo som komparator. Patienterne fortsætter med den nuværende behandling på nær i Bel 2014 (SIRIUS) og Rabe 2018 (VENTURE), hvor der nedtrappes daglig OCS. Fagudvalget har defineret den underliggende standardbehandling som højdosis ICS med 2nd controller og/eller daglig OCS. Det betyder, at en del af patienterne i dupilumabstudierne, DRI12544 og QUEST, ikke får den definerede standardbehandling, da inklusionskriteriet i disse studier er moderat dosis ICS plus 2nd controller.

Omalizumab: Tre studier er ublindede med følgende komparatorer: best standard care (Ayres 2004), optimised asthma therapy (Bousquet 2011) og LABA + ICS (Rubin 2012). De øvrige studier anvender placebo som komparator.

Karakteristika af studier, der indgår i datagrundlaget for vurderingen af dupilumab.

	Studiedesign	Dosis regime	Opfølg-ningstid	Alder	Effektmål	Eosinofil inflammation	IgE	Tidligere eksacerba-tioner (seneste år)	Inhalations-steroid	2nd controller	Oralt steroid	Antal patienter (randomiserede)
Wenzell 2016 (DRI125544) Corren 2019a (QoL)	Randomized, double-blind, placebo-controlled trial	200 mg q2w 300 mg q2w 200 mg q4w 300 mg q4w	24 uger	≥18 år	Eksacerba-tionsrate FEV_1 ACQ-5 AQLQ SAE Frafald	Ikke inklusions-kriterie Relevant subgruppe: Blod: ≥ 150 celler/µL ved screening	Ikke et krav	≥1	Medium-høj dosis	Skal benytte 2nd controller	Tilladt men ikke et krav	776*
Castro 2018 (QUEST) Castro 2019 (lungefunktion) Corren 2019b (allergiske subgrupper)	Randomized, double-blind, placebo-controlled trial	200 mg q2w 300 mg q2w	52 uger	≥12 år	Eksacerba-tionsrate FEV_1 ACQ-5 AQLQ SAE Frafald	Ikke inklusions-kriterie Relevant subgruppe: Blod: ≥ 150 celler/µL ved screening	Ikke et krav – subgruppen med allergisk allergi ≥ 30 UI/mL	≥1	Medium -høj dosis	Skal benytte 2nd controller	Ikke beskrevet	1902*
Rabe 2018 (VENTURE) Rabe 2019 (lungefunktion)	Randomized, double-blind, placebo-controlled trial	300 mg q2w	24 uger	≥12 år	Eksacerba-tionsrate FEV_1 ACQ-5 AQLQ SAE Frafald	Ikke inklusions-kriterie Relevant subgruppe: Blod: ≥ 150 celler/µL ved screening	Ikke et krav	Intet krav	Medium-højdosis	Skal benytte 2nd controller	5-35 mg/dag prednisolon ækvivalent	210*
Pavord 2012 (DREAM)	Randomized, double-blind, placebo-controlled trial	3 aktive arme i.v., 75 mg, 250 mg, 750, placebo	52 uger	12-74 år	Eksacerba-tionsrate FEV_1 ACQ-6 AQLQ SAE Frafald	i det foregående år: Sputum: ≥ 3 % eller FE_{NO}: ≥ 50 ppb eller Blod: ≥ 300 celler/µL	Ikke et krav	≥ 2	Højdosis	Skal benytte 2nd controller	Tilladt, men ikke et krav	621
Ortega 2014 (MENSA)	Randomized, double-blind, double-dummy, placebo-	2 aktive arme, 100 mg s.c., 75 mgi.v. placebo i.v. og placebo s.c.	32 uger	Over 12 år	Eksacerba-tionsrate FEV_1 ACQ-5 SGRQ SAE Frafald	Blod: ≥ 150 celler/µL ved screening eller ≥ 300 celler/µL i det foregående år	Ikke et krav	≥ 2	Højdosis	Skal benytte 2nd controller	Tilladt, men ikke et krav	576

	controlled trial											
Bel 2014 (SIRIUS)	Randomized, double-blind, placebo-controlled trial with four phases	100 mg s.c., placebo	24 uger	Over 12 år	Eksacerbationsrate OCS-reduktion FEV_1 ACQ-5 SGRQ SAE Frafald	Blod: ≥ 150 celler/µL ved screening eller ≥ 300 celler/µL i det foregående år	Ikke et krav	Intet krav	Højdosis	Skal benytte 2nd controller	5-35 mg/dag i de seneste 6 måneder	135
Chupp 2017 (MUSCA)	Randomized, double-blind, placebo-controlled trial	100 mg s.c., placebo	24 uger	Over 12 år	SGQR FEV_1 ACQ-5 Eksacerbationsrate SAE Frafald	Blod: ≥ 150 celler/µL ved screening eller ≥ 300 celler/µL i det foregående år	Ikke et krav	≥ 2	Højdosis	Skal benytte 2nd controller	Tilladt, men ikke et krav	556
Busse 2001 (main) *Finn 2003 (QoL)* *Lanier 2003 (extension)*	Randomised, double-blind, placebo-controlled trial	Jf. Indikation	52 uger	12-75 år	Eksacerbationer FEV_1 AQLQ SAE Frafald	-	Total serum IgE 30- 700 IU/mL	Intet krav	Medium-højdosis (420-840 µg BDP)	Ikke tilladt	Ikke tilladt	525
Soler 2001 (main) *Buhl 2002a (QoL)* *Buhl 2002b (extension)*	Randomised, double-blind, placebo-controlled trial	Jf. Indikation	52 uger	12-75 år	Eksacerbationer FEV_1 AQLQ SAE Frafald	-	Total serum IgE 30-700 IU/mL	Intet krav	Højdosis (500-1200 µg BDP)	Ikke tilladt	Ikke tilladt	546
Holgate 2004	Randomised, double-blind, placebo-controlled trial	Jf. Indikation	32 uger	12-75 år	Eksacerbationer FEV_1 AQLQ SAE Frafald	-	Total serum IgE 30- 700 IU/mL	Ikke beskrevet	Højdosis (≥ 1000 µg fluticasone)	LABA tilladt men ikke et krav	Tilladt men ikke et krav	246

Vignola 2004 (SOLAR)	Randomised, double-blind, placebo-controlled trial	Jf. Indika-tion	28 uger	12-75 år	Eksacerba-tioner FEV_1 AQLQ SAE Frafald	-	Total serum IgE 30- 1300 IU/mL	≥ 2 eller ≥ 3 inden for de seneste 2 år	Medium-højdosis (400-2400 µg budesonide)	LABA tilladt men ikke et krav	Ikke tilladt	405
Ayres 2004 (main) *Niven 2008 (severe subgroup)*	Randomised, open-label trial omalizumab *vs* BSC	Jf. Indika-tion	52 uger	12-75 år	Eksacerba-tioner FEV_1 AQLQ SAE Frafald Sygefravær	-	Total serum IgE 30- 700 IU/mL	≥ 2 hvoraf 1 havde krævet akut kontakt til skadestue eller indlæggelse	Medium-højdosis (≥ 400 µg BDP [unge] ≥ 800 µg [voksne])	LABA tilladt men ikke et krav	Tilladt men ikke et krav	312 svær astma subgruppe: OMA (N=115), komparator (N=49)
Humbert 2005 (INNOVATE)	Randomised, double-blind, placebo-controlled trial	Jf. Indika-tion	28 uger	12-75 år	Eksacerba-tioner FEV_1 Asthma symptoms AQLQ SAE Frafald	-	Total serum IgE 30- 700 IU/mL	≥ 2 eller 1 alvorlig eksacerbation med akut kontakt til skadestue eller indlæggelse	Højdosis (≥ 800 µg BDP eller ≥ 400 µg FT)	LABA er et krav	Tilladt op til 20 mg/dag men ikke et krav	482
Bousquet 2011 (main) *Siergiejko 2011 (OCS subgroup*)	Randomised, open-label trial omalizumab *vs* OAT	Jf. Indika-tion	32 uger	12-75 år	Eksacerba-tioner FEV_1 OCS-reduktion ACQ SAE Frafald	-	Total serum IgE 30-700 IU/mL	≥ 1	Højdosis (> 1000 µg BDP eller equivalent)	LABA er et krav andre controllere er tilladt	Tilladt men ikke et krav	400 OCS subgruppe 82
Hanania 2011	Randomised, double-blind, placebo-controlled trial	Jf. Indika-tion	48 uger	12 -75 år	Eksacerba-tioner AQLQ SAE Frafald	-	Total serum IgE 30-700 IU/mL	> 1 årlig eksacerbation plus ekstra krav om nat- eller dagsymp-tomer dokumenteret i to uger af run-in fasen	Højdosis (≥ 500 µg fluticasone or equivalent)	LABA er et krav andre controllere er tilladt	Tilladt men ikke et krav	848
Bardelas 2012	Randomised, double-blind,	Jf. Indika-tion	24 uger	≥ 12 år	Eksacerba-tioner FEV_1	-	Total serum IgE 30- 700 IU/mL	Intet krav	Minimum medium dosis	Skal benytte 2nd controller	Ikke tilladt	271

	placebo-controlled trial				Astmakontrol Frafald Sygefravær							
Rubin 2012 (QUALITX)	Randomised, open-label,	Jf. Indikation	20 uger	12-75 år	Eksacerbationer FEV_1 AQLQ SAE Frafald	-	Total serum IgE 30-700 IU/mL	≥ 2	Højdosis > 500 µg flucticasone eller ækvivalent	LABA er et krav	Tilladt men ikke et krav	116
Busse 2013	Randomised, double-blind, placebo-controlled trial	Jf. Indikation	24 uger	12-75 år	Eksacerbationer FEV_1 SAE Frafald	-	Total serum IgE: 30-1300 IU/mL	Intet krav	Medium-højdosis	Controller tilladt men ikke et krav	Ikke tilladt	328
Li 2016	Randomised, double-blind, placebo-controlled trial	Jf. Indikation	24 uger	18-75 år	Eksacerbationer FEV_1 ACQ AQLQ SAE Frafald	-	Total serum IgE 30-700 IU/mL	≥ 2 eller ≥ 3 inden for de seneste 2 år	Medium-højdosis (> 500 µg BDP eller equivalent)	LABA er et krav	Ikke beskrevet	609
Mukherjee 2019	Randomised, double-blind, placebo-controlled trial	Jf. Indikation	32 uger	18-75 år	Eksacerbationer FEV_1 ACQ-5 SAE Frafald	-	Forhøjet serum IgE ikke yderligere specificeret	Ikke specificeret	Højdosis < 1500 µg flucticasone eller ækvivalent	Ikke tilladt	Tilladt	9

Omalizumab was generally administered SC at a dose approximately ≥ 0.016 mg/kg IgE (IU/mL) every 2 or 4 weeks, based on the patient's body weight and baseline total serum IgE level. In Mukherjee 2019, the dose was not specified. References in italics are secondary publications of the primary reference above. ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; AQLQ, Asthma Quality of Life Questionnaire; BDP, beclomethasone dipropionate; beta2-AR, beta2-adrenoceptors; BSC, best standard care; CT, conventional therapy; ER, emergency room; FEV_1, forced expiratory volume in 1 s; FT, fluticasone propionate; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroids; IgE, immunoglobulin E; LABA, long-acting beta agonist; mITT, modified intention-to-treat; NAEPP, National Asthma Education and Prevention Program Expert Panel Report; OAT, optimised asthma therapy; OCS, oral corticosteroids; OMA, omalizumab; PBO, placebo; PC20, provocative concentration of inhaled methacholine needed to reduce FEV_1 by 20 %; PEF, peak expiratory flow; QoL, quality of life; SABA, short-acting bronchodilator; SAE, serious adverse event; SC, subcutaneously; TASS, Total Asthma Symptom Severity.

** inkluderer alle doser, frekvenser og subgrupper*

18 Bilag 2 Baselinekarakteristik

Studie	Female %	Etnicitet kaukasisk %	Alder gennemsnit år	BMI, gennemsnit kg/m^2	Antal eksacerbationer indenfor seneste år, gennemsnit	LABA og andre 2nd controllers	ICS dosis (fluticasone propionate ækvivalente)	% som får OCS, daglig dosis gennemsnit prednisolonækvivalent	Præbronkodilator FEV$_1$, gennemsnit L/gennemsnit % af forventet
dupilumab									
Wenzell 2016 (DRI125544) Corren 2019a (QoL) Corren 2019b (allergi subgruppe)	63 %	78 %	48,6	29,45	2,17	100 % Inklusions-kriterium	51% højdosis	Ikke angivet	1,84/ 60,8 %
Castro 2018 (QUEST) Castro 2019 (lungefunktion)	61,3-67,9 %	Ikke angivet	47,9-48,2	29,05-29,76	2,02-2,31	100 % Inklusions-kriterium	50,2-54,3 % højdosis	Ikke angivet	1,75-1,78/ 58,4 %
Rabe 2018 (VENTURE) Rabe 2019 (lungefunktion)	60-61 %	97-100	50,7-51,9	28,88-29,77	2,01-2,17	100 % inklusions-kriterium	Inklusionskrite-rium: > 500 µg	inklusionskriterium Før justeringsperiode: 11,83-11,79 mg/dag Efter justeringsperiode: 11,75-11,75 mg/dag	1,53-1,63 /52,2 %
mepolizumab									
Pavord 2012 (DREAM)	63-68 %	90-91 %	46,4-50,2	28,3-28,4	3,7	LABA: 93-97 % Inklusions-kriterium	ikke angivet	29-30 % 10 mg	1,81-1,9
Ortega 2014 (MENSA)	55-60 %	77-79 %	49-51	27,6-28	3,5-3,8	Ikke angivet Inklusions-kriterium	ikke angivet	23-27 % 12-15,1 mg	1,73-1,86
Chupp 2017 (MUSCA)	54-64 %	ikke angivet	49,8-52,1	27,9-28,5	2,7-2,9	LABA: 99 -> 99 % Inklusions-kriterium	ikke angivet	23-24 % 12,6-13,4 mg	1,7-1,8
Bel 2014 (SIRIUS)	45-64 %	92-97 %	50	27,8-29,5	2,9-3,3	ikke angivet inklusions-kriterium	ikke angivet	Inklusionskriterium Ved screening: 12,5-15 mg Efter optimering: 10,0-12,5 mg	1,9-2

Omalizumab									
Busse 2001 (main) Finn 2003 (QoL)	59,0	89,0	39,2	Ikke angivet	Ikke angivet	Ikke tilladt	569,0	Ikke tilladt	68,0 %
Lanier 2003 (extension)	58,3		39,1	Ikke angivet	Ikke angivet	Ikke tilladt	558,5	Ikke tilladt	68,5 %
Soler 2001 (main) Buhl 2002a (QoL)	50-51	83,1-91,2	39,5-40,5	Ikke angivet	Ikke angivet	Ikke tilladt	770,6-771,7	Ikke tilladt	69,9 %
Buhl 2002b (extension)	51,0		40,0	Ikke angivet	Ikke angivet	11-17	770,5	Ikke tilladt	70,0 %
Holgate 2004	60,9	Ikke angivet	40,8	Ikke angivet	Ikke angivet	43-49	1369,0	Ikke angivet	64,5 %
Vignola 2004 (SOLAR)	55 %	Ikke angivet	38,4	Ikke angivet	2,1	36-41	871,6	Ikke tilladt	78,2 %
Ayres 2004 (main)	70,5	Ikke angivet	38,4	Ikke angivet	Ikke angivet	78	2000,0	18-23	71,4 %
Niven 2008 (severe subgroup)	73 %	Ikke angivet	39,0	Ikke angivet	Ikke angivet	97-100		65-80	64,9 %
Humbert 2005 (INNOVATE)	66,6	78,0	43,3	Ikke angivet	4-4,7	LABA påkrævet	2330,0	21-24	61,3 %
Bousquet 2011 (main)	64,8	Ikke angivet	45,7	Ikke angivet	2,1	99,8	99,8	18-22	62,4 %
Siergiejko 2011 (OCS subgroup)	66 %	100,0	45,4	74,4	2,7-3,3	LABA påkrævet	Ikke angivet	100 %, 13 mg	61,1 %
Hanania 2011	65,7	74,4	44,5	31,8	1,9-2	83,0	Ikke angivet	17	64,9 %
Bardelas 2012	66,4	75,3	41,3	Ikke angivet	Ikke angivet	77-85	Ikke angivet	Ikke tilladt	75,5 %
Rubin 2012 (QUALITX)	77 %	66 %	44,5	Ikke angivet	Ikke angivet	LABA påkrævet	Ikke angivet	Ikke angivet	Ikke angivet
Busse 2013	69,0	70,5	37,0	Ikke angivet	Ikke angivet	79-80	508,2	Ikke tilladt	85,8 %
Li 2016 (Chinese)	53,9	0,0	46,5	Ikke angivet	2,2-2,3	LABA påkrævet	Ikke angivet	Ikke angivet	63,3 %
Mukherjee 2019	20-25	Ikke angivet	54,5-58,8	Ikke angivet	Ikke angivet	Ikke tilladt	Ikke angivet	25 %, 12,5 mg	51,6-60 %

19 Bilag 3: Vurdering af evidensens kvalitet

Til vurdering af evidensens kvalitet anvendes GRADE som fremgangsmåde. Her indgår følgende domæner: Risiko for bias, inkonsistens, indirekthed, unøjagtighed samt andre overvejelser. Domænerne gennemgås i de følgende afsnit for hvert klinisk spørgsmål.

19.1 Cochrane Risk of Bias

Dupilumabstudier

Vurdering af risiko for bias ved Cochranes RoB 2.0 assessment tool.

Tabel 6: QUEST. Castro et al. 2018. NCT02414854

Bias	Risk of bias	Elaboration
Risk of bias arising from the randomization process	**Low**	*Randomization was conducted by means of interactive voice‐Web response technology.*
Risk of bias due to deviations from the intended interventions		
Effect of assignment to intervention	**Low**	*Double-blind, placebo-controlled trial. Efficacy analyses were performed in the intention-to-treat population, defined as all the patients who underwent randomization; data were analyzed according to the assigned intervention, whether an intervention was received or not.*
Missing outcome data	**Low**	*Flowchart fremgår ikke, men 1902 patients underwent randomization, 1897 received the assigned intervention, Ved analyse: 1434 patients completed the 52-week intervention period, 235 had treatment ongoing, and 228 discontinued the intervention.*
Risk of bias in measurement of the outcome	**Low**	*An independent data and safety monitoring committee conducted blinded monitoring of patient safety data. Studiet er dobbeltblindet, derfor er der sandsynligvis ikke forskel på effektmålingen mellem grupperne.*
Risk of bias in selection of the reported result	**Some concerns**	*På clinicaltrials.gov fremgår det, at antallet af sekundære effektmål er ændret – den 8. april 2015 var der 7, mens der den 19. oktober 2018 var 37.*
Overall risk of bias	**Some concerns**	*Studiet vurderes at være metodisk velgennemført i forhold til randomisering, blinding og dataindsamling.* *Dog vurderes der at være risiko for, at de rapporterede resultater for sekundære effektmål er selekteret, efter der er gennemført analyser for 37 effektmål frem for de 7, der var protokolleret.*

Tabel 7: VENTURE. Rabe et al. 2018. NCT02528214

Bias	Risk of bias	Elaboration
Risk of bias arising from the randomization process	**Low**	*Randomization was conducted by means of interactive voice‐Web response technology.*
Risk of bias due to deviations from the intended interventions		
Effect of assignment to intervention	**Low**	*Double-blind, placebo-controlled trial. Efficacy analyses were performed in the intention-to-treat population, which included all the patients who underwent randomization; data were analyzed according to the assigned trial group, regardless of the trial regimen received.*
Missing outcome data	**Low**	*Two patients in the dupilumab group and one in the placebo group discontinued the trial or had missing data regarding the oral glucocorticoid dose at week 24.*

Risk of bias in measurement of the outcome	**Low**	*An independent data and safety monitoring committee conducted blinded monitoring of patient safety data. Studiet er dobbeltblindet, derfor er der sandsynligvis ikke forskel på effektmålingen mellem grupperne.*
Risk of bias in selection of the reported result	**Some concerns**	*På clinicaltrials.gov fremgår det, at primære effektmål er ændret 2 år efter final data collection data for primary outcome measure – desuden er der tilføjet 7 effektmål.*
Overall risk of bias	**Some concerns**	*Studiet vurderes at være metodisk velgennemført i forhold til randomisering, blinding og dataindsamling.* *Dog vurderes der at være risiko for, at de rapporterede resultater er selekterede, idet det primære effektmål er ændret efter dataindsamlingens afslutning, og der er tilkommet yderligere effektmål (ifølge clinicaltrials.gov).*

Tabel 8: DRI12544. Wenzel et al. 2016. NCT01854047

Bias	**Risk of bias**	**Elaboration**
Risk of bias arising from the randomization process	**Low**	*Patients were randomised (1:1:1:1:1) by a centralized treatment allocation system. Patients were randomly allocated according to a central randomisation scheme provided by an interactive voice response system or an interactive web response system.* *Der er ikke angivet baselinekarakteristika opdelt på dupilumab versus placebo.*
Risk of bias due to deviations from the intended interventions		
Effect of assignment to intervention	**Low**	*Double-blind, placebo-controlled trial. Study patients, investigators, and site personnel remained masked to study treatment. Intention to treat analyses.*
Missing outcome data	**Low**	*Ikke stor forskel på antallet af drop-outs, som ligger på 6-13 % ved 24 uger (figur 1). Missing data-points were not imputed.*
Risk of bias in measurement of the outcome	**Low**	*An independent data monitoring committee reviewed safety data throughout the trial. Ingen beskrivelse af øvrig dataindsamling.*
Risk of bias in selection of the reported result	**High**	*På clinicaltrials.gov fremgår det, at primære effektmål er ændret 2,5 år efter final data collection data for primary outcome measure – desuden er der tilføjet 16 effektmål.*
Overall risk of bias	**Some concerns**	*Studiet vurderes at være metodisk velgennemført i forhold til randomisering, blinding og dataindsamling.* *Dog vurderes der at være risiko for, at de rapporterede resultater er selekterede, idet det primære effektmål er ændret efter dataindsamlingens afslutning, og der er tilkommet yderligere effektmål (ifølge clinicaltrials.gov).*

Mepolizumabstudier

Risk of bias er vurderet ved Cochrane Risk of Bias Tool. I Pavord 2012 er der ikke gjort rede for *blindingen af outcome assessors*, hvorfor risikoen for bias vurderes at være uklar. Ingen øvrige risici er identificeret. Samlet set vurderes studierne at have lav risiko for bias for alle effektmål.

Mepolizumab	**Random sequence generation (selection bias)**	**Allocation concealment (selection bias)**	**Blinding of participants and personnel (performance bias)**	**Blinding of outcome assessement (detection bias)**	**Incomplete outcome data (attrition bias)**	**Selective reporting (reporting bias)**	**Other bias**
Pavord 2012 (DREAM)	low	low	low	unclear	low	low	low
Ortega 2014 (MENSA)	low	low	low	low	low	low	low
Chupp 2017 (MUSCA)	low	low	low	low	low	low	low
Bel 2014 (SIRIUS)	low	low	low	low	low	low	low

Omalizumabstudier

Risk of bias er vurderet ved Cochrane Risk of Bias Tool. Der vurderes generelt at være risiko for bias for alle effektmål undtaget *frafald*.

Fem studier (Ayres 2004, Bousquet 2011, Hoshino 2012, Rubin 2012 og Siergiejko 2011) har et ublindet design og dermed høj risiko for bias. Lanier 2003 vurderes at have høj risiko for bias på baggrund af et stort og ulige frafald i grupperne. Chanez 2010 har høj risiko for bias i domænet 'other bias', idet studiet formentlig ikke har statistisk styrke til at estimere relevante effektmål, da hovedformålet var at se på "reduction of Fc3RI expression on basophils".

Generelt er der i mange af studierne mangelfuld beskrivelse af procedurerne, hvilket medfører, at der for mange af domænerne vurderes at være uklar risiko for bias. Vurderingen af risiko for bias for de enkelte effektmål beror på, hvilke studier der er medtaget i analysen. De to metodisk bedste og bedst beskrevne studier, Busse 2011 og Busse 2013, har begge lav risiko for bias i alle domæner.

I Mukherjee 2019-studiet er der kun inkluderet 11 patienter, hvilket formentligt er for få til at påvise en forskel i de effektmål, der ønskes vurderet. Data fra studiet er kun inkluderet i analysen for frafald af patienter i studiet.

Omalizumab	**Random sequence generation (selection bias)**	**Allocation concealment (selection bias)**	**Blinding of participants and personnel (performance bias)**	**Blinding of outcome assessement (detection bias)**	**Incomplete outcome data (attrition bias)**	**Selective reporting (reporting bias)**	**Other bias**
Busse 2001 (main) Finn 2003 (QoL)	unclear	unclear	low	unclear	low	unclear	low
Lanier 2003 (extension)	unclear	unclear	low	unclear	high	unclear	low
Soler 2001 (main) Buhl 2002a (QoL)	unclear	unclear	low	unclear	unclear	unclear	low
Buhl 2002b (extension)	unclear	unclear	low	unclear	unclear	unclear	low
Holgate 2004	unclear	unclear	low	low	low	unclear	low
Vignola 2004 (SOLAR)	unclear	unclear	low	unclear	unclear	unclear	low
Ayres 2004 (main)	unclear	unclear	high	high	low	unclear	low
Niven 2008 (severe subgroup)	unclear	unclear	high	high	unclear	unclear	low
Humbert 2005 (INNOVATE)	unclear	unclear	low	low	low	unclear	low
Bousquet 2011 (main)	low	low	high	high	low	unclear	high
Siergiejko 2011 (OCS subgroup)	unclear	unclear	high	high	low	low	low

Hanania 2011	low	low	low	low	low	unclear	low
Bardelas 2012	unclear	unclear	unclear	unclear	low	unclear	low
Rubin 2012 (QUALITX)	unclear	unclear	high	high	low	unclear	low
Busse 2013	low	low	low	low	low	low	low
Li 2016	unclear	unclear	low	unclear	low	low	low
Mukherjee 2019	unclear	low	unclear	unclear	high	high	low

19.2 GRADE evidensprofiler

Ifølge GRADE er den samlede evidens for en indirekte sammenligning lig med den laveste kvalitet af evidensen for de kritiske effektmål fra de studier, der indgår, vurderet ud fra de fem domæner.

19.2.1 Klinisk spørgsmål 1

Dupilumab vs. mepolizumab til patienter > 12 år med svær astma med type 2-inflammation karakteriseret ved eosinofili

Nedenfor ses GRADE-profiler hvor evidensens kvalitet er vurderet for de enkelte effektmål fra henholdsvis dupilumab- og mepolizumabstudierne. For klinisk spørgsmål 1 er de kritiske effektmål med lavest vurderet evidenskvalitet, eksacerbationsrate samt peroral vedligeholdelsesbehandling med kortikosteroid (lav evidenskvalitet).

Samlet set er evidensens kvalitet for klinisk spørgsmål 1 derfor vurderet at være lav.

Risk of bias

Der ikke nedgraderet for risk of bias for hverken dupilumab- eller mepolizumabstudierne, som vurderes at være metodisk velgennemført i forhold til randomisering, blinding og dataindsamling. Dog vurderes der at være risiko for selektionsbias i dupilumabstudierne, idet der er ændret på effektmålene efter afslutning af dataindsamlingen. Dette vurderes imidlertid ikke at medføre høj risiko for bias i denne sammenhæng, da de effektmål, der er medtaget, er prædefinerede i protokollen.

Indirekthed

Evidensens kvalitet er nedgraderet for indirekthed for alle effektmål fra dupilumabstudierne, da fagudvalget vurderer, at evidensen er indirekte i forhold til patientpopulationen og den underliggende standardbehandling, som ikke er direkte overførbar til danske forhold. Dette skyldes især inklusion af patienter med moderat sværhedsgrad af astma og den manglende systematiske udredning i alle studier, hvilket ikke afspejler dansk standard. For mepolizumabstudierne er der ikke nedgraderet for indirekthed.

Inkonsistens

Der nedgraderes for inkonsistens på effektmålene eksacerbationsrate samt peroral vedligeholdelsesbehandling med kortikosteroid, fordi der kun er data fra ét studie (fra henholdsvis dupilumab- og mepolizumabstudierne). Når der kun er data fra ét studie, kan det ikke vurderes, om data fra flere studier ville have vist et ensartet resultat, eller om resultaterne fra dette studie er ekstremt.

Imprecision (unøjagtighed)

Der er nedgraderet et niveau for unøjagtighed for effektmålene ophør af peroral vedligeholdelsesbehandling med kortikosteroid og livskvalitet fra mepolizumabstudierne. Der nedgraderes, fordi konfidensintervallet er bredt og indeholder estimater, der ville føre til forskellige konklusioner.

Andre overvejelser

Der er ikke fundet anledning til at nedgradere på baggrund af andre overvejelser. Der vurderes ikke at være nok studier (< 10 studier) til at give en retmæssig vurdering af eventuel publikationsbias.

GRADE-profil dupilumab vs. placebo/standardbehandling (QUEST + VENTURE + DRI12544)

Kvalitetsvurdering							Antal patienter		Effekt		Kvalitet (GRADE)	Kritisk / vigtigt
Antal studier	Studiedesign	Risk of bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	dupilumab	placebo	Relativ [95 % CI]	Absolut		
Årlig eksacerbationsrate, reduktion												
1	Randomised trial	Not serious [a]	Serious [b]	Serious [c]	Not serious	None	1264	638	0,44 [0,34; 0,58]	-0,6 [-0,8; 0,3]	⊕⊕◯◯ LOW	CRITICAL
Risk ratio: andel der opnår 0 eksacerbationer												
1	Randomised trial	Not serious [a]	Serious [b]	Serious [c]	Not serious	None	1264	638	1,33 [1,16; 1,51]	18 % [10; 25]	⊕⊕◯◯ LOW	CRITICAL
Peroral vedligeholdelsebehandling med kortikosteroid (Gennemsnitlig %-reduktion i daglig dosis)												
0												CRITICAL
Peroral vedligeholdelsebehandling med kortikosteroid (Andel af patienter som ophører)												
1	Randomised trial	Not serious [a]	Serious [b]	Serious [c]	Not serious	None	103	107	1,85 [1,22; 2,81]	25 % [10; 40]	⊕⊕◯◯ LOW	CRITICAL
Peroral vedligeholdelsebehandling med kortikosteroid (Andel af patienter som opnår ≥ 50 % reduktion)												
1	Randomised trial	Not serious [a]	Serious [b]	Serious [c]	Not serious	None	103	107	1,57 [1,23; 2,0]	30 % [16; 45]]	⊕⊕◯◯ LOW	CRITICAL
Gennemsnitlig ændring i lungefunktion, FEV_1												
3	Randomised trials	Not serious [a]	Not serious	Serious [c]	Not serious	None			-	A: 210 mL [15; 280] B: 250 mL [180; 320] C: 220 mL [60; 380]	⊕⊕⊕◯ MODERATE	IMPORTANT
Astmakontrol, ændring (ACQ)												
3	Randomised trials	Not serious [a]	Not serious	Serious [c]	Not serious	none			-	A1: -0,48 [-0,72; 0,23] A2: -0,42 [-0,58; -0,26] C: -0,47 [-0,76; -0,18]	⊕⊕⊕◯ MODERATE	IMPORTANT
Livskvalitet, ændring												
2	Randomised trial	Not serious [a]	Not serious	Serious [c]	Not serious	none				A1: 0,49 [0,24; 0,75] A2: 0,26 [0,09; 0,42] C: 0,35 [0,07; 0,63]	⊕⊕⊕◯ MODERATE	IMPORTANT
Serious adverse events (antal)												
3	Randomised trials	Not serious [a]	Not serious	Serious [c]	Not serious	none	68/882 7,7 %	41/578 7 %	1,19 [0,50; 2,84] 0,93 [0,59; 1,48] 1,56 [0,58; 4,22]	-	⊕⊕⊕◯ MODERATE	IMPORTANT
Frafald												
3	Randomised trials	Not serious [a]	Not serious	Serious [c]	Not serious	none	83/882 9,4 %	55/582 9,5 %	0,98 [0,45; 2,15] 0,93 [0,64; 1,34] 0,42 [0,08; 2,09]	-	⊕⊕⊕◯ MODERATE	IMPORTANT
Sygefravær (ændring, antal dage) - not reported												
0												IMPORTANT

Kvalitetsvurdering							Antal patienter		Effekt		Kvalitet (GRADE)	Kritisk / vigtigt
Antal studier	Studiedesign	Risk of bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	dupilumab	placebo	Relativ [95 % CI]	Absolut		

CI: *Confidence interval;* ***RR:*** *Risk ratio;* ***MD:*** *Mean difference;* ***SMD:*** *Standardised mean difference*
A: 24-32 uger (A1: DRI12544, A2: QUEST)
B: 52 uger
C:OCS-afhængig astma 24 uger

a. *Studiet/studierne vurderes at være metodisk velgennemførte i forhold til randomisering, blinding og dataindsamling. Dog vurderes der at være risiko for selektionsbias, idet der er ændret på effektmålene efter afslutning af dataindsamlingen. Dette vurderes imidlertid ikke at medføre høj risiko for bias i denne sammenhæng, da de effektmål, der er medtaget, er prædefinerede i protokollen.*

b. *Kun et studie ligger til grund for dette effektmål. Der nedgraderes for inkonsistens, idet det ikke ud fra ét studie kan vurderes, om data fra flere studier ville have vist et ensartet resultat, eller om dette studie er ekstremt.*

c. *Generelt er der i studierne manglende systematisk udredning for svær astma, og studiepopulationerne inkluderer patienter med moderat astma. Dette svarer ikke direkte til danske forhold. Derfor nedgraderes ét niveau for indirekthed.*

GRADE-profil mepolizumab vs. placebo (DREAM + MENSA + MUSCA + SIRIUS)

Kvalitetsvurdering							Antal patienter		Effekt		Kvalitet (GRADE)	Kritisk / vigtigt
Antal studier	Studiedesign	Risk of bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	mepolizumab	placebo	Relativ: RR [95 % CI]	Absolut, RD [95 % CI]		
Årlig eksacerbationsrate, reduktion												
1	randomised trial	Not serious	Serious [a]	Not serious	Not serious	None	153	155	0,52 [0,39; 0,69]	-1,16	⊕⊕⊕◯ MODERATE	CRITICAL
Risk ratio: andel der opnår 0 eksacerbationer												
1	randomised trial	Not serious	Serious [a]	Not serious	Not serious	None	153	155	1,65 [1,26; 2,16]	21 % [11; 32]	⊕⊕⊕◯ MODERATE	CRITICAL
Peroral vedligeholdelsebehandling med kortikosteroid (Gennemsnitlig %-reduktion i daglig dosis)												
0												CRITICAL
Peroral vedligeholdelsebehandling med kortikosteroid (Andel af patienter som ophører)												
1	randomised trial	Not serious	Serious [a]	Not serious	Serious [b]	None	69	66	1,91 [0,69; 5,30]	7 % [-4; 17]	⊕⊕◯◯ LOW	CRITICAL
Peroral vedligeholdelsebehandling med kortikosteroid (Andel af patienter som opnår ≥ 50 % reduktion)												
1	randomised trial	Not serious	Serious [a]	Not serious	Not serious	None	69	66	1,61 [1,07; 2,41]	20 % [4; 37]	⊕⊕⊕◯ MODERATE	CRITICAL
Gennemsnitlig ændring i lungefunktion, FEV_1												
4	randomised trials	Not serious	Not serious	Not serious	Not serious	None	871	671	-	A1: 120 mL [47; 192] A2: 99 mL [38; 160] B: 61 mL [-39; 161] C: 114 mL [-42; 271]	⊕⊕⊕⊕ HIGH	IMPORTANT
Astmakontrol, ændring (ACQ)												
4	randomised trials	Not serious	Not serious [c]	Not serious	Not serious	none	873	673	-	A1: -0,4 [-0,6; 0,2] A2: -0,43 [-0,56; -0,29] B: -0,16 [-0,39; 0,07] C: -0,52 [-0,87; -0,17]	⊕⊕⊕⊕ HIGH	IMPORTANT
Livskvalitet, ændring												

Kvalitetsvurdering							Antal patienter		Effekt		Kvalitet (GRADE)	Kritisk / vigtigt
Antal studier	**Studiedesign**	**Risk of bias**	**Inkonsistens**	**Indirekthed**	**Unøjagtighed**	**Andre overvejelser**	**mepolizumab**	**placebo**	**Relativ: RR [95 % CI]**	**Absolut, RD [95 % CI]**		
4	randomised trials	Not serious	Not serious [c]	Not serious	Serious [b]	None	872	672	-	A1: -7,7 [-10,5; -4,9] A2: -6,7 [-9,1; -4,4] B: 0,08 [-0,16; 0,32] C: -5,8 [-10,6; -1,0]	⊕⊕⊕◯ MODERATE	IMPORTANT
Serious adverse events (antal)												
4	randomised trials	Not serious	Not serious [d]	Not serious	Not serious	None	66/880 7,5 %	86/690 12,5 %	0,81 [0,47; 1,40] 0,55 [0,34; 0,90] 0,69 [0,37; 1,31] 0,08 [0,01; 0,60]	-	⊕⊕⊕⊕ HIGH	IMPORTANT
Frafald												
4	randomised trials	Not serious	Not serious	Not serious	Not serious	None	57/881 6,5 %	58/689 8,4 %	0,87 [0,53; 1,43] 1,03 [0,53; 2,01] 0,36 [0,13; 0,99] 0,72 [0,17; 3,08]	-	⊕⊕⊕⊕ HIGH	IMPORTANT
Sygefravær (ændring, antal dage) - not reported												
0												IMPORTANT

CI: *Confidence interval;* ***RR:*** *Risk ratio;* ***MD:*** *Mean difference;* ***SMD:*** *Standardised mean difference*
A: 24-32 uger (A1: MUSCA, A2: MENSA).
B: 52 uger.
C: OCS-afhængig astma 24 uger.
a. Kun et studie ligger til grund for dette effektmål. Der nedgraderes for inkonsistens, idet det ikke ud fra ét studie kan vurderes, om data fra flere studier ville have vist et ensartet resultat, eller om dette studie er ekstremt.
b. Konfidensintervallet er bredt og indeholder estimater, der ville føre til forskellige konklusioner. Derfor nedgraderes for unøjagtighed.
c. Der vurderes at være heterogenitet. En mulig forklaring kan være forskel i studievarighed (24-32 vs. 52 uger), hvorfor der ikke nedgraderes for inkonsistens.
d. Der vurderes at være heterogenitet. Det er subgruppen af patienter med OCS-afhængig astma, der adskiller sig. Dette kan forklare de forskellige resultater, hvorfor der ikke nedgraderes for inkonsistens.

19.2.2 Klinisk spørgsmål 2

Dupilumab vs. omalizumab til patienter > 12 år med svær astma med type 2-inflammation karakteriseret ved allergi og samtidig eosinofili eller karakteriseret ved allergi og samtidig forhøjet FeNO

Nedenfor ses GRADE-profiler, hvor evidensens kvalitet er vurderet for de enkelte effektmål fra henholdsvis dupilumab- og omalizumabstudierne. For klinisk spørgsmål 2 er de kritiske effektmål med lavest vurderet evidenskvalitet eksacerbationsrate. For sammenligningen mellem dupilumab og omalizumab er der nedgraderet yderligere ét niveau for indirekthed, da studierne adskiller sig fra hinanden (meget lav evidenskvalitet). Der er ikke fundet data, der gør det muligt at sammenligne dupilumab og omalizumab med hensyn til effektmålet peroral vedligeholdelsesbehandling med kortikosteroid. Selv om dette er er kritisk effektmål, er det samlede evidensniveau ikke nedgraderet yderligere af den grund.

Samlet set er evidensens kvalitet for klinisk spørgsmål 2 derfor vurderet at være meget lav.

Risk of bias

For dupilumabstudierne er der ikke nedgraderet for risk of bias. Studierne vurderes at være metodisk velgennemført i forhold til randomisering, blinding og dataindsamling. Dog vurderes der at være risiko for selektionsbias, idet der er ændret på effektmålene efter afslutning af dataindsamlingen. Dette vurderes imidlertid ikke at medføre høj risiko for bias i denne sammenhæng, da de effektmål, der er medtaget, er prædefinerede i protokollen. For omalizumabstudierne er der for alle effektmål nedgraderet ét niveau for risk of bias, da der i studierne er risiko for bias i relation til randomiseringsproceduren og blindingen i studiet/studierne.

Indirekthed

Evidensens kvalitet er nedgraderet for indirekthed for alle effektmål fra både dupilumab- og omalizumabstudierne, da fagudvalget vurderer, at evidensen er indirekte i forhold til patientpopulationen og den underliggende standardbehandling, som ikke er direkte overførbar til danske forhold. Dette skyldes især inklusion af patienter med moderat sværhedsgrad af astma og den manglende systematiske udredning i alle studier, hvilket ikke afspejler dansk standard. For sammenligningen mellem dupilumab og omalizumab er der nedgraderet yderligere ét niveau for indirekthed, da studierne adskiller sig fra hinanden.

Inkonsistens

For dupilumab nedgraderes ét niveau for inkonsistens for alle effektmål, på nær SAE's og frafald. Der nedgraderes for inkonsistens, fordi kun ét studie ligger til grund for effektmålene, og der ikke ud fra ét studie kan vurderes, om data fra flere studier ville have vist et ensartet resultat. For omalizumab nedgraderes ét niveau for inkonsistens for effektmålene lungefunktion, astmakontrol og frafald. For astmakontrol nedgraderes for inkonsistens, idet der kun foreligger data fra ét studie. For de øvrige to effektmål nedgraderes for inkonsistens, idet der er forskelle mellem studiernes resultater, som ikke umiddelbart kan forklares.

Imprecision (unøjagtighed)

For dupilumab nedgraderes ét niveau for unøjagtighed for effektmålene lungefunktion og astmakontrol. For omalizumab nedgraderes ét niveau for unøjagtighed for effektmålet lungefunktion. Der nedgraderes fordi konfidensintervallerne er brede og indeholder estimater, der ville føre til forskellige konklusioner.

Andre overvejelser

Der er ikke fundet anledning til at nedgradere på baggrund af andre overvejelser. Der vurderes ikke at være nok studier (< 10 studier) til at give en retmæssig vurdering af eventuel publikationsbias.

GRADE-profil dupilumab vs. placebo/standardbehandling (subgruppe med allergisk astma fra QUEST-studiet, VENTURE, DRI12544)

Kvalitetsvurdering							Antal patienter		Effekt		Kvalitet (GRADE)	Kritisk / vigtigt
Antal studier	**Studiedesign**	**Risk of bias**	**Inkonsistens**	**Indirekthed**	**Unøjagtighed**	**Andre overvejelser**	**dupilumab**	**placebo**	**Relativ: RR [95 % CI]**	**Absolut, RD [95 % CI]**		
Årlig eksacerbationsrate, reduktion												
1	Randomised trial	Not serious [a]	Serious [b]	Serious [c]	Not serious	None	509	266	0,58 [0,40; 0,86]	0,4	⊕⊕◯◯ LOW	CRITICAL
Risk ratio: andel der opnår 0 eksacerbationer												
1*	Randomised trial	Not serious [a]	Serious [b]	Serious [c]	Not serious	None	631	317	1,23 [1,10; 1,37]	13 % [6,6; 19,6]	⊕⊕◯◯ LOW	CRITICAL
Peroral vedligeholdelsebehandling med kortikosteroid												
0												CRITICAL
Gennemsnitlig ændring i lungefunktion, FEV_1												
1	Randomised trial	Not serious [a]	Serious [b]	Serious [c]	Serious [d]	None	509	266	-	180 mL [109; 251]	⊕◯◯◯ VERY LOW	IMPORTANT
Astmakontrol, ændring (ACQ)												
1	Randomised trial	Not serious [a]	Serious [b]	Serious [c]	Serious [d]	None	509	266	-	-0,4 [-0,6; -0,2]	⊕◯◯◯ VERY LOW	IMPORTANT
Livskvalitet, ændring												
1	Randomised trial	Not serious [a]	Serious [b]	Serious [c]	Not serious	None	509	266	-	0,29 [0,15; 0,44]	⊕⊕◯◯ LOW	IMPORTANT
Serious adverse events (antal)												
3	Randomised trials	Not serious [a]	Not serious	Serious [c]	Not serious	None	68/882 (7,7 %)	41/578 (7,1 %)	1,19 [0,50; 2,84] 0,93 [0,59; 1,48] 1,56 [0,58; 4,22]	1,1 [-4,4; 6,5] 0,9 [0,6; 1,5] 1,6 [0,6; 4,2]	⊕⊕⊕◯ MODERAT	IMPORTANT
Frafald												
3	Randomised trials	Not serious [a]	Not serious [e]	Serious [c]	Not serious	None	83/882 (9,4 %)	55/582 (9,4 %)	0,98 [0,45; 2,15] 0,93 [0,64; 1,34] 0,42 [0,08; 2,09]	-0,2 [-6,1; 5,8] -0,9 [-5,2; 3,4] -2,7 [-7,5; 2,1]	⊕⊕⊕◯ MODERAT	IMPORTANT
Sygefravær (ændring, antal dage) - not reported												
0												IMPORTANT

***CI**: Confidence interval; **RR**: Risk ratio; **RR**: risk difference; **MD**: Mean difference; **SMD**: Standardised mean difference*
**Hele ITT-populationen fra QUEST studiet*
a. Studiet/studierne vurderes at være metodisk velgennemført i forhold til randomisering, blinding og dataindsamling. Dog vurderes der at være risiko for selektionsbias, idet der er ændret på effektmålene efter afslutning af dataindsamlingen. Dette vurderes imidlertid ikke at medføre høj risiko for bias i denne sammenhæng, da de effektmål der er medtaget, er prædefinerede i protokollen.
b. Kun et studie ligger til grund for dette effektmål. Der nedgraderes for inkonsistens, idet det ikke ud fra ét studie kan vurderes, om data fra flere studier ville have vist et ensartet resultat, eller om dette studie er ekstremt.
c. Generelt er der i studierne manglende systematisk udredning for svær astma, og studiepopulationerne inkluderer patienter med moderat astma. Dette svarer ikke direkte til danske forhold. Derfor nedgraderes ét niveau for indirekthed.
d. Konfidensintervallet er bredt og indeholder estimater, der ville føre til forskellige konklusioner. Derfor nedgraderes for unøjagtighed.
e. Der er en vis inkonsistens i punktestimaterne, som muligvis skyldes en lav eventrate i ét af studierne. Der er dog tilstrækkelig konsistens, når konfidensintervallet tages i betragtning, derfor nedgraderes ikke for inkonsistens.

GRADE-profil omalizumab vs. placebo/standardbehandling

Kvalitetsvurdering							Antal patienter		Effekt		Kvalitet (GRADE)	Kritisk / vigtigt
Antal studier	**Studiedesign**	**Risk of bias**	**Inkonsistens**	**Indirekthed**	**Unøjagtighed**	**Andre overvejelser**	**Omalizumab**	**Komparator**	**Relativ: RR [95 % CI]**	**Absolut, RD [95 % CI]**		
Årlig eksacerbationsrate, reduktion												
3	Randomised trials	Serious [a]	Not serious	Serious [b]	Not serious	None	657	578	0,56 [0,41; 0,76] 0,42 [0,31; 0,57] 0,41 [0,29; 0,58]	0,4 0,5 1,8	⊕⊕◯◯ LOW	CRITICAL
Risk ratio: andel der opnår 0 eksacerbationer												
12	Randomised trials	Serious [a]	Not serious [c]	Serious [b]	Not serious	None	1421/1846 (77 %)	1220/1724 (71 %)	Range: 0,71 – 1,26	Range: -19 % to 18 %	⊕⊕◯◯ LOW	CRITICAL
Peroral vedligeholdelsebehandling med kortikosteroid												
0												CRITICAL
Gennemsnitlig ændring i lungefunktion, FEV_1												
7	Randomised trials	Serious [a]	Serious [d]	Serious [b]	Serious [e]	None	982	773	-	Range: -85 to 310 mL	⊕◯◯◯ VERY LOW	IMPORTANT
Astmakontrol, ændring (ACQ)												
1	Randomised trial	Serious [a]	Serious [f]	Serious [b]	Not serious	None	1220	1067	-	-0,2 [-0,4; 0,1]	⊕◯◯◯ VERY LOW	IMPORTANT
Livskvalitet, ændring												
4	Randomised trials	Serious [a]	Not serious	Serious [b]	Not serious	None	1002	977	-	Range: 0,25 to 0,45	⊕⊕◯◯ LOW	IMPORTANT
Serious adverse events (antal patienter)												
13	Randomised trials	Serious [a]	Not serious [g]	Serious [b]	Not serious	None	188/2746 (6,8 %)	182/2419 (7,5 %)	-	-	⊕⊕◯◯ LOW	IMPORTANT
Frafald												
15	Randomised trials	Serious [a]	Serious [h]	Serious [b]	Not serious	None	302/2885 10,5 %	360/2573 14 %	Range 0,31 to 8,31	Range -13,7 to 6,8 %	⊕◯◯◯ VERY LOW	IMPORTANT
Sygefravær (ændring, antal dage)												
0												IMPORTANT

CI: *Confidence interval;* ***RR:*** *Risk ratio;* ***RD****: risk difference;* ***MD:*** *Mean difference;* ***SMD:*** *Standardised mean difference*

a. Der er risiko for bias i relation til randomiseringsproceduren og blindingen i studiet/studierne. Der nedgraderes derfor for risiko for bias.

b. Generelt er der i studierne manglende systematisk udredning for svær astma, og studiepopulationerne inkluderer patienter med moderat astma. Dette svarer ikke direkte til danske forhold. Derfor nedgraderes ét niveau for indirekthed.

c. Der er en vis inkonsistens i estimaterne på grund af ét studie, som skiller sig ud: Murkherjee 2019, som er et meget lille studie (11 patienter i alt). Resultaterne herfra vurderes at vægte meget lavt i den samlede vurdering og estimaterne er ikke medtaget i evidensprofilen. Den øvrige inkonsistens mellem studierne vurderes at kunne forklares ved varierende studievarighed. Derfor er der ikke nedgraderet for inkonsistens.

d. Der er en vis inkonsistens i estimaterne, som ikke umiddelbart kan forklares. Derfor nedgraderes ét niveau for inkonsistens.

e. Konfidensintervallet er bredt, og indeholder estimater, der ville føre til forskellige konklusioner. Derfor nedgraderes ét niveau for unøjagtighed.

f. Kun ét studie ligger til grund for dette effektmål. Der nedgraderes for inkonsistens, idet det ikke ud fra ét studie kan vurderes, om data fra flere studier ville have vist et ensartet resultat, eller om dette studie er ekstremt.

g. Der er en vis inkonsistens mellem resultaterne fra de inkluderede studier, som ikke umiddelbart kan forklares. Derfor nedgraderes ét niveau for inkonsistens.

h. Ved visuel inspektion vurderes der at være heterogenitet, som ikke umiddelbart kan forklares. Der nedgraderes derfor for inkonsistens.

Medicinrådet

Application for the assessment of Dupixent® as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised FeNO in adults and adolescents 12 years and older

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1 Basic information

TABLE 1 CONTACT INFORMATION

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TABLE 2 OVERVIEW OF THE PHARMACEUTICAL

Proprietary name	Dupixent®
Generic name	dupilumab
Marketing authorisation holder in Denmark	Sanofi Aventis, Sanofi-aventis groupe, 54 rue La Boétie, 75008 Paris, France
ATC code	D11AH05
Pharmacotherapeutic group	Other dermatological preparations, agents for dermatitis, excluding corticosteroids
Active substance	dupilumab
Pharmaceutical form	200 mg or 300 mg solution for injection
Mechanism of action	Dupilumab binds specifically to the interleukin-4 receptor alpha (IL-4Rα) subunit shared by the IL-4 and IL-13 receptor complexes and thereby inhibits both IL-4 and IL-13-mediated signalling. Dupilumab inhibits IL-4 signalling via the Type I receptor (IL-4Rα/γc), and both IL-4 and IL-13 signalling through the Type II receptor (IL-4Rα/IL-13Rα). Together with IL-5, IL-4 and IL-13 are key Type 2 inflammation cytokines involved in severe asthma. IL-4 is the central mediator of naïve T cells differentiating into Type 2 cytokine-producing effectors cells, eosinophil trafficking, growth of B cells, and initiation of isotype class switching to IgE. IL-13 has additional roles in mediating goblet cell hyperplasia, smooth muscle contractility, bronchoepithelial production of fractionated exhaled nitric oxide (FeNO), and loss of epithelial integrity. In clinical trials, treatment with dupilumab was associated with decreases from baseline in Type 2 inflammation biomarkers, such as FeNO, TARC/CCL17, periostin, and eotaxin-3 as well as total and allergen-specific IgE in serum. Hence, by dual blocking of IL-4 and IL-13 signalling, dupilumab acts on both structural and immunological components of the disease, including eosinophil trafficking, IgE production, and FeNO secretion.

Dosage regimen	The recommended dose of dupilumab for adults and adolescents (12 years of age and older) is: • For patients with severe asthma and who are on oral corticosteroids or for patients with severe asthma and co-morbid moderate-to-severe atopic dermatitis, an initial dose of 600 mg (two 300 mg injections), followed by 300 mg every other week administered as subcutaneous injection. • For all other patients, an initial dose of 400 mg (two 200 mg injections), followed by 200 mg every other week administered as subcutaneous injection.
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Dupixent is indicated in adults and adolescents 12 years and older as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised FeNO, who are inadequately controlled with high dose ICS plus another medicinal product for maintenance treatment.
Other approved therapeutic indications	Dupixent is indicated for the treatment of moderate-to-severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy.
Will dispensing be restricted to hospitals?	No. Treatment should be initiated by healthcare professionals experienced in the diagnosis and treatment of conditions for which dupilumab is indicated, but patients can self-administer dupilumab if their healthcare professional determines that this is appropriate.
Combination therapy and/or co-medication	Dupixent is indicated as add-on treatment to high dose ICS plus another medicinal product for maintenance treatment.
Packaging – types, sizes/number of units, and concentrations	Dupixent 200 mg or 300 mg solution for injection in pre-filled syringe: Pack size: • 1 pre-filled syringe • 2 pre-filled syringes • Multipack containing 3 (3 packs of 1) pre-filled syringes • Multipack containing 6 (3 packs of 2) pre-filled syringes
Orphan drug designation	No

2 Abbreviations

ACQ	Asthma Control Questionnaire
ACT	Asthma Control Test
AD	Atopic dermatitis
ADRI	Asthma deterioration-related incidents
AE	Adverse event
AQLQ	Asthma Quality of Life Questionnaire
ATS	American Thoracic Society
BDP	Beclomethasone dipropionate
BSC	Best standard care
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
ECG	Electrocardiogram
EGPA	Eosinophilic granulomatosis with polyangiitis
EOS	Blood eosinophils
EPAR	European Public Assessment Report
ERS	European Respiratory Society
FeNO	Fractional exhaled nitric oxide
FEV1	Forced expiratory volume in 1 s
GINA	Global Initiative for Asthma
ICS	Inhaled corticosteroids
IgE	Immunoglobulin E
IL	Interleukin
ITT	Intention-to-treat
IV	Intravenous(ly)
LABA	Long-acting beta agonist
LCL	Lower confidence limit
LS	Least square
MCID	Minimal clinically important difference
mITT	Modified intention-to-treat
OAT	Optimised asthma therapy
OCS	Oral corticosteroids
OAT	Optimised asthma therapy
PEF	Peak expiratory flow
PICO	Patients, intervention, comparator, outcomes
ppb	Parts per billion
q2w	Every 2 weeks
q4w	Every 4 weeks
QoL	Quality of life
RD	Risk difference or rate difference
RQLQ	Rhinitis Quality of Life Questionnaire
RR	Relative risk or rate ratio
SAE	Serious adverse event
SC	Subcutaneous(ly)
SD	Standard deviation
SE	Standard error
SGRQ	St George's Respiratory Questionnaire
SmPC	Summary of Product Characteristics
TASS	Total Asthma Symptom Severity
vs	Versus

3 Summary

Product and indication

Dupilumab is the active pharmaceutical ingredient of Dupixent and is a recombinant human monoclonal antibody of the immunoglobulin G4 (IgG4) type directed against the interleukin-4 receptor alpha (IL-4Rα) subunit and thereby inhibits both IL-4 and IL-13-mediated signalling. Dupixent is indicated in adults and adolescents 12 years and older as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils (EOS) and/or raised fractional exhaled nitric oxide (FeNO), who are inadequately controlled with high-dose inhaled corticosteroids (ICS) plus another medicinal product for maintenance treatment. The recommended dose of dupilumab for adults and adolescents is 200 mg every 2 weeks (q2w), and 300 mg q2w for patients with severe asthma on oral corticosteroids (OCS) or for patients with severe asthma and co-morbid moderate-to-severe atopic dermatitis.

Clinical questions

The following 3 comparators and patient populations were defined by the Medicines Council:

- Dupilumab compared with mepolizumab in treatment of patients >12 years of age with severe asthma with type 2 inflammation characterised by eosinophilia
- Dupilumab compared with omalizumab in treatment of patients >12 years of age with severe asthma with type 2 inflammation characterised by allergy and concomitant eosinophilia and/or increased FeNO
- Dupilumab compared with placebo in treatment of patients >12 years of age with severe asthma with type 2 inflammation characterised by increased FeNO with no concomitant eosinophilia and without concomitant allergy

Methods and data used

The methods used followed the general requirements defined in the Process and Methods Guide (version 2.0) of the Danish Medicines Council for new medicines and new indications and the specific requirements in the protocol for dupilumab. One inevitable deviation from the protocol was the definition of the population with increased FeNO, since data were only available for patients with increased FeNO regardless of EOS and allergy status.

The systematic literature searches were performed in MEDLINE via PubMed and in CENTRAL via Cochrane Library on 01-Jul-2019 and identified 33 publications reporting a total of 23 studies. Data for relevant outcomes were retrieved from 2 dupilumab studies, 3 mepolizumab studies and 16 omalizumab studies in uncontrolled, persistent asthma, and from 1 dupilumab study and 1 mepolizumab study in OCS-dependent asthma.

In accordance with the approved indication and dosage regimen, the results for patients with uncontrolled, persistent asthma are presented for the 200 mg q2w dose, and the results for patients with OCS-dependent asthma for the 300 mg dose.

Clinical relevance of the observed effects was assessed based on the adjusted minimal clinically relevant differences (MCID) defined by the Medicines Council for each outcome in the protocol and the 95% confidence interval (CI) for the absolute difference between dupilumab and the comparator.

Dupilumab vs mepolizumab – severe eosinophilic asthma

For lung function, a statistically significant larger improvement in forced expiratory volume in 1 s (FEV1) of 0.189 L was found with dupilumab compared to mepolizumab in patients with uncontrolled, persistent asthma after 1 year of treatment; however, the lower confidence limit (LCL) did not reach the adjusted MCID of 100 mL. For the remaining efficacy outcomes, the indirect comparative analyses did not show any statistically significant differences between dupilumab and mepolizumab. With regard to quality of life (QoL), a statistically significant improvement in QoL was seen both at week 24 and week 52 with dupilumab compared to placebo. In contrast, no benefit of mepolizumab compared to placebo was shown in QoL after 52 weeks of follow up. For safety, no statistically significant differences were found between dupilumab and mepolizumab in the proportion of patients with serious adverse events (SAEs) in patients with uncontrolled, persistent asthma. In patients with OCS-dependent eosinophilic asthma, an increased risk of SAEs was found with dupilumab, with a relative risk (RR) (95% confidence interval [CI]) of 19.5 (2.1 to 184.6). This was mainly driven by the SIRIUS study having extreme mepolizumab *vs* placebo SAE rates of 1/69 *vs* 12/66, since no noticeable differences between dupilumab (8.7% of patients with an SAE) and placebo (5.6% of patients with an SAE) were observed in the by-study results. The absolute difference in proportion of patients with SAEs was 26%-points, and since the LCL (1.5%-points) was below the MCID of 2.5% the difference was not assessed as clinically relevant. In contrast to the risk of SAEs, the risk of discontinuations, as a proxy for the overall adverse reaction load, was 42.1% lower with dupilumab compared to mepolizumab, although the difference was not statistically significant.

Dupilumab vs omalizumab – severe allergic asthma with increased EOS and/or FeNO

The indirect comparative analyses of dupilumab *vs* omalizumab showed a statistically significantly larger increase in FEV1 of 0.096 L with dupilumab compared to omalizumab. However, since the LCL (0.011 L) did not meet the MCID, the difference was not clinically relevant. No other statistically significant or clinically relevant differences between dupilumab and omalizumab were found for any of the efficacy or safety outcomes assessed.

Dupilumab vs placebo – severe asthma with increased FeNO

In patients with uncontrolled, persistent asthma, the direct comparative analyses showed statistically significant and clinically relevant differences between dupilumab and placebo for the annual rate of severe exacerbations (risk reduction 65% and upper confidence limit 0.5 events/patient-year lower), the proportion of patients with 0 annual exacerbations (37% higher chance and LCL 11.7%-points more patients with 0 annual exacerbations), change in FEV1 (0.3L and LCL 0.22L), proportion of patients with ≥200 mL improvement in FEV1 (55.6% higher chance and LCL 13.1%-points more patients with ≥200 mL improvement) and asthma control as assessed with ACQ-5 (improvement of 0.39 and LCL 0.25).

In OCS-dependent patients, the direct comparative analyses showed statistically significant and clinically relevant differences between dupilumab and placebo for the proportion of patients with 0 annual exacerbations (84% higher chance and LCL 20.4%-points more patients with 0 annual exacerbations), mean % reduction in OCS maintenance dose (LCL ≥2.2 mg/day prednisone/prednisolone equivalent), proportion of patients no longer requiring OCS (81% higher chance and LCL 10.5% more patients with no OCS use), and the proportion of patients with ≥50% reduction in OCS dose (49% higher chance and LCL 14.1%-points more patients with ≥50% reduction).

For safety, no statistically significant differences between dupilumab 200 mg or 300 mg and placebo were found in the proportion of patients with SAEs or the proportion of patients discontinued from the study.

Anaphylactic reactions

For dupilumab, mepolizumab and omalizumab a low number of anaphylactic events were reported in the included studies, suggesting a low immunogenic potential. In the Summary of Product Characteristics (SmPCs), anaphylactic reactions are listed as very rare (<1/10,000) adverse reaction for dupilumab based on the asthma development program, as rare (<1/1,000) for mepolizumab, based on spontaneous post marketing reporting, and as rare (<1/1,000) for omalizumab.

Conclusion

In conclusion, compared to mepolizumab, dupilumab showed a statistically significant improvement in lung function for patients with uncontrolled, persistent eosinophilic asthma, which did, however, not fully reach the MCID. With regard to QoL, a statistically significant improvement in QoL was seen both at week 24 and week 52 with dupilumab compared to placebo. In contrast, no benefit of mepolizumab compared to placebo was shown in QoL after 52 weeks of follow up. The risk of SAEs seemed higher with dupilumab compared to mepolizumab in patients with OCS-dependent eosinophilic asthma; this was, however not above the MCID and was not reflected in higher risk of discontinuations. A statistically significant difference in improvement in lung function and numeric differences in improvements of other critical and important efficacy outcomes favoured dupilumab compared to omalizumab in patients with uncontrolled, persistent allergic asthma with increased EOS and/or FeNO. No notable differences in safety outcomes were observed between dupilumab and omalizumab. Finally, in asthma patients with elevated FeNO, dupilumab clearly showed consistent statistically significant improvements above active background medication and placebo beyond the protocol-specified MCID values across the range of reported critical and important efficacy outcomes and with no differences in any of the safety outcomes. Dupilumab therefore offers a new treatment option for patients with uncontrolled, persistent asthma and elevated FeNO, eosinophilic or allergic phenotypic traits, or with common type 2 inflammation associated comorbidities such as atopic dermatitis.

4 Literature search

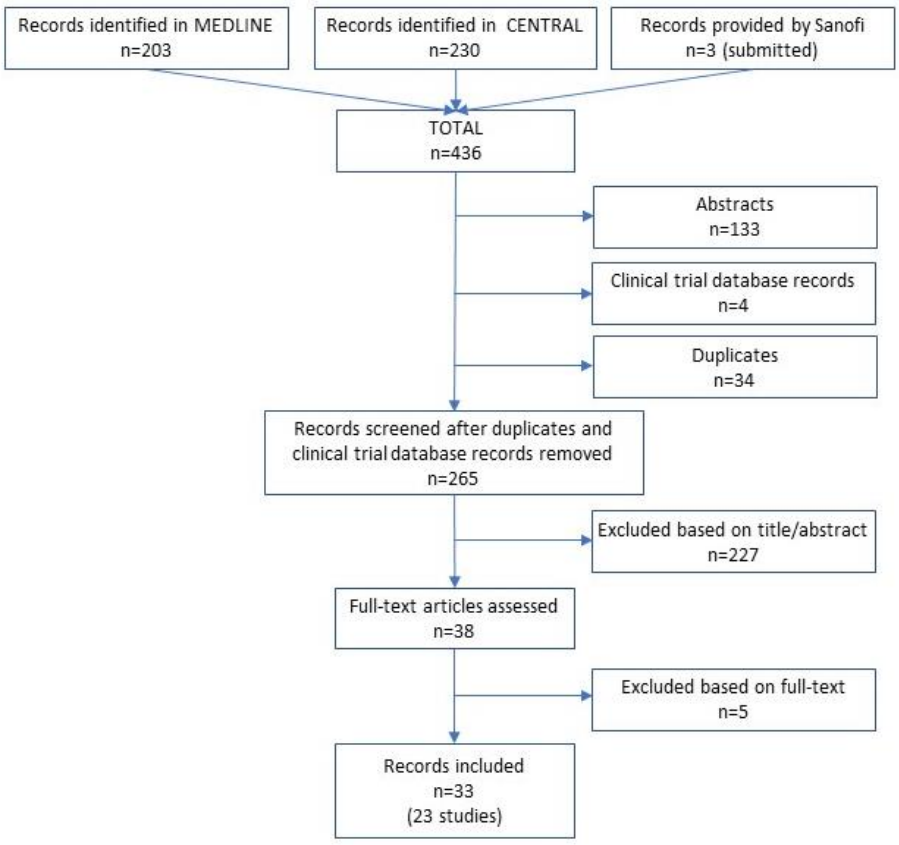
4.1 Databases and search strategy

Systematic literature searches were performed in MEDLINE via PubMed and in CENTRAL via Cochrane Library on 01-Jul-2019 according to the search strategies provided in the protocol for assessment of dupilumab [1]. No language or date limits were applied. The complete search strategies are summarised in appendix 8.1, Table 42 and Table 43, respectively. A total of 203 records were identified in MEDLINE and 230 in CENTRAL (Trials). In addition, 3 submitted manuscripts were provided by Sanofi. After removal of duplicates, abstracts/posters and clinical trial database records, 265 records were left for screening. The records were screened and assessed by 2 researchers independently based on the PICOs (patients, intervention, comparator, outcomes) and inclusion and exclusion criteria as described in the protocol for dupilumab [1]. The inclusion and exclusion criteria are summarised in appendix 8.1, Table 44.

Based on screening at the title and abstract level, 227 references were excluded. Full-text screening was performed for 38 publications, and 5 publications were excluded based on full-text read. These are included in the list of excluded references in appendix 8.1, Table 45. A PRISMA flow diagram of the selection process is provided in Figure 1. Any disagreements during the selection process were resolved by discussion between the 2 reviewers.

After selection of relevant articles, data were extracted into a project-specific Microsoft Excel table by one researcher and a second researcher independently checked the data extraction for accuracy and completeness. Any disagreements were resolved by discussion between the 2 reviewers.

FIGURE 1 PRISMA FLOW DIAGRAM



4.2 Relevant studies

The relevant studies included in this application for the assessment of each clinical question, as defined in the protocol, are listed in Table 3.

Both studies in uncontrolled, persistent asthma in and oral corticosteroid (OCS)-dependent asthma were included. For studies in uncontrolled, persistent asthma, relevant outcomes were available from 2 dupilumab studies, 3 mepolizumab studies and 16 omalizumab studies. For studies in OCS-dependent asthma, relevant outcomes were available from 1 dupilumab study and 1 mepolizumab study.

According to the protocol, the added clinical value of dupilumab should be assessed in patients with severe asthma [1]. The Danish Society of Respiratory Medicine and the European Respiratory Society (ERS)/American Thoracic Society (ATS) define severe asthma as asthma that for ≥1 year has required treatment with high-dose inhaled corticosteroids (ICS) and ≥1 second controller and/or that has required treatment with OCS for ≥50% of the time to prevent it from becoming uncontrolled or that remains uncontrolled despite this therapy [2]. Results from patients on high-dose ICS are not reported separately for the dupilumab phase 2b and QUEST studies, which include a mixed patient population with moderate-to-severe asthma. However, the results from a pre-specified analysis of the QUEST study, that assessed the efficacy of dupilumab by disease severity determined by baseline ICS dose (high/medium), demonstrated that there is no difference in treatment results between patients on medium-dose *vs* high-dose ICS at baseline [3]. Therefore, it was considered reasonable to include data from these 2 studies in patients on medium-to-high-dose ICS in this application.

The patient populations included in the 2 omalizumab studies published by Busse 2001 and Soler 2001, respectively, were assessed to have moderate asthma based on current standards for high-dose ICS treatment (see section 8.2.3 and the current Global Initiative for Asthma (GINA) guidelines [4]). However, although the protocol states that studies not reporting on severe asthma should be excluded, we decided to include these 2 studies, since they were also included in the Medicines Council's background for the treatment guideline for biological treatment of severe asthma [5].

Studies reporting ≥1 of the relevant outcomes were included. Not all studies reported on all outcomes, and several of the omalizumab studies reported only on few outcomes that were relevant for this application.

TABLE 3 RELEVANT STUDIES INCLUDED IN THE ASSESSMENT

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and completion date)	Relevant for clinical question[1]
Dupilumab studies				
Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. Wenzel S, et al. Lancet, 2016 [6]. Dupilumab improves symptoms, quality of life, and productivity in uncontrolled persistent asthma. Corren J, et al. Ann Allergy Asthma Immunol, 2019 [7].	A randomized, double-blind, placebo-controlled, dose-ranging study to evaluate dupilumab in patients with moderate to severe uncontrolled asthma	01854047	Jun-2013 to Apr-2015	5.1
Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. Castro M, et al. N Engl J Med, 2018 [8]. Dupilumab efficacy in patients with uncontrolled, moderate-to-severe allergic asthma. Corren J, et al. J Allergy Clin Immunol, 2019 [9] Dupilumab improves lung function in patients with uncontrolled, moderate-to-severe asthma. Castro M, et al. Eur Respir J, 2019 [10] (submitted for publication)	A randomised, double blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of dupilumab in patients with persistent asthma LIBERTY ASTHMA QUEST	02414854	Apr-2015 to Nov-2017	5.1 5.2 5.3
Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. Rabe KF, et al. N Engl J Med, 2018 [11]. The effect of dupilumab on lung function parameters in patients with oral corticosteroid-dependent severe asthma. Rabe KF, et al. Respir Med, 2019 [12] (submitted for publication)	A randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of dupilumab in patients with severe steroid dependent asthma LIBERTY ASTHMA VENTURE	02528214	Oct-2015 to Nov-2017	5.1 5.3
Mepolizumab studies				
Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. Pavord ID, et al. Lancet, 2012 [13].	A multicenter, randomised, double-blind, placebo-controlled, parallel group, dose ranging study to determine the effect of mepolizumab on exacerbation rates in subjects with severe uncontrolled refractory asthma. DREAM	01000506	Nov-2009 to Mar-2012	5.1
Mepolizumab treatment in patients with severe eosinophilic asthma. Ortega HG, et al. N Engl J Med, 2014 [14].	MEA115588 A randomised, double-blind, double-dummy, placebo-controlled, parallel-group, multi-centre study of the efficacy and safety of mepolizumab adjunctive therapy in subjects with severe uncontrolled refractory asthma. MENSA	01691521	Oct-2012 to Jan-2014	5.1
Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. Bel EH, et al. N Engl J Med, 2014 [15].	MEA115575: A randomised, double-blind, placebo-controlled, parallel-group, multicenter study of mepolizumab adjunctive therapy to reduce steroid use in subjects with severe refractory asthma. SIRIUS	01691508	Oct-2012 to Dec-2013	5.1

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and completion date)	Relevant for clinical question[1]
Efficacy of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma (MUSCA): a randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3b trial. Chupp GL, et al. Lancet Respir Med, 2017 [16].	A randomised, double-blind, placebo-controlled, parallel-group, multi-centre 24-week study to evaluate the efficacy and safety of mepolizumab adjunctive therapy in subjects with severe eosinophilic asthma on markers of asthma control. MUSCA	02281318	Dec-2014 to Jun-2016	5.1
Omalizumab studies				
Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. Busse W, et al. J Allergy Clin Immunol, 2001 [17]B. Omalizumab improves asthma-related quality of life in patients with severe allergic asthma. Finn A, et al. J Allergy Clin Immunol, 2003 [18]. Omalizumab is effective in the long-term control of severe allergic asthma. Lanier BQ, et al. Ann Allergy Asthma Immunol, 2003 [19].		Not found	Not reported	5.2
The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. Soler M, et al. Eur Respir J, 2001 [20]. Omalizumab provides long-term control in patients with moderate-to-severe allergic asthma. Buhl R, et al. Eur Respir J, 2002 [21]. The anti-IgE antibody omalizumab improves asthma-related quality of life in patients with allergic asthma. Buhl R, et al. Eur Respir J, 2002 [22].		Not found	Not reported	5.2
Efficacy and safety of a recombinant anti-immunoglobulin E antibody (omalizumab) in severe allergic asthma. Holgate ST, et al. Clin Exp Allergy, 2004 [23].		Not found	Not reported	5.2
Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with concomitant allergic asthma and persistent allergic rhinitis: SOLAR. Vignola AM, et al. Allergy, 2004 [24].		Not found	Not reported	5.2
Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with poorly controlled (moderate-to-severe) allergic asthma. Ayres JG, et al. Allergy, 2004 [25]. Effectiveness of omalizumab in patients with inadequately controlled severe persistent allergic asthma: an open-label study. Niven R, et al. Respir Med, 2008 [26].		Not found	Not reported	5.2

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and completion date)	Relevant for clinical question[1]
Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. Humbert M, et al. Allergy, 2005 [27].	Ph III, 28-wk, multicenter, randomised, double-blind, placebo-controlled, parallel-group study to assess efficacy, safety, tolerability of sc omalizumab in adults and adolescents w/ severe persist. allergic asthma & are inadequately controlled despite GINA (2002) step 4 Tx	00046748	Dec-2001 to Apr-2004	5.2
Efficacy and safety of omalizumab in an Asian population with moderate-to-severe persistent asthma. Ohta K, et al. Respirology, 2009 [28].	Study of omalizumab in moderate to severe bronchial asthma	00232050	Oct-2002 to May-2005	5.2
Omalizumab-induced decrease of FcεRI expression in patients with severe allergic asthma. Chanez P, et al. Respir Med, 2010 [29].	Double blind placebo controlled study to assess the expression of IgE on basophils and dendritic cells during omalizumab treatment	00454051	Dec-2006 to Mar-2008	5.2
Persistency of response to omalizumab therapy in severe allergic (IgE-mediated) asthma. Bousquet J, et al. Allergy, 2011 [30]. Oral corticosteroid sparing with omalizumab in severe allergic (IgE-mediated) asthma patients. Siergiejko Z,et al. Curr Med Res Opin, 2011 [31].	A randomised, open label, parallel-group, international, multicenter study evaluating persistency of response to omalizumab during 32 weeks treatment given as add on to optimized asthma therapy in adult and adolescent patients with severe persistent allergic asthma, who remain inadequately controlled despite GINA (2004) step 4 therapy	00264849	Nov-2005 to Sep-2008	5.2
Omalizumab in severe allergic asthma inadequately controlled with standard therapy: a randomised trial. Hanania NA, et al. Ann Intern Med, 2011 [32].	A phase IIIb multicenter, randomised, double-blind, placebo-controlled study of Xolair in subjects with moderate to severe persistent asthma who are inadequately controlled with high-dose inhaled corticosteroids and long-acting beta-agonists	00314574[2]	Dec-2005 to Nov-2009	5.2
A 26-week, randomised, double-blind, placebo-controlled, multicenter study to evaluate the effect of omalizumab on asthma control in patients with persistent allergic asthma. Bardelas J, et al. J Asthma, 2012 [33].	A 26-week, randomized, double-blind, parallel-group, placebo-controlled, multi-center study to evaluate the effect of omalizumab on improving the tolerability of specific immunotherapy in patients with at least moderate persistent allergic asthma inadequately controlled with inhaled corticosteroids	00267202	Dec-2005 to Apr-2008	5.2
Effects of adding omalizumab, an anti-immunoglobulin E antibody, on airway wall thickening in asthma. Hoshino M, Ohtawa J. Respiration, 2012 [34].		Not found	Not reported	5.2
Effect of omalizumab as add-on therapy on asthma-related quality of life in severe allergic asthma: a Brazilian study (QUALITX). Rubin AS, et al. J Asthma, 2012 [35].	A randomized, open-label, multicenter study to evaluate the effect of Xolair (omalizumab) as add-on therapy to inhaled corticosteroid + long-acting beta agonist in fixed or flexible dosing compared to isolated inhaled corticosteroid + long-acting beta agonist in fixed or flexible dosing in the asthma-related quality of life in patients with severe persistent allergic asthma. QUALITX	00567476	Nov-2007 to Apr-2010	5.2

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and completion date)	Relevant for clinical question[1]
High eosinophil count: a potential biomarker for assessing successful omalizumab treatment effects. Busse W, et al. J Allergy Clin Immunol, 2013 [36].		Not found	Not reported	5.2
Omalizumab improves quality of life and asthma control in Chinese patients with moderate to severe asthma: A randomised phase III study. Li J, et al. Allergy Asthma Immunol Res, 2016 [37].	A 24-week, phase III Randomised, double-blind, placebo controlled, parallel-group, multicenter study of Xolair® (omalizumab) in patients with moderate to severe persistent allergic asthma who remain not adequately controlled despite GINA (2009) step 4 therapy	01202903	Sep-2010 to Oct-2013	5.2
Omalizumab in patients with severe asthma and persistent sputum eosinophilia. Mukherjee M, et al. Allergy Asthma Clin Immunol, 2019 [38].	Randomised double blind placebo controlled trial of the steroid sparing effect of Xolair (omalizumab) in patients with persistent eosinophilic bronchitis	02049294	Mar-2014 to Sep-2017	5.2

[1] Multiple clinical questions are defined in the protocol. Numbering according to the protocol and in agreement with the numbering in this application

[2] In the publication, the NCT number is stated as NCT00314575, however, this number does not exist. The NCT number appears to be NCT00314574.

4.3 Main characteristics of included studies

The main characteristics of the studies included in the assessment are presented below. An overview of the main study characteristics is provided in appendix 8.2 and baseline characteristics for each study are summarised in appendix 8.3. As agreed with the Medicines Council, the tables provided resemble the study and baseline characteristics tables in the Medicines Council's background for the treatment guideline for biological treatment of severe asthma [5].

4.3.1 Dupilumab studies

The 3 dupilumab studies which are relevant for this application are presented below.

Phase 2b, DRI12544 (Wenzel et al 2016)

DRI12544 was a randomised, double-blind, placebo-controlled, parallel-group, pivotal phase 2b study that assessed the efficacy and safety of dupilumab in patients with uncontrolled moderate-to-severe asthma [6, 7].

A total of 776 patients aged ≥18 years were randomised (1:1:1:1:1) according to a centralised randomisation scheme and by use of a centralised treatment allocation system to receive subcutaneous (SC) dupilumab 200 mg every 2 weeks (q2w) or every 4 weeks (q4w) (loading dose 400 mg), 300 mg q2w or q4w (loading dose 600 mg), or placebo for 24 weeks. Patients continued their background therapy with ICS plus a long-acting beta agonist (LABA) at a stable dose throughout the randomised treatment period and during the 16 weeks follow-up period. Throughout the study, patients could administer a short-acting β2-adrenergic receptor agonist as needed for relief of asthma symptoms.

The study included patients with a physician diagnosis of moderate-to-severe, uncontrolled asthma for ≥12 months based on the GINA 2009 guidelines, treated with moderate or high-dose ICS/LABA, with forced expiratory volume in 1 s(FEV1) of 40 to 80% of the predicted normal, 5-item Asthma Control Questionnaire (ACQ-5) score ≥1.5, reversibility ≥12% and 200 mL in FEV1, and who had experienced within the prior year hospitalisation, emergency or urgent care visit or systemic corticosteroid treatment for worsening asthma. Patients were recruited irrespective of baseline blood EOS count or elevations of any other biomarker for type 2 inflammation, e.g. fractional exhaled nitric oxide (FeNO) or Immunoglobulin E (IgE). Hence, a broad patient population was enrolled. However, to ensure a balanced distribution of blood EOS counts in patients across treatment regimens, randomisation was stratified by central laboratory blood EOS count at screening (≥300 cells/µL, 200–299 cells/µL and <200 cells/µL) and by country. Current smokers or former smokers with a smoking history of >10 pack years, and patients with chronic obstructive pulmonary disease (COPD) or other lung diseases were excluded.

The primary outcome measures were change from baseline at week 12 in FEV1 (L) in patients with baseline blood EOS counts of ≥300 cells/µL and in the broad intention-to-treat (ITT) population. Secondary endpoints were prespecified at week 12 and week 24 for both the broad ITT population and for the subgroup with EOS counts of ≥300 cells/µL and included annualised severe asthma exacerbation rate, change from baseline at week 12 and week 24 in the ACQ-5 score, Asthma Quality of Life Questionnaire (AQLQ) score and safety. A severe exacerbation event was defined as deterioration of asthma that required use of systemic corticosteroids for ≥3 days or hospital admission or emergency department visit because of asthma treated with systemic corticosteroids.

Efficacy analyses were performed based on the broad ITT population and safety analyses based on the safety population that included all patients who received ≥1 dose of study drug.

QUEST (Castro et al 2018)

QUEST was a randomised, double-blind, placebo-controlled, parallel-group, phase 3 study that assessed the efficacy and safety of dupilumab in patients with uncontrolled moderate-to-severe asthma [8-10].

A total of 1902 patients aged ≥12 years were randomised (2:2:1:1) by use of a centralised treatment allocation system to receive SC dupilumab 200 mg q2w (loading dose 400 mg), 300 mg q2w (loading dose 600 mg) or 2 matched-volume placebo groups for 52 weeks. Background asthma-controller medicines were continued at a stable dose throughout the trial. Use of LABA, long-acting muscarinic antagonists, antileukotriene agents and methylxanthines was permitted. Throughout the trial, patients were permitted to use a short-acting β2-adrenergic-receptor agonist as necessary for symptom relief.

The study included patients with physician-diagnosed persistent asthma for ≥12 months according to the GINA 2014 guidelines, current treatment with medium-to-high-dose ICS plus up to 2 additional controllers, FEV1 of ≤80% of the predicted normal (or ≤90% of the predicted normal in patients 12-17 years old), FEV1 reversibility of ≥12% and 200 mL; ACQ-5 score of ≥1.5 and a worsening of asthma in the previous year that led to hospitalisation, emergency medical care or treatment with systemic glucocorticoids for ≥3 days. Patients were recruited irrespective of baseline blood EOS count or levels of biomarkers of type 2 inflammation, e.g. FeNO or IgE. Randomisation was stratified according to age (<18 years or ≥18 years), peripheral-blood EOS count (<300 or ≥300/µL) at screening, ICS dose (medium or high) and by country. Current smokers or former smokers with a smoking history of >10 pack years, and patients with COPD or other lung diseases were excluded.

The primary efficacy outcomes were the annualised rate of severe exacerbation events during the 52-week intervention period and the absolute change from baseline in the FEV1 before bronchodilator use at week 12 in the broad ITT population. A severe asthma exacerbation was defined as a deterioration of asthma leading to treatment for ≥3 days with systemic glucocorticoids or hospitalisation or an emergency department visit leading to treatment with systemic glucocorticoids. Secondary outcomes and pre-specified subgroup analyses included the annualised rate of severe exacerbation events and change from baseline in FEV1 at week 12 in patients with elevated FeNO (≥25ppb), blood EOS count ≥150 cells/µL and ≥300 cells/µL, change from baseline in ACQ-5 score and AQLQ score at week 24, and safety.

Efficacy analyses were performed in the broad ITT population, defined as all the patients who underwent randomisation.

VENTURE (Rabe et al 2018)

VENTURE was a randomised, double-blind, placebo-controlled, parallel-group, phase 3 study that assessed the efficacy and safety of dupilumab in patients with OCS-dependent severe asthma [11, 12].

After an OCS dose-adjustment period of 3-10 weeks, a total of 210 patients were randomised 1:1 by use of a centralised treatment allocation system to receive dupilumab 300 mg q2w (loading dose 600 mg) or placebo. The 24-week intervention period consisted of a 4-week induction period, during which the adjusted OCS dose was continued; a 16-week period (weeks 4 to 20) during which the OCS dose was adjusted down every 4 weeks according to a protocol prespecified algorithm; and a 4-week maintenance period, during which patients continued the OCS dose that was established at week 20. The adjusted OCS dose was defined as the lowest dose that a patient could receive without having an increase of ≥0.5 (i.e., the minimal clinically relevant difference [MCID]) in the ACQ-5 score, a severe exacerbation or any clinically significant event leading to an upward adjustment in the OCS dose. Background asthma controllers were

continued at a stable dose and the use of a short-acting β2-agonist was permitted as needed for asthma symptoms.

The study included patients ≥12 years who had had physician-diagnosed asthma for ≥1 year according to the GINA 2014 guidelines and who had been receiving treatment with regular systemic glucocorticoids in the previous 6 months (5 to 35 mg/ day of prednisone or prednisolone or equivalent). During the 4 weeks before screening, their treatment had to also include a high-dose ICS (fluticasone propionate at a total daily dose of >500 µg or equipotent equivalent) in combination with up to 2 controllers (i.e. a LABA or leukotriene-receptor antagonist) for ≥3 months; FEV1 before bronchodilator use of ≤80% of the predicted normal value (or ≤90% of the predicted normal value in adolescents), FEV1 reversibility of ≥12% and 200 mL, or airway hyperresponsiveness documented in the 12 months before screening. Patients were recruited with no minimum requirements regarding a baseline blood or sputum EOS count or any other type 2 biomarkers. Randomisation was stratified according to the adjusted OCS dose (≤10 mg/day *vs* >10 mg/day of prednisone or prednisolone) and by country. Current smokers or former smokers with a smoking history of >10 pack years, and patients with COPD or other lung diseases were excluded.

The primary efficacy outcome was the % reduction in the OCS dose from baseline to week 24 while asthma control was maintained. Between weeks 20 and 24 asthma control was considered to be maintained if no clinically significant event (based on investigator judgment) leading to an upward adjustment in the OCS dose occurred. For patients who had an exacerbation, the final OCS dose was considered to be 1 step higher than the dose they had been receiving at the time of the exacerbation. Key secondary efficacy endpoints that were assessed in patients with maintained asthma control were the proportion of patients with a reduction from baseline of ≥50% in the OCS dose and the proportion of patients who had a reduction in the OCS dose to ≤5 mg per day. Other endpoints included the proportion of patients who no longer used oral glucocorticoids, the annualised rate of severe exacerbation events (defined as events leading to hospitalisation, an emergency department visit or treatment for ≥3 days with systemic glucocorticoids at ≥2 times the current dose of OCS) during the 24-week intervention period; the absolute change from baseline in the FEV1 before bronchodilator use at weeks 2, 4, 8, 12, 16, 20, and 24; and the change from baseline in ACQ-5 score and AQLQ score at week 24, and safety. Prespecified subgroup analyses included patients with elevated FeNO (≥25ppb), blood EOS count ≥150 cells/µL and ≥300 cells/µL.

Efficacy analyses were performed in the broad ITT treat population, which included all randomised patients. The safety population included all the patients who received ≥1 dose or a partial dose of dupilumab or placebo, and data were analysed according to the treatment regimen received.

Studies in non-OCS dependent asthma and OCS-dependent asthma

The Medicines Council's protocol [1] states that data for the outcomes related to maintenance OCS treatment should be presented for the 300 mg dupilumab dose, while data on all other outcomes should be presented for the 200 mg dose. The 300 mg dose is indicated for patients with severe asthma treated with OCS, and for patients with severe asthma and co-morbid atopic dermatitis for which dupilumab is also approved in the EU, including Denmark.

Since patients treated with maintenance OCS can be considered a separate population, it was agreed with the Medicines Council to present the results for the 300 mg dose for all outcomes. This is also deemed relevant since approximately 50% of the Danish patients <18 years could be candidates for treatment with 300 mg dupilumab due to concomitant atopic dermatitis and approximately 10-20% of the Danish adult patients could be candidates for treatment with the 300 mg dose due to maintenance treatment with OCS [1].

Thus, for 2 of the clinical questions (increased EOS population *vs* mepolizumab and increased FeNO population *vs* placebo), where data are available, we present data both for the 200 mg dupilumab dose in a patient population with moderate-to-severe uncontrolled, persistent asthma, and for the 300 mg dupilumab dose in a patient population with severe asthma treated with maintenance OCS.

Dupilumab subgroups covering the protocol-defined populations

The 3 pivotal dupilumab studies had broad eligibility criteria, and patients were not selected for enrolment based on phenotypic traits. Different subgroup analyses of the 3 studies have been performed based on EOS and FeNO levels, which largely cover the 3 patient populations defined in the protocol provided by the Medicines Council. Thus, where available, we used data for the following dupilumab subgroups in this application:

- Increased EOS subgroup to assess the added clinical value of dupilumab *vs* mepolizumab. This subgroup includes patients with baseline blood EOS ≥150 cells/µL.
- Allergic subgroup to assess the added clinical value of dupilumab *vs* omalizumab. This subgroup includes patients with allergy, defined as total serum IgE ≥30 IU/mL and ≥1 positive perennial aeroallergen-specific IgE value (≥0.35 kU/L), and concomitant baseline blood EOS ≥150 cells/µL, or allergy and concomitant FeNO ≥25 ppb at baseline.
- Increased FeNO subgroup to assess the added clinical value of dupilumab *vs* placebo. The protocol provided by the Medicines Council defines this subpopulation as patients with increased FeNO *without* concomitant eosinophilia and *without* concomitant allergy. However, data for this subgroup are not reported. Therefore, available data for patients with elevated baseline FeNO (≥25 ppb) regardless of EOS and allergy status is provided.

Asthma is a heterogeneous disease and most patients are characterised by having more than 1 of several phenotypic traits. Hence, patients with eosinophilic asthma are often also allergic and *vice versa*. This has been confirmed in a recent real-world practice study, including patients from Europe [39]. Similarly, patients with elevated FeNO will often possess phenotypic traits of eosinophilic and/or allergic asthma as well. This has also recently been confirmed in another real-world study, including patients from Sweden [40]. Only 49 patients in the QUEST study matched the “FeNO only” patient population defined in the protocol, which only includes the patients who are not included in any of the other 2 populations. As data from these 49 patients are not available, and since there is also a significant overlap between the eosinophilic and allergic patient populations defined by current Danish treatment guidelines, we have provided available data for patients with elevated baseline FeNO (≥25 ppb) regardless of EOS and allergy status (Figure 2).

FIGURE 2 PATIENT POPULATIONS IN SEVERE ASTHMA

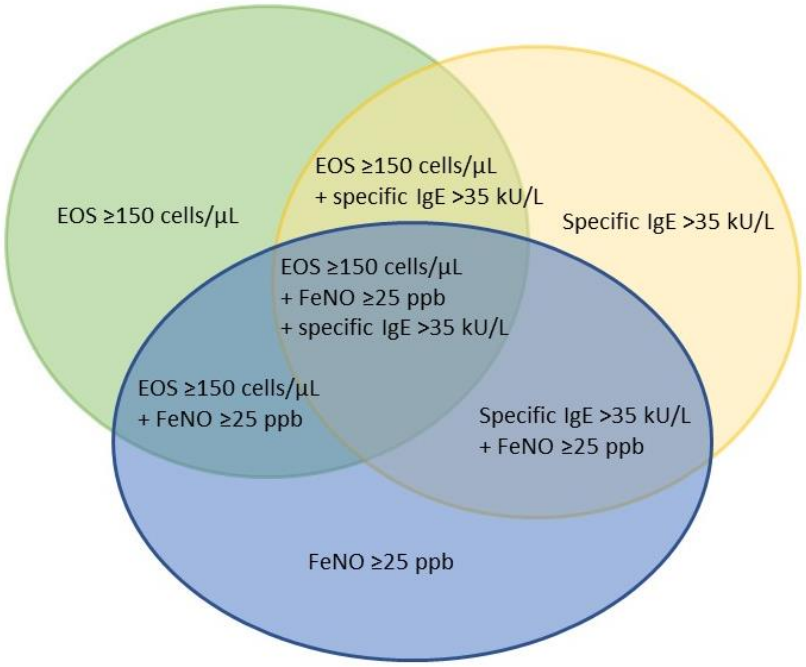


Table 4 provides a summary of the main study characteristics of the 3 dupilumab studies, while Table 5 summarises the subgroups where relevant published data are available. For each of the clinical questions, some outcomes were not available in the specific dupilumab subgroup. In those cases, we provide data for the best alternative population, for example data for the entire allergic population regardless of EOS and FeNO status or, in some cases, data for the ITT population.

TABLE 4 OVERALL SUMMARY OF THE DUPILUMAB STUDIES

Dupilumab population	Study	N	Dupilumab dose(s)	Study population	Asthma severity	ICS dose	2nd controller required?	OCS	Age
ITT	Phase 2b, DRI12544 (Wenzel 2016)	776[a]	200 mg q2w 300 mg q2w 200 mg q4w 300 mg q4w	Uncontrolled, persistent asthma	Moderate -severe	Medium-high	Yes, LABA	Allowed	≥18
	QUEST (Castro 2018)	1902[a]	200 mg q2w 300 mg q2w	Uncontrolled, persistent asthma	Moderate -severe	Medium-high	Yes, LABA or other	Not specified	≥12
	VENTURE (Rabe 2018)	210	300 mg q2w	OCS-dependent asthma	Severe	High	Yes, LABA or other	5-35 mg/day prednisone or equivalent	≥12

[a] includes all doses and dosing frequencies. Only data for the relevant dose and frequency (200 mg q2w) are used in this application
More details are provided in appendix 8.2.1
ICS, inhaled corticosteroids; ITT, intention-to-treat; LABA, long-acting beta agonist; N, number of subjects randomised; OCS, oral corticosteroids; q2w, every 2 weeks; q4w, every 4 weeks

TABLE 5 RELEVANT SUBGROUPS FROM THE DUPILUMAB STUDIES WITH AVAILABLE PUBLISHED DATA

Dupilumab subgroup	Study	N (% of ITT)	Dupilumab dose relevant for application	EOS level at baseline (cells/µL)	FeNO level at baseline (ppb)	IgE/ allergens
Asthma with type 2-inflammation characterised by eosinophilia						
Increased EOS subgroups	DRI12544	247 (32%)	200 mg q2w	≥150	Any level	Any level
	QUEST	669 (35%)	200 mg q2w	≥150	Any level	Any level
	VENTURE	150 (71%)	300 mg q2w	≥150	Any level	Any level
Asthma characterised by allergy and concomitant eosinophilia or characterised by allergy and concomitant increased FeNO						
Allergic subgroups	QUEST	384 (20%)	200 mg q2w	≥150	Any level	Total serum IgE ≥30 IU/mL and ≥1 positive perennial aeroallergen-specific IgE value (≥0.35 kU/L)[a]
		284 (15%)	200 mg q2w	Any level	≥25	
		543 (29%)	200 mg q2w	Any level	Any level	
Asthma characterised by increased FeNO						
Increased FeNO subgroups	QUEST	461 (24%)	200 mg q2w	Any level	≥25	Any level
	VENTURE	114 (54%)	300 mg q2w	Any level	≥25	Any level

[a] includes the following perennial allergens: *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, *Alternaria alternata*, *Cladosporium herbarum*, cat and dog danders, German cockroach, oriental cockroach and *Aspergillus fumigatus*. Percutaneous allergy skin testing was not performed, and symptoms on relevant exposure for the antigen were not recorded

EOS, blood eosinophils; FeNO, fractional exhaled nitric oxide; IgE, immunoglobulin E; ITT, intention-to-treat; ppb, parts per billion; q2w, every 2 weeks

4.3.2 Mepolizumab studies

The 4 mepolizumab studies relevant for this application are presented below.

DREAM (Pavord et al 2012)

DREAM was a randomised, placebo controlled, double-blind, parallel-group, multicentre, phase 2 study in patients with severe, uncontrolled, refractory asthma [13]. The study consisted of a 2-week run-in period, 52-week blinded treatment period and 4 weeks of follow-up. A total of 616 patients were randomly assigned in a 1:1:1:1 ratio to receive 1 of 3 different doses of intravenous (IV) mepolizumab (75 mg, 250 mg or 750 mg) or matched placebo, using a computer generated randomly permuted block schedule and a central telephone-based system. Randomisation was stratified based on whether the patients required daily treatment with OCS. Mepolizumab and placebo were prepared by unmasked site staff who were not involved in study assessments. Both treatments were identical in appearance and were given to patients by a masked member of the site staff. Data analysts were masked to treatment allocation.

Eligible patients were 12–74 years and had a clinical diagnosis of asthma supported by ≥1 other characteristics: variability in diurnal peak expiratory flow (PEF) ≥20% for ≥3 days during the 2-week run-in period, FEV1 reversibility of ≥12% and 200 mL, a variability in FEV1 ≥20% between 2 consecutive clinic visits in 12 months, or a provocative concentration of inhaled methacholine needed to reduce FEV1 by 20% (PC20) of 8 mg/mL or less documented in the 12 months before study entry. Participants had a history of ≥2 exacerbations requiring systemic corticosteroid treatment in the previous year and evidence of eosinophilic inflammation (a sputum EOS count of ≥3%, FeNO ≥50 ppb, peripheral blood EOS count of ≥300 cells/µL, or prompt deterioration of asthma control after a ≤25% reduction in regular maintenance inhaled or OCS). Patients met the ATS criteria for a diagnosis of refractory asthma [41]; all had stable treatment requirements of ≥880 µg fluticasone propionate equivalent per day (delivered dose), with or without maintenance OCS, and required additional controller drugs. Participants had to maintain their treatment (standard of care) throughout the study. Current smokers or former smokers with a smoking history of ≥10 pack years, and patients with a known pre-existing, clinically important lung condition other than asthma were excluded.

The primary endpoint was the rate of clinically significant asthma exacerbations, defined as worsening of asthma requiring use of OCS for ≥3 days, admission, or a visit to the emergency department. Secondary endpoints included FEV1, ACQ scores, AQLQ scores and safety. Analyses were performed in the ITT population.

MENSA (Ortega et al 2014)

MENSA was a multicentre, randomised, double-blind, double-dummy, placebo controlled phase 3 study in patients with severe refractory asthma with elevated blood EOS [14]. The study consisted of a run-in period of 1-6 weeks, followed by a 32-week treatment phase and 8-week follow up. A total of 576 patients were randomly assigned to receive mepolizumab (either 75 mg IV or 100 mg SC) or placebo q4w for 32 weeks. Randomisation was performed with the use of a centralised computer-generated, permuted-block schedule. The investigators and patients were masked to treatment assignment. Mepolizumab and placebo were identical in appearance and were administered by a staff member who was unaware of the study group assignments.

Eligible patients were ≥12 years old, had a clinical diagnosis of asthma by a physician and FEV1 ≤80% of the predicted value (adults) or FEV1 of ≤90% of the predicted value or a ratio of the FEV1 to the forced vital capacity (FVC) of ≤0.8 (adolescents). In addition, patients were required to have ≥1 of the following 3 test results: FEV1 reversibility of ≥12%, positive results on methacholine or mannitol challenge, FEV1 variability ≥20%. All patients had to have had ≥2 asthma exacerbations in the previous year that were treated with systemic glucocorticoids while they were receiving treatment with ≥880 µg of fluticasone propionate or the equivalent by inhalation per day and ≥3 months of treatment with an additional controller. In addition, all patients had to have EOS ≥150 cells/µL at screening or ≥ 300 cells/µL during the previous year. Patients were allowed to continue their current antiasthma therapy throughout the study. Current smokers or former smokers with a smoking history of ≥10 pack years and patients with a known pre-existing, clinically important lung condition other than asthma were excluded.

The primary outcome was the annualised frequency of clinically significant exacerbations, defined as worsening of asthma requiring use of OCS for ≥3 days, or a visit to an emergency department or hospitalisation. Secondary outcomes included FEV1, ACQ-5 and St. George's Respiratory Questionnaire (SGRQ) scores, and safety. All patients who were randomised and received ≥1 dose of study drug were included in the modified intention-to-treat (mITT) analyses

SIRIUS (Bel et al 2014)

SIRIUS was a multicentre, randomised, placebo-controlled, double-blind, parallel-group, phase 3 study in patients with severe, OCS-dependent, eosinophilic asthma [15]. The study had 4 phases: optimisation of the OCS regimen (weeks -8 to 0), induction (weeks 0 to 4), reduction in the OCS dose (weeks 4 to 20), and maintenance phase (weeks 20-24). Safety follow-up was performed at week 32. After optimisation of the OCS regimen, a total of 135 patients were randomised in a 1:1 ratio to receive mepolizumab or placebo. Randomisation was performed by use of a centralised, computer-generated, permuted-block design and stratified according to country and duration of previous use of OCS (<5 years *vs* ≥5 years). The investigators and patients were masked to treatment assignment. The 2 preparations were identical in appearance and were administered in a blinded fashion.

Eligible patients had at history of maintenance treatment with systemic glucocorticoids (5 to 35 mg per day of prednisone or equivalent) in the previous ≥6 months. The presence of eosinophilic inflammation was determined by a blood EOS level of ≥300 cells/µL during the 12-month period before screening or ≥150 cells/µL during the optimisation phase. All patients were treated with high-dose ICS (≥880 µg/day

fluticasone propionate (ex-actuator) or equivalent daily) and an additional controller. Current smokers or former smokers with a smoking history of ≥10 pack years and patients with a known pre-existing, clinically important lung condition other than asthma were excluded.

The primary endpoint was the % reduction in the daily OCS dose during weeks 20 to 24 as compared with the dose determined during the optimisation phase, using the following categories: 90-100% reduction, 75- <90% reduction, 50 - <75% reduction, >0 - <50% reduction, and no decrease in the OCS dose, lack of asthma control during weeks 20-24, or withdrawal from treatment. Secondary outcomes included the proportion of patients with ≥50% reduction in the OCS dose, the proportion of patients who had a total cessation in OCS use, the annualised rates of asthma exacerbations, FEV1, ACQ-5 scores, SGRQ scores and safety. A clinically significant exacerbation was defined as a worsening of asthma leading to the doubling (or more) of the existing maintenance dose of OCS for ≥3 days, hospital admission or an emergency department visit for asthma treatment. The primary analysis was performed in the ITT population, which included all randomised patients.

MUSCA (Chupp et al 2017)

MUSCA was a randomised, placebo-controlled, double-blind, parallel-group, multicentre phase 3b study in patients with in severe eosinophilic asthma [16]. The study consisted of a run-in period of 1-4 weeks, followed by 24 weeks randomised treatment in addition to standard of care. A total of 556 patients were randomly assigned in a 1:1 ratio using an interactive voice response system to receive a SC injection of either mepolizumab 100 mg or placebo. The randomisation sequence was centrally computer generated using a permuted-block design and the randomisation was done separately for each country. Mepolizumab and placebo were prepared by staff members who were aware of study-group assignments but were not involved in study assessments. The 2 preparations were identical in appearance and were administered in a masked manner. Patients, investigators, other site staff, and the entire study team including those assessing outcomes data were masked to treatment assignment.

Eligible patients were ≥12 years with severe eosinophilic asthma (blood EOS ≥ 300 cells/µL within 12 months before screening or ≥150 cells/µL at screening) who had experienced ≥2 exacerbations requiring treatment with systemic corticosteroids in the previous 12 months (for patients on maintenance OCS, two-fold or greater dose increases were required for inclusion), treatment with high-dose ICS in the 12 months before screening, plus ≥1 additional controller medication for ≥3 months before screening, FEV1 ≤80% predicted (adults) or ≤90% predicted (12–17 years). Current smokers or former smokers with a smoking history of ≥10 pack years, and patients with a known pre-existing, clinically important lung condition other than asthma were excluded.

The primary endpoint was change from baseline in SGRQ score. Secondary endpoints included exacerbation events, FEV1, ACQ-5 scores and safety. Clinically significant exacerbations were defined as worsening of asthma requiring systemic corticosteroids administered IV or orally for ≥3 days or as a single intramuscular dose, or an emergency room visit or admission to hospital. All randomised patients who received ≥1 dose of study medication were included in the mITT population for efficacy analyses.

4.3.3 Omalizumab studies

The main study characteristics of the 16 omalizumab studies relevant for this application are summarised below.

Busse et al 2001

This was a double-blind, placebo-controlled, multi-centre, parallel-group study in patients with allergic asthma [17]. At study entry, patients were switched from their usual ICS to an equivalent dose of beclomethasone dipropionate (BDP) that during the run-in period was adjusted to maintain previous asthma control and was maintained at a stable dose for 4 weeks prior to randomisation. A total of 525 patients were randomised to SC omalizumab, equivalent to 0.016 mg/kg IgE (IU/mL) q4w, or placebo. The baseline BDP dose was maintained unchanged during the stable steroid phase (weeks 1-16), and during the subsequent steroid reduction phase (weeks 16-28), the dose was reduced by approximately 25% of the baseline dose q2w for 8 weeks until discontinuation or worsening of asthma symptoms according to protocol-defined criteria.

Eligible patients were allergic asthmatics 12-75 years old, who were symptomatic despite treatment with ICS, with duration of asthma ≥1 year, positive immediate responses on skin prick testing to ≥ 1 common allergen (including *Dermatophagoides farinae*, *D. pteronyssinus*, cockroach, dog or cat), total serum IgE 30-700 IU/mL; FEV1 reversibility of ≥12%, baseline FEV1 40-80% of predicted, and treatment with 420 to 840 µg/day of BDP or its equivalent ICS for ≥3 months. Exclusion criteria included acute upper respiratory tract infection within 1 month, <3 months of stable immunotherapy, elevated IgE levels for reasons other than atopy, and regular treatment with β adrenergic antagonists.

The primary outcome was the number of exacerbation episodes experienced by a patient during the steroid reduction period and during the stable steroid phase. Secondary outcomes included number of patients experiencing ≥1 exacerbation; daily asthma symptoms; rescue medication use, pulmonary function (PEF, FEV % predicted), global evaluation of effectiveness, AQLQ scores and safety [18]. Statistical analyses were performed using all randomised patients (ITT population). The long-term effect of omalizumab in patients with severe allergic asthma was evaluated in a 24-week, double-blind extension phase [19].

Soler et al 2001

This was a multicentre, randomised, double-blind, placebo-controlled, parallel-group study in patients with moderate-to-severe allergic asthma [20]. After a run-in period, a total of 546 patients were randomised to receive SC placebo or omalizumab every 2 or 4 weeks (≥0.016 mg/kg/IgE (IU/mL) q4w depending on body weight and serum total IgE) for 7 months. A constant BDP dose was maintained during a 16-week stable-steroid phase and progressively reduced to the lowest dose required for asthma control over the following 8 weeks.

Eligible subjects were patients aged 12–75 years with a diagnosis of asthma of ≥1 year duration who met the standard criteria of the ATS, had a positive skin prick test to ≥1 of the allergens *Dermatophagoides farinae*, *D. pteronyssinus*, dog or cat; serum total IgE level 30-700 IU/mL, baseline FEV1 40-80% of predicted, FEV1 increasing by ≥12% within 30 minutes of taking inhaled salbutamol, treatment with ICS in doses equivalent to 500–1,200 mg of BDP/day for ≥3 months and use of β2-adrenoceptor agonists on an as-needed or regular basis. Asthma had to be stable, with no significant change in regular medication and no acute exacerbation requiring additional corticosteroid treatment for ≥1 month prior to the screening visit. Patients regularly taking OCS were not included.

The primary outcome was asthma exacerbations, defined as a worsening of symptoms requiring treatment with systemic corticosteroids or doubling the baseline dose of BDP. Secondary outcomes included the number of patients experiencing ≥1 asthma exacerbation during both the stable-steroid and the steroid-reduction phases, % reduction in the BDP dose at the end of the steroid-reduction phase, salbutamol rescue use, asthma symptom scores, morning PEF and FEV1 as % predicted, AQLQ scores and safety [22].

Statistical analyses were performed using all randomised patients (ITT population).The long-term effect of omalizumab in patients with severe allergic asthma was evaluated in a 24-week, double-blind extension phase [21].

Holgate et al 2004

This randomised, double-blind, placebo-controlled study evaluated the ability of omalizumab to improve disease control sufficiently to enable reduction of ICS in patients with severe allergic asthma [23]. After a run-in period when patients received an optimised fluticasone dose (≥1000 µg/day) for 4 weeks, patients were randomised to receive SC omalizumab (≥0.016mg/kg/IgE (IU/mL) q4w; n=126) or matching placebo (n=120) at an interval of 2 or 4 weeks. The study comprised a 16-week add-on treatment phase followed by a 16-week fluticasone-reduction phase.

Eligible patients were aged 12–75 years with severe asthma. All patients required ≥1000 µg/day fluticasone for symptom control (patients were all switched to inhaled fluticasone during the run-in period), demonstrated positive skin prick test to aeroallergen(s), and had total serum IgE 30-700 IU/mL. Short-acting beta-agonists were allowed as needed, as was continued use of LABA. Patients taking theophylline or anti-leukotrienes, with a history of anaphylaxis, recent near-fatal asthma, respiratory infection within 4 weeks of the study, parasitic infection or an elevated serum total IgE for reasons other than atopy were excluded.

The primary outcome was the percentage reduction from baseline in fluticasone dose after 32 weeks of treatment. Secondary outcomes included absolute reduction in fluticasone dose compared to baseline, asthma exacerbations (defined as a worsening of asthma requiring treatment with systemic corticosteroids), use of rescue medication, asthma symptom score, PEF, post-bronchodilator spirometry, AQLQ scores and safety. Between-group differences for efficacy variables were analysed on the ITT population.

Vignola et al 2004

The SOLAR study was a randomised, double-blind, placebo-controlled study evaluating the safety and efficacy of omalizumab in patients with concomitant allergic asthma and persistent allergic rhinitis [24]. In total, 405 patients receiving stable treatment (≥400 µg budesonide) were randomised to receive SC omalizumab (≥0.016 mg/kg/IgE (IU/mL) q4w) or placebo for 28 weeks.

Eligible patients were aged 12-75 years with a history of allergic asthma for ≥1 year with ≥12% increase in FEV1 after 400 µg salbutamol, and a history of moderate-to-severe persistent allergic rhinitis symptoms for ≥2 years. Patients had to have a positive skin prick test to ≥1 indoor allergen that they would be exposed to daily during the study, and IgE 30-1300 IU/mL. All patients received ≥400 µg/day of ICS and had a history of ≥2 unscheduled medical visits for their asthma during the past year or ≥3 in the past 2 years. Participants were also required to have total scores of >64/192 (32 items, amended to use a 0-6 scale) in the AQLQ and >56/168 (28 items, 0-6 scale) in the Rhinitis Quality of Life Questionnaire (RQLQ) at baseline, corresponding to a minimum quality of life (QoL) score worse than that of mild symptoms in both diseases. Patients receiving the following treatments were excluded: systemic corticosteroids, long-acting antihistamines, cromolyn sodium, nedocromil sodium, oral beta-adrenoreceptor agonists, theophylline, leukotriene-receptor antagonists, inhaled anticholinergics, methotrexate, gold salts, cyclosporin and allergen-specific immunotherapy. Patients with seasonal allergic rhinitis at baseline, acute sinusitis, chest infection, persistent nonallergic rhinitis, pregnancy, or a platelet count of ≤130 $\times 10^9$/L were also excluded.

The co-primary efficacy outcomes were the incidence of asthma exacerbations over the 28-week treatment period and the proportion of patients with improvement in both asthma and rhinitis QoL scores. An asthma

exacerbation was defined as worsening of asthma requiring treatment with systemic corticosteroids or doubling of the baseline inhaled budesonide dose. QoL assessments were made every 8 weeks, and the primary outcome was the change from baseline in both the AQLQ and RQLQ at week 28. The primary analysis compared the proportion of responders (defined as a patient with a ≥1.0-point improvement from baseline in both AQLQ and RQLQ). A secondary analysis assessed the number of patients achieving 0.5, 1.0 and 1.5-point improvements, which indicate the minimal important difference in QoL, a moderate change and a large change in QoL, respectively. Secondary outcomes included rescue medication use, separate AQLQ and RQLQ evaluations, Wasserfallen asthma and rhinitis clinical symptom scores, patient and investigator global evaluations of treatment effectiveness, pulmonary function tests (FEV1, FVC, morning (PEF)), ICS use and safety. Three patient populations were defined for analysis: ITT (all randomised patients), per protocol (all patients who completed the study without major deviations from protocol procedures) and safety (all patients randomised who received ≥1 dose of study medication).

Ayres et al 2004

This randomised, open-label study evaluated the efficacy and tolerability of omalizumab treatment *vs* best standard care (BSC) in patients with poorly controlled (moderate-to-severe) allergic asthma [25]. In total, 312 patients were randomised to receive BSC with or without SC omalizumab (≥0.016 mg/kg/IgE (IU/mL) q4w) for 12 months.

Eligible patients were aged 12-75 years with persistent (>2 years) moderate-to-severe allergic asthma, with poorly controlled disease (defined as ≥1 emergency room visit/hospitalisation and ≥1 additional course of OCS due to asthma in the last year). All patients had FEV1 reversibility of ≥12% within 30 minutes of taking inhaled salbutamol and were receiving ≥400 µg/day (adolescents, age <18 years) or ≥800 µg/day (adults) inhaled BDP (or equivalent). Patients had a positive skin prick test to ≥2 clinically relevant antigens, total serum IgE 30-700 IU/mL and body weight suitable for optimum omalizumab dosing. Exclusion criteria included pregnancy and lactation, female patients of child-bearing potential not using adequate contraception, a history of smoking ≥10 pack-years, active lung disease except allergic asthma or any other significant systemic disease, immunocompromised, and elevated serum IgE levels for reasons other than atopy. Patients receiving desensitisation immunotherapy were also excluded.

The primary outcome was the annualised number of asthma deterioration-related incidents (ADRIs) defined as ≥1 of the following events because of asthma: course of systemic corticosteroids or antibiotics for ≥2 days, ≥2 missed school/work days (or significantly reduced performance for nonworking adult patients, as judged by the patient), unscheduled physician visit, or hospitalisation/ emergency room visit. Consecutive ADRIs were counted as individual incidents if they were separated by ≥2 ADRI-free days. The ADRIs may also have been recorded as asthma worsening adverse events (AEs). If the asthma worsening AE required the administration of systemic corticosteroids, it was also recorded as an asthma exacerbation AE. For patients on maintenance systemic corticosteroids, only short-term supplemental bursts of systemic corticosteroids related to an asthma exacerbation were included within the definition of an ADRI/asthma exacerbation. Secondary outcomes included the annualised number of clinically significant asthma exacerbations, defined as episodes of asthma worsening requiring treatment with systemic corticosteroids, lung function (morning FEV1), use of rescue salbutamol, Wasserfallen asthma symptom score and safety. In a subgroup of patients with comorbid asthma and rhinitis at baseline, asthma and rhinitis symptoms were evaluated using the Wasserfallen symptom score. All efficacy analyses were completed on the ITT population. The efficacy of omalizumab in the subgroup of patients with inadequately controlled severe persistent allergic asthma was evaluated separately [26].

Humbert et al 2005

The INNOVATE study was a randomised, double-blind, placebo-controlled study of omalizumab as add-on therapy in patients with severe persistent asthma who were inadequately controlled despite best available therapy [27]. Following a run-in phase, patients inadequately controlled despite therapy with high-dose ICS and LABA were randomised to receive SC omalizumab (≥0.016 mg/kg/IgE (IU/mL) every 2 or 4 weeks) or placebo for 28 weeks.

Eligible patients were aged 12-75 years with persistent allergic asthma requiring regular treatment with >1000 µg/day BDP or equivalent and LABA, FEV1 ≥12 %, FEV1 ≥40% and <80% of predicted, positive skin prick test to ≥1 perennial aeroallergen to which they were likely to be exposed during the study, total serum IgE 30-700 IU/mL, ≥2 asthma exacerbations requiring systemic corticosteroids, or 1 severe exacerbation (PEF/FEV1 <60% of personal best, requiring systemic corticosteroids) resulting in hospitalisation or emergency room treatment, in the past 12 months. Additional asthma medications, taken regularly from >4 weeks prior to randomisation were permitted, including theophyllines, oral beta-agonists and antileukotrienes. Maintenance OCS (maximum 20 mg/day) were permitted providing ≥1 exacerbation in the previous 12 months had occurred while on this therapy. Exclusion criteria included: Smokers or smoking history of ≥10 pack-years, treatment for an exacerbation within 4 weeks of randomisation, use of methotrexate, gold salts, troleandomycin or cyclosporin within 3 months of the first visit, and prior omalizumab treatment.

The primary outcome was the rate of clinically significant asthma exacerbations (defined as a worsening of asthma symptoms requiring treatment with systemic corticosteroids) during the 28-week double-blind treatment phase. Hospitalisation, emergency visit and unscheduled doctor's visits for exacerbations were also recorded. Secondary outcomes included the clinical symptom score, PEF, use of rescue medication and safety. QoL was assessed using the AQLQ. Following scientific advice from the European Union Committee on Proprietary Medicinal Products (CPMP), efficacy analyses were performed on the patient population randomised after implementation of a protocol amendment. Patients randomised post-amendment comprised the primary ITT population. The safety population comprised all patients who received treatment.

Ohta et al 2009

This was a randomised, double-blind, placebo-controlled study evaluating the efficacy and safety of omalizumab in an Asian population with moderate-to-severe persistent asthma [28]. Japanese patients with uncontrolled asthma, despite receiving high-dose ICS and other standard therapies, were randomised to receive add-on SC treatment with omalizumab (≥0.016 mg/kg/IgE (IU/mL) every 2 or 4 weeks) or placebo for 16 weeks.

Eligible patients were aged 20-75 years, with moderate-to-severe asthma according to Japanese Guidelines, treated with BDP chlorofluorocarbon (or equivalent) at ≥800 µg/day plus one or more of the following additional controller medications: LABA, sustained-release theophylline, leukotriene receptor antagonist, OCS. Patients should have a positive skin prick test to ≥1 perennial aeroallergen to which they were likely to be exposed during the study, total serum IgE 30-700 IU/mL, and insufficient asthma control meeting one of the following 5 criteria: asthma symptoms interfere with night-time sleep ≥1 day/week, asthma symptoms restrict daily activities, rescue medication (short-acting inhaled beta-agonist) needed ≥1 day/week, PEF diurnal variation ≥20% on ≥1 day/week, and FEV1 or mean PEF value 40-80% of predicted. Exclusion criteria included the presence of complicated pulmonary disease considered to interfere with the evaluation, chronic use of OCS (>10 mg/day of prednisolone), use of an immunosuppressant drug within 3 months of the first visit, a positive skin reaction to the study drug, and a history of anaphylaxis.

The primary outcome was the change from baseline in morning PEF (L/min), as recorded on diary cards. Asthma symptoms, daily activity status, sleep status and use of asthma medications were also recorded on diary cards, and the scores were calculated as secondary outcomes, which also included safety. Worsening of asthma that required use of a systemic corticosteroid was regarded as a clinically significant asthma exacerbation event leading to withdrawal from the study, and the number of patients who experienced such events was compared between the treatment arms. The statistical analyses were performed for the full analysis set (modified ITT population), defined as patients who were randomised to treatment, took study drug at least once and had ≥1 post-dose efficacy measurement.

Chanez et al 2010

This was a randomised, double-blind, placebo-controlled study [29]. Patients with severe, persistent allergic asthma uncontrolled by high-dose ICS and LABA received either SC omalizumab (n=20) (≥0.016 mg/kg/IgE (IU/mL) q4w) or placebo (n=11) over 16 weeks.

Eligible patients were aged ≥18 years with severe persistent allergic asthma, FEV1<80% of predicted, frequent daily symptoms (≥4 days/week average) or nocturnal awakening (≥1/week average), multiple severe asthma exacerbations (≥2), severe asthma exacerbations requiring an unscheduled medical intervention with systemic corticosteroid in the past year, or hospitalisation/emergency room visit for an asthma exacerbation in the past year, high-dose ICS >1000 µg BDP or equivalent and an inhaled LABA, positive skin prick test or *in vitro* reactivity to a perennial aeroallergen, total serum IgE 30-700 IU/mL, and suitable total serum IgE level and weight according to omalizumab dosing tables. Exclusion criteria included: smoking history >20 pack-years, asthma exacerbation within 4 weeks prior to randomisation, history of food or drug-related severe anaphylactoid/anaphylactic reaction, elevated serum IgE levels for reasons other than allergy, previous use of omalizumab and uncontrolled chronic diseases including cancer.

The primary outcome was the cell surface expression of IgE high-affinity receptor (FcεRI) on basophils and plasmacytoid dendritic cells between baseline and week 16, as determined by flow cytometry. Secondary outcomes included asthma control and symptoms, exacerbations, use of rescue medication, lung function (FEV1, PEF), sick leave and safety. All patients receiving 1 dose of study medication with ≥1 post-dose efficacy assessment were included in the ITT population, which was used for the efficacy analyses. AEs were recorded for all patients receiving ≥1 dose of study medication with ≥1 post-dose safety assessment.

Bousquet et al 2011

This was a randomised, open-label study of omalizumab *vs* optimised asthma therapy (OAT) in severe allergic (IgE-mediated) asthma [30]. Patients with severe allergic asthma, uncontrolled despite GINA 2004 Step 4 therapy, received OAT and omalizumab (n=272) or OAT (n=128) for 32 weeks. Response or nonresponse was evaluated at weeks 16 and 32. Omalizumab was administered SC at a dose of ≥0.016 mg/kg/IgE (IU/mL) every 2 or 4 weeks, based on the patient's body weight and baseline total serum IgE level.

Eligible patients were aged 12-75 years with severe persistent allergic (IgE-mediated) asthma and ≥2 severe asthma exacerbations (requiring treatment with systemic corticosteroids) while receiving ≥800 µg BDP or equivalent plus a LABA in the 3 years prior to screening, with ≥1 severe exacerbation within the previous year, body weight of 20-150 kg, positive skin prick or radioallergosorbent test to ≥1 perennial allergen, total serum IgE 30-700 IU/mL, ≥12% reversibility in FEV1 within 30 minutes of taking 200-400 µg salbutamol, FEV1 40-80% of predicted. Additional asthma medications (e.g. OCS, theophyllines, cromones, anti-leukotrienes) were allowed if established >4 weeks prior to randomisation. Short-acting beta-agonists were permitted as rescue medication. Exclusion criteria included systemic corticosteroids (for reasons other than

asthma), beta-adrenergic antagonists, immunosuppressants, anticholinergics, or desensitisation therapy with <3 months of stable maintenance doses prior to the first visit, history of food or drug-related anaphylaxis or allergy to antibiotics, asthma related to aspirin or nonsteroidal anti-inflammatory drugs, smoking history >10 pack-years, active lung disease other than allergic asthma, elevated serum IgE levels for reasons other than allergy, significant underlying medical conditions, or abnormal ECG or laboratory test values, and previous treatment with omalizumab.

The primary outcome was the persistency rate (%) of response in patients receiving omalizumab. Response was based on the investigator's (physician's) global evaluation of treatment effectiveness. Secondary outcomes included persistency rate (%) of nonresponse in patients receiving omalizumab, persistency rates of response/nonresponse in patients receiving OAT alone, patient's global evaluation of treatment effectiveness, change from baseline in FEV1 and %-predicted FEV1, clinically significant asthma exacerbations (defined as worsening of asthma requiring treatment with rescue systemic corticosteroids), severe exacerbations (defined as clinically significant exacerbations with ≥1 of the following: hospital admission and/or intubation, an emergency care visit, breathlessness at rest or PEF or FEV1 < 60% of predicted/personal best, or a > 30% fall from personal best PEF on 2 successive days), hospitalisations and total emergency visits because of asthma exacerbation and change from baseline in the ACQ overall score. Efficacy analyses were based on a modified ITT population, consisting of all randomised patients who had ≥1 post-baseline efficacy assessment. All safety analyses were based on the safety population, which included all patients who received any study drug and had ≥1 post-baseline safety assessment. A subgroup analysis evaluated the OCS-sparing effect of omalizumab added to OAT, compared with OAT alone [31].

Hanania et al 2011

This was a randomised, double-blind, placebo-controlled study evaluating the efficacy and safety of omalizumab in 850 patients with inadequately controlled severe asthma who were receiving high-dose ICS and LABAs, with or without additional controller therapy [32]. SC omalizumab was dosed at a minimum dose of 0.008 mg/kg of body weight per IgE (IU/mL) q2w or 0.016 mg/kg/IgE (IU/mL) q4w.

Eligible patients were aged 12-75 years with a history of severe allergic asthma for ≥1 year before screening, with asthma that was not well-controlled despite treatment with high-dose ICS (≥500 µg fluticasone or equivalent) and LABAs with or without other controllers (including OCS). Asthma was considered not well-controlled if patients had persistent asthma symptoms with current therapy, defined as an average of ≥1 night-time awakenings per week and daytime asthma symptoms requiring the use of rescue medication for ≥2 days/week in the 4 weeks before screening and for 2 consecutive weeks of up to 4 weeks before randomisation. Patients were required to have ≥1 documented asthma exacerbation during the past 12 months, defined as increased asthma symptoms requiring treatment with systemic corticosteroid rescue therapy, positive skin prick test or *in vitro* response (radioallergosorbent test) to dog, cat, cockroach, *Dermatophagoides farinae* or *D. pteronyssinus* in the 12 months before screening, total serum IgE 30-700 IU/mL, baseline prebronchodilator FEV1 of 40-80% of predicted, and body weight of 30-150 kg. Exclusion criteria included asthma exacerbation requiring intubation in the 12 months before screening or an exacerbation requiring treatment with systemic corticosteroids (or an increase in the baseline dose of OCS) in the 30 days before screening, active lung disease other than asthma, treatment with omalizumab in the 12 months before screening, elevated serum IgE levels for reasons other than allergy, and smoking history of ≥10 pack-years.

The primary outcome was the rate of protocol-defined asthma exacerbations during the 48-week treatment period. A protocol-defined asthma exacerbation was worsening asthma symptoms requiring treatment with systemic corticosteroids for 3 or more days; for patients receiving long-term OCS, an

exacerbation was a 20-mg or more increase in the average daily dose of oral prednisone (or a comparable dose of another systemic corticosteroid). Secondary outcomes included change from baseline in Total Asthma Symptom Severity score (TASS), mean puffs/day of albuterol, AQLQ scores and safety. The primary analysis population included all randomly assigned patients who received ≥1 dose of study treatment according to randomisation. Safety analyses were conducted in all patients who received the study drug according to the actual treatment received.

Bardelas et al 2012

This was a randomised, double-blind, placebo-controlled study evaluating the effect of omalizumab on asthma control in patients with persistent allergic asthma [33]. In total, 271 patients received omalizumab at a dose of ≥0.016 mg/kg/IgE (IU/mL) (n=136) or placebo (n=135) every 2 or 4 weeks for 24 weeks.

Eligible patients were aged ≥12 years, were receiving ambulatory care and had inadequately controlled persistent allergic asthma, positive skin prick test or radioallergosorbent test to ≥1 perennial aeroallergens in the prior 12 months, total serum IgE 30-700 IU/mL, physician diagnosis of asthma ≥12 months prior to screening visit date or symptoms compatible with asthma for ≥12 months if diagnosis was made within 12 months of screening, prescription for at least a medium-dose ICS plus LABA (fluticasone 250 µg/salmeterol 50 µg one inhalation or budesonide 160 µg/formoterol 4.5 µg 2 inhalations twice daily), a medium-dose ICS plus either a leukotriene receptor antagonist, theophylline, or zileuton for 23 months, body weight ≤150 kg, and nonsmoking history of ≥1 year (former smokers had a smoking history of ≤10 pack-years). Uncontrolled was defined as Asthma Control Test (ACT) total score ≤19 plus ≥1 of the following: symptoms >2 days/week, night-time awakenings ≥once/week, use of short-acting bronchodilators >2 days/week, or FEV1 ≤80% of predicted. Exclusion criteria included history of intubation for asthma or anaphylaxis, systemic steroid treatment for asthma exacerbation within 4 weeks, <3 months stable maintenance OCS therapy or stable maintenance desensitisation immunotherapy, active lung disease other than allergic asthma, current or anticipated use of beta-blockers or use of methotrexate, gold salts, cyclosporin, or troleandomycin within 3 months of enrollment, elevated serum lgE levels for reasons other than atopy or combination of lgE level and weight that required an omalizumab dose >750 mg q4w.

The primary outcome was change from baseline in ACT total score. Secondary outcomes included the investigator's global evaluation of treatment effectiveness and safety. Exploratory efficacy assessments included the effect of asthma on occupational function (self-assessed using the Work Productivity and Activity Impairment Questionnaire), daytime asthma symptoms, night-time awakenings, short-acting bronchodilator use, change from baseline in FEV1, and the use of rescue systemic corticosteroids to treat asthma exacerbations. All efficacy variables were analysed using the full analysis set of randomised patients to whom study drug had been assigned through randomisation (modified ITT population).

Hoshino et al 2012

This was a randomised, open-label study of the effect of omalizumab *vs* conventional therapy on airway wall thickening in Japanese patients with asthma [34]. In total, 30 patients with severe persistent asthma were randomised to conventional therapy with (n=14) or without SC omalizumab (n=16) for 16 weeks. The dose of omalizumab was ≥0.016 mg/kg/IgE (IU/mL) every 2 or 4 weeks.

Eligible patients were aged 20-75 years, nonsmokers, with severe allergic asthma, who were symptomatic despite treatment with a high-dose ICS plus a LABA, with positive skin prick test to ≥1 common allergen (*Dermatophagoides pteronyssinus*, *D. farinae*, cat, dog), total serum IgE 30-700 IU/mL, FEV 1 reversibility of <12% after inhalation of 200 µg salbutamol, methacholine provocation concentration causing a 20% fall in FEV1 <8 mg/mL, and treatment with ≥400 µg fluticasone propionate or equivalent ICS and LABA for

8 weeks. Other asthma medications, including theophylline and anti-leukotrienes taken regularly from >8 weeks prior to randomisation were permitted, as were maintenance OCS (maximum prednisolone 20 mg/day), providing ≥1 exacerbation had occurred in the previous year. Severe asthma was considered not to be well controlled if patients had persistent asthma symptoms with an ICS plus a LABA, defined as an average of ≥1 night-time awakenings/week and daytime asthma symptoms requiring the use of rescue medication for ≥2 days/week. Exclusion criteria included prior omalizumab treatment, requirement of omalizumab doses of >750 mg per 4 weeks on the basis of serum IgE and body weight, and treatment for an exacerbation within 4 weeks of randomisation.

The primary outcome (assumed, not specified) was airway dimensions as assessed by a validated computed tomography technique. Secondary outcomes included the percentage of eosinophils in induced sputum, pulmonary function (FEV1 and PEF), AQLQ scores and safety.

Rubin et al 2012

The QUALITX study was a randomised, open-label Brazilian study of the effect of omalizumab as add-on therapy on asthma-related QoL in patients with severe allergic asthma inadequately controlled despite regular treatment with ICS plus LABA [35]. In total, 116 patients were randomised to the study groups for 20 weeks: 78 in the omalizumab group and 38 in the control group. The SC dose of omalizumab was ≥0.016 mg/kg/IgE (IU/mL) every 2 or 4 weeks.

Eligible patients were aged 12-75 years, with body weight between 20 and 150 kg, and had severe persistent asthma uncontrolled despite treatment with, at least, ICS (≥500 µg/day of fluticasone or equivalent) plus LABA, a positive skin prick test (diameter of wheal 23 mm) for ≥1 perennial aeroallergen, total serum IgE 30-700 IU/mL, daily or persistent asthma symptoms, night symptoms at least once a week, ≥2 exacerbations treated with OCS or ≥1 severe exacerbation treated with OCS and hospitalisation/ emergency room visit in last year, and FEV1 >40% and <80% of predicted. All included patients could read and understand the AQLQ. Exclusion criteria included patients with a known history of allergy or hypersensitivity to omalizumab, medical history of psychiatric disorder, outside the defined age and body-weight ranges, history of severe anaphylactoid reactions to food or drugs, use of systemic corticosteroids for any reason other than asthma, and use of methotrexate, gold salts, cyclosporine, or any other immunosuppressant or beta-2 antagonist medications in the last 3 months prior to screening.

The primary outcome was the mean change from baseline in overall AQLQ score in omalizumab-treated patients compared with the control group. Secondary outcomes included rescue medication use, incidence of asthma exacerbations, perception of treatment efficacy among patients, mean change from baseline in AQLQ score, >1.5-point increase in overall AQLQ score, pulmonary function (FEV1) and safety. Efficacy and safety analyses were performed on the ITT population.

Busse et al 2013

This was a randomised, double-blind, placebo-controlled study evaluating the effectiveness of omalizumab in patients with atopic asthma (elevated serum total IgE levels) who remained symptomatic and uncontrolled on ICS with or without other controller medications despite having normal lung function [36]. In total, 328 patients were randomised to receive SC omalizumab (n=157) or placebo (n=171) treatment. Omalizumab was dosed at a minimum dose of 0.008 mg/kg of body weight per IgE (IU/mL) q2w or 0.016 mg/kg/IgE (IU/mL) q4w.

Eligible patients were aged 12-75 years with elevated total serum IgE levels (>30-<1300 IU/mL), FEV1 >80% of predicted (normal lung function), and inadequate symptom control defined as a daytime asthma symptom score of ≥1 on ≥20 days and a mean symptom score of ≥1.5, or night-time awakening due to

asthma symptoms > 4 times during the 4-week run-in period. Exclusion criteria included chronic systemic corticosteroids (oral or IV) within 3 months or a burst of OCS within 2 weeks prior to screening, omalizumab therapy at any time within 12 months prior to screening, a significant medical illness/active lung disease other than asthma and use of immunosuppressants or other investigational drugs within 30 days prior to screening.

The primary outcome was the average rate of asthma exacerbations during the 24-week treatment period, starting from the first dosing date and ending 30 days following the last dosing date/date of study completion or early discontinuation, whichever was earlier. A sensitivity analysis was conducted to evaluate the effect of omalizumab on ATS/ERS-defined exacerbations, which excluded doubling of the patient's baseline ICS dose from the protocol definition of an exacerbation. Secondary outcomes included change from baseline to week 24 in nocturnal and daytime asthma symptom scores, relative change from baseline to week 24 in % predicted FEV1 and safety. Efficacy and analyses were performed on all randomised patients who received ≥1 dose of the study drug, defined as a modified ITT population.

Li et al 2016

This was a randomised, double-blind, placebo-controlled study on the effect of omalizumab on QoL and asthma control in Chinese patients with moderate-to-severe persistent allergic asthma who remain inadequately controlled despite GINA (2009) step 4 therapy [37]. In total, 609 patients were randomised to receive either add-on omalizumab (≥0.016 mg/kg/IgE (IU/mL) q4w) or add-on placebo by SC injections for 24 weeks.

Eligible patients were aged 18-75 years, with confirmed diagnosis of moderate-to-severe persistent allergic asthma (inadequately controlled symptoms despite medium-to-high-dose ICS+LABA [GINA step 4] therapy) for ≥1-year duration at screening, weighing >20-≤150 kg, positive reaction to ≥1 perennial aeroallergen, total serum IgE 30-700 IU/mL, reported ≥2 or ≥3 exacerbation events in previous 12 or 24 months, respectively, FEV1 of 40-80% of predicted, post-bronchodilator reversibility of ≥12% within 30 minutes and compliance with completion of PEF/electronic diary during the 4-week run-in period. Exclusion criteria included a history of malignancy, hypersensitivity, or severe food- or drug-related anaphylaxis, active lung disease other than allergic asthma, clinically significant electrocardiogram (ECG) or chest X-ray abnormality, elevated total serum IgE level without increase in specific IgE, or use of other investigational drugs within ≥30 days/5 half-lives of enrolment.

The primary outcome was the mean change from baseline in morning PEF. Secondary outcomes included FEV1 % predicted, ACQ scores, asthma symptom scores and rescue medication use, standardised AQLQ scores, global evaluation of treatment effectiveness responder analysis and safety. The rate and seasonal effect of protocol-defined asthma exacerbations (clinically significant worsening of asthma requiring addition or increase in dose/dosing-frequency of systemic corticosteroids or IV theophylline) were assessed as exploratory outcomes. All efficacy variables were analysed, unless specified, using the full analysis set (modified ITT population), consisting of all patients who received ≥1 dose of the study drug.

Mukherjee et al 2019

This was a randomised, double-blind, placebo-controlled study of omalizumab in patients with severe asthma and persistent sputum eosinophilia [38]. In total, 11 patients were randomised to either omalizumab or placebo for 16 weeks (either once monthly for 4 months or q2w for 4 months, dependent on the body weight and IgE level). From weeks 16-32, a standardised corticosteroid reduction at intervals of 4 weeks while on the same intervention/placebo regime was carried out.

Eligible patients were aged 18-75 years with confirmed asthma (FEV1 ≥12% or provocative concentration of inhaled methacholine needed to reduce FEV1 by 20% of <8 mg/mL), positive skin prick test to common aeroallergens, elevated serum IgE levels (range not specified), who were symptomatic (ACQ-5 ≥1.5) with evidence of sputum eosinophils (>3%) despite high-dose maintenance corticosteroid therapy (<1500 µg fluticasone propionate or equivalent).

The primary outcome was reduction in sputum eosinophils. Secondary outcomes were exacerbation rates, reduction in ICS dose, FeNO, ACQ-5, lung function (FEV1). Analyses were done on a modified ITT analysis set.

5 Clinical questions

5.1 What is the added clinical value of dupilumab compared with mepolizumab in treatment of patients >12 years of age with severe asthma with type 2 inflammation characterised by eosinophilia?

Population

Patients >12 years with severe asthma with type 2-inflammation characterised by eosinophilia defined as blood EOS ≥150 cells/µL observed within the last month or blood EOS ≥300 cells/µL observed within the last year, or with sputum eosinophilia ≥3 % within the last year.

Intervention

Dupilumab in a loading dose of 400 mg (two 200 mg SC injections), followed by 200 mg SC injection q2w as add-on to standard treatment.

For patients in maintenance treatment with OCS or for patients with concomitant moderate-to-severe atopic dermatitis: Dupilumab in a loading dose of 600 mg (two 300 mg SC injections), followed by 300 mg SC injection q2w as add-on to standard treatment.

Comparator

Mepolizumab (100 mg) SC injection q4w as add-on to standard treatment. Data from studies using mepolizumab 75 mg IV dosing can be used as comparator since this dose is regarded as equivalent to 100 mg SC dosing by the Medicines Council [1].

5.1.1 Presentation of relevant studies

Dupilumab studies

The phase 2b study (DRI12544) [6, 7] and the QUEST phase 3 study [8, 10] reported data for the increased EOS subgroup in a population with uncontrolled moderate-to-severe persistent asthma. The VENTURE study [11, 12] reported data for the increased EOS subgroup in a patient population with severe OCS-dependent asthma. The 3 studies are presented in section 4.3.1 and summaries of main study characteristics are presented in appendix 8.2.1. Baseline characteristics for the ITT populations are summarised in appendix 8.3.1.

From the dupilumab phase 2b and QUEST studies, only data for the treatment arms with the relevant dosage regimen are presented, i.e. the 200 mg dose q2w and matching placebo groups. For the dupilumab VENTURE study in OCS-dependent asthma patients, results are presented for the 300 mg q2w dose *vs* placebo.

Mepolizumab studies

The DREAM [13], MENSA [14]and MUSCA [16] studies reported results for patients with severe, eosinophilic asthma, while the SIRIUS study [15] reported results for a patient population with severe OCS-dependent asthma. The studies are presented in section 4.3.2 and summaries of main study characteristics are presented in appendix 8.2.2. Baseline characteristics for the ITT populations are summarised in appendix 8.3.2.

The mepolizumab studies in patients with severe eosinophilic asthma tested different dosage regimens. The MUSCA study compared 100 mg SC mepolizumab with placebo, the DREAM study compared 75 mg IV mepolizumab with placebo, and the MENSA study compared both a 75 mg IV and a 100 mg SC dose with placebo. Since the 75 mg IV and 100 mg SC doses are considered equivalent [1], data for the SC and IV dosage regimens in the MENSA study are pooled in this application. The mepolizumab SIRIUS study in OCS-dependent asthma patients compared the 100 mg SC dose with placebo.

5.1.2 Relevant differences between studies

The ITT populations in the dupilumab studies varied from those in the mepolizumab studies in some patient inclusion criteria and baseline characteristics. The dupilumab studies included patients with moderate-to-severe asthma and medium-to-high-dose ICS, while the mepolizumab studies only included patients with severe asthma and use of high-dose ICS. Results from patients on high-dose ICS are not reported separately for the dupilumab phase 2b and QUEST studies. However, the results from a pre-specified analysis of the QUEST study, that assessed the efficacy of dupilumab by disease severity determined by baseline ICS dose (high/medium), demonstrated that there is no difference in treatment results between patients on medium-dose *vs* high-dose ICS at baseline [3].

Patients in the dupilumab studies had a lower number of exacerbations in the last year (mean number of exacerbations 1.9-2.3 across groups) than patients in the mepolizumab studies (mean number of exacerbations 2.7-3.8 across groups). On the other hand, mean ACQ scores across treatment groups were slightly higher (indicating less control) in the dupilumab studies (2.4-2.8) compared to the mepolizumab studies (2.0-2.5). In OCS-dependent patients, the patients in the dupilumab VENTURE study had a lower FEV1 and FEV1 % predicted (1.53-1.63 L and 51.6-52.7%) compared to the patients in the mepolizumab SIRIUS study (1.90-2.00 L and 57.8-59.6%) (appendix 8.3.1 and 8.3.2), indicating poorer lung function.

The inclusion criteria for EOS in the mepolizumab studies were similar to the criteria for eosinophilia defined by the Medicines Council: blood EOS ≥150 cells/µL observed within the last month, or blood EOS ≥300 cells/µL observed within the last year, or sputum eosinophilia ≥3 % within the last year [1]. In the DREAM study [13], patients could also be included based on increased FeNO (≥50 ppb) or deterioration of asthma control with ≥25% reduction in ICS or OCS. However, for dupilumab, the increased EOS subgroup used in this application was defined as blood EOS ≥150 cells/µL at baseline. Thus, since patients in the mepolizumab studies could be included based on old EOS data, the actual EOS values could have declined before inclusion into the study. This might be reflected in the mean EOS values at baseline being slightly higher in the dupilumab ITT populations (325-370 cells/µL) than in the mepolizumab populations (250-350 cells/µL) (appendix 8.3.1 and 8.3.2).

5.1.3 Results per study

By-study results extracted from the publications, European Public Assessment Report (EPARs) and/or SmPCs are summarised in appendix 8.5.1 for the dupilumab studies and appendix 8.5.2 for the mepolizumab studies. No discrepancies between published data, the EPARs and/or SmPCs were noted.

Efficacy results – uncontrolled, persistent eosinophilic asthma

Reduction in annual number of exacerbation events

All studies reported the annualised rates of severe exacerbation events. Severe exacerbations were in all studies defined as a deterioration of asthma leading to treatment for ≥3 days with systemic glucocorticoids or hospitalisation or an emergency department visit leading to treatment with systemic glucocorticoids. In

the 2 studies in OCS-dependent severe eosinophilic asthma, the dose of systemic glucocorticoids used should be ≥2 times the current dose of OCS.

Patients with uncontrolled, persistent eosinophilic asthma

The 2 studies with 1 year of follow-up had comparable, statistically significant rate ratios for annual exacerbation rates; 0.442 for dupilumab *vs* placebo and 0.52 for mepolizumab *vs* placebo (Table 6). Generally, slightly lower rate ratios were reported for the studies with shorter duration of follow-up. The absolute reductions in annual number of severe exacerbation rates were across all studies in the range of 0.6-1.2 events/patient-year compared to placebo. The larger rate differences in the DREAM and MENSA studies resulted from larger annual exacerbation rates in both treatment arms; however, since the CIs could not be estimated, these results should be interpreted with caution.

TABLE 6 SUMMARY OF ANNUALISED EXACERBATION RATES – UNCONTROLLED, PERSISTENT EOSINOPHILIC ASTHMA

Study	Follow up	Rate (95% CI)		RD (95% CI)	RR (95% CI)
Dupilumab studies		**Dupilumab**	**Placebo**		
Wenzel 2016 (DRI12544)	24 weeks	0.290 (0.159; 0.529)	1.052 (0.693; 1.598)	-0.762 (-1.218; -0.306)	0.276 (0.138; 0.552)
Castro 2018 (QUEST)	52 weeks	0.445 (0.368; 0.538)	1.007 (0.814; 1.245)	-0.561 (-0.785; -0.338)	0.442 (0.337; 0.581)
Mepolizumab studies		**Mepolizumab**	**Placebo**		
Pavord 2012 (DREAM)	52 weeks	1.24 (NR; NR)	2.4 (NR; NR)	-1.16 (NE; NE)	0.52 (0.39; 0.69)
Ortega 2014 (MENSA)	32 weeks	0.88 (NR; NR)	1.74 (NR; NR)	-0.86 (NE; NE)	0.506 (NE; NE)
Chupp 2017 (MUSCA)	24 weeks	0.51 (NR; NR)	1.21 (NR; NR)	-0.7 (NE; NE)	0.42 (0.31; 0.56)

Data from Wenzel 2016 (DRI12544) and Castro 2018 (QUEST) are for the 200 mg dose q2w and respective placebo group only
Source: Table 46, Table 47, Table 55, Table 56, Table 57. If not published, RD (95%) and RR (95% CI) were calculated according to appendix 8.4
CI, confidence interval; NE, not estimable; NR, not reported; q2w, every 2 weeks; RD, rate difference; RR, rate ratio

Patients with OCS-dependent eosinophilic asthma

In OCS-dependent severe eosinophilic asthma, statistically significant rate ratios of 0.418 and 0.68 were reported for dupilumab and mepolizumab, respectively, *vs* placebo with absolute reductions in annual number of severe exacerbation rates in the range of 0.7-0.9 events/year compared to placebo (Table 7).

TABLE 7 SUMMARY OF ANNUALISED EXACERBATION RATES –OCS-DEPENDENT EOSINOPHILIC ASTHMA

Study	Follow up	Rate (95% CI)		RD (95% CI)	RR (95% CI)
Dupilumab studies		**Dupilumab**	**Placebo**		
Rabe 2018 (VENTURE)	24 weeks	0.642 (0.425; 0.971)	1.536 (1.139; 2.071)	-0.894 (-1.414; -0.374)	0.418 (0.254; 0.689)
Mepolizumab studies		**Mepolizumab**	**Placebo**		
Bel 2014 (SIRIUS)	24 weeks	1.44 (NR; NR)	2.12 (NR; NR)	-0.68 (NE; NE)	0.68 (0.47; 0.99)

Source: Table 48, Table 58. If not published, RD (95%) and RR (95% CI) were calculated according to appendix 8.4
CI, confidence interval; NE, not estimable; NR, not reported; OCS, oral corticosteroids; RD, rate difference; RR, rate ratio

Proportion of patients with 0 annual exacerbations

Patients with uncontrolled, persistent eosinophilic asthma

The proportion of patients with 0 annual exacerbations was reported in 3 studies of which 2 studies had 1 year of follow-up. In the phase 2b study (DRI12544), the proportion of patients with 0 annual exacerbations was only reported for the ITT population. Since the mean baseline EOS in the phase 2b study was 361.1 (352.7) cells/µL and 342.3 (300.0) cells/µL in the dupilumab 200 mg q2w and placebo groups, respectively [6], and since 80% of the population had EOS ≥150 cells/µL (120/150 patients in the dupilumab 200 mg q2w group and 127/158 patients in the placebo group, see Table 46), these results are considered indicative of the effect of dupilumab in a population with uncontrolled, persistent asthma with increased EOS.

The chance of having 0 annual exacerbations was greater with both dupilumab and mepolizumab compared to placebo with relative risks (RRs) of 1.325 and 1.649, respectively (Table 8). Across all 3 studies, the proportion of patients with 0 annual exacerbations was in the range of 17-21% greater with dupilumab or mepolizumab compared to placebo.

TABLE 8 SUMMARY OF PROPORTION OF PATIENTS WITH 0 EXACERBATIONS DURING THE TREATMENT PERIOD – UNCONTROLLED, PERSISTENT EOSINOPHILIC ASTHMA

Study	Follow up	Proportion (95% CI) (%)		RD (95% CI)	RR (95% CI)
Dupilumab studies		**Dupilumab**	**Placebo**		
Wenzel 2016 (DRI12544)	24 weeks	91.2 (86.7; 95.8)	74.1 (67.2; 80.9	17.17 (8.95; 25.38)	1.232 (1.109; 1.368)
Castro 2018 (QUEST)	52 weeks	71.4 (67.2; 75.6)	53.9 (47.5; 60.3)	17.52 (9.83; 25.20)	1.325 (1.160; 1.514)
Mepolizumab studies		**Mepolizumab**	**Placebo**		
Pavord 2012 (DREAM)	52 weeks	54.2 (46.4; 62.1)	32.9 (25.5; 40.3)	21.35 (10.53; 32.16)	1.649 (1.261; 2.155)

Data from Wenzel 2016 (DRI12544) and Castro 2018 (QUEST) are for the 200 mg dose q2w and respective placebo group only
Data from Wenzel 2016 (DRI12544) are for the ITT population
Source: Table 46, Table 47, Table 55. If not published, RD (95%) and RR (95% CI) were calculated according to appendix 8.4
CI, confidence interval; ITT, intention-to-treat; q2w, every 2 weeks; RD, risk difference; RR, relative risk

Patients with OCS-dependent eosinophilic asthma

For OCS-dependent eosinophilic asthma, the proportion of patients with 0 exacerbations was only reported in the dupilumab VENTURE study. The proportion of patients with 0 exacerbations in the 24-week treatment period was 77.8% (68.7 to 86.8%) with dupilumab and 53.6% (41.9 to 65.4%) with placebo (Table 48). Compared to placebo, the chance of having 0 exacerbations during the 24-week treatment period was statistically significantly higher with dupilumab with a RR (95% CI) of 1.450 (1.131; 1.859) and an absolute difference (95% CI) of 24.15 (9.31; 39.00) %-points more patients with 0 exacerbations.

Mean % reduction in daily OCS dose

In the dupilumab VENTURE study, the % reduction in daily OCS dose was statistically significantly greater in the dupilumab group compared to the placebo group with a least square mean (LSmean) difference (95% CI) *vs* placebo of 29.39% (15.67; 43.12%) (Table 48). The observed median (interquartile range) % reduction in the OCS dose from baseline to week 24 was 100% (62.5; 100%) in the dupilumab group, as compared with 50% (0; 100%) in the placebo group [11]. In the mepolizumab SIRIUS study, the median (95% CI) % reduction from baseline was 50% (20.0; 75.0%) and 0% (-20.2; 33.3%) for mepolizumab and

placebo, respectively (p-value for difference 0.007) (Table 58). Since no additional data were reported for this outcome, differences between groups could not be estimated for the SIRIUS study.

Proportion of patients no longer requiring OCS

Compared to placebo, the chance of no longer requiring maintenance OCS treatment at the end of the 24-week treatment period was approximately 85% and 91% greater with dupilumab and mepolizumab, respectively; with only the result for dupilumab being statistically significant. In the VENTURE study, a statistically significant difference of approximately 25% more patients in the dupilumab group compared to the placebo group no longer required OCS. The absolute difference of 7%-points for mepolizumab *vs* placebo was not statistically significant (Table 9).

TABLE 9 SUMMARY OF PROPORTION OF PATIENTS NO LONGER REQUIRING OCS – OCS-DEPENDENT EOSINOPHILIC ASTHMA

Study	Follow up	Proportion (95% CI) (%)		RD (95% CI)	RR (95% CI)
Dupilumab studies		**Dupilumab**	**Placebo**		
Rabe 2018 (VENTURE)	24 wk	54 (42; 66)	30 (19; 43)	24.91 (9.58; 40.24)	1.847 (1.215; 2.808)
Mepolizumab studies		**Mepolizumab**	**Placebo**		
Bel 2014 (SIRIUS)	24 wk	14.5 (6.2; 22.8)	7.6 (1.2; 14.0)	6.92 (-3.56; 17.39)	1.913 (0.690; 5.300)

Source: Table 48, Table 58. If not published, RD (95%) and RR (95% CI) were calculated according to appendix 8.4
CI, confidence interval; OCS, oral corticosteroids; RD, risk difference; RR, relative risk

Proportion of patients with ≥50% reduction in OCS dose

Compared to placebo, the chance of obtaining a ≥50% reduction in maintenance OCS dose at the end of the 24-week treatment period was statistically significantly increased with approximately 57% and 61% for dupilumab and mepolizumab, respectively. Compared to placebo, 30%-points more patients treated with dupilumab and 20%-points more patients treated with mepolizumab had a ≥50% reduction in OCS dose; both results being statistically significant (Table 10).

TABLE 10 SUMMARY OF PROPORTION OF PATIENTS WITH ≥50% REDUCTION IN OCS DOSE – OCS-DEPENDENT EOSINOPHILIC ASTHMA

Study	Follow up	Proportion (95% CI) (%)		RD (95% CI)	RR (95% CI)
Dupilumab studies		**Dupilumab**	**Placebo**		
Rabe 2018 (VENTURE)	24 wk	84 (74; 90)	53 (41; 65)	30.33 (16.10; 44.55)	1.566 (1.233; 1.989)
Mepolizumab studies		**Mepolizumab**	**Placebo**		
Bel 2014 (SIRIUS)	24 wk	53.6 (41.9; 65.4)	33.3 (22.0; 44.7)	20.3 (3.9; 36.7)	1.61 (1.07; 2.41)

Source: Table 48, Table 58. If not published, RD (95%) and RR (95% CI) were calculated according to appendix 8.4
CI, confidence interval; OCS, oral corticosteroids; RD, risk difference; RR, relative risk

Mean change from baseline in lung function

Patients with uncontrolled, persistent eosinophilic asthma

The mean change in FEV1 from baseline to the end of treatment was reported in all studies. However, for the dupilumab phase 2b study (DRI12544), data for the increased EOS subgroup were only reported at 12 weeks. For the QUEST study, FEV1 in the increased EOS subgroup was reported at weeks 12, 24 and 52. Since the effect of dupilumab on FEV1 was relatively stable from week 12 until the end of the study (see

Figure 3), week 12 and week 24 data are shown below together with the week 52 data to provide support for the single data point with week 52 data (corresponding to the longest possible duration of follow up).

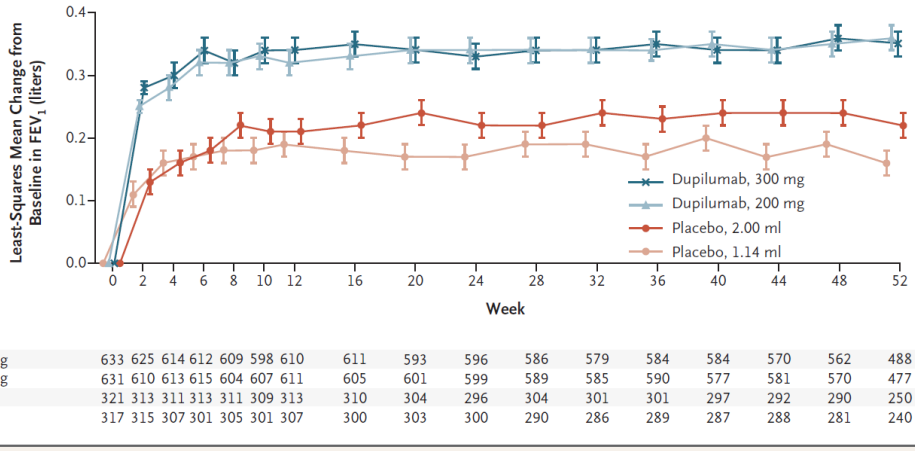
At week 52, a statistically significant LSmean difference of 0.25 L was found in change from baseline in FEV1 between dupilumab and placebo in the QUEST study. Since the lower end of the 95% CI was above the adjusted MCID of 100 mL defined by the Medicines Council [1], the improvement was assessed as clinically relevant. Changes from baseline to weeks 12 and 24 were similar although slightly lower. In the DREAM study, mepolizumab did not result in a statistically significant change from baseline to week 52 in FEV1, and in the MENSA and MUSCA studies, the statistically significant changes from baseline to weeks 32 and 24, respectively, were not clinically relevant, since the lower end of the 95% CI was below the adjusted MCID of 100 mL (Table 11).

TABLE 11 SUMMARY OF CHANGES FROM BASELINE IN FEV1 – UNCONTROLLED, PERSISTENT EOSINOPHILIC ASTHMA

Study	Timepoint	LSsmeans (95% CI) change from baseline (L)		LSmeans difference (95% CI) (L)
Dupilumab studies		**Dupilumab**	**Placebo**	
Wenzel 2016 (DRI12544)	Week 12	0.32 (0.242; 0.398)	0.09 (0.012; 0.168)	0.23 (0.13; 0.33)
Castro 2018 (QUEST)	Week 12	0.36 (0.321; 0.399)	0.19 (0.131; 0.249)	0.17 (0.11; 0.23)
Castro 2018 (QUEST)	Week 24	0.38 (0.341; 0.419)	0.16 (0.101; 0.219)	0.21 (0.15; 0.28)
Castro 2018 (QUEST)	Week 52	0.40 (0.361; 0.439)	0.15 (0.091; 0.209)	0.25 (0.18; 0.32)
Mepolizumab studies		**Mepolizumab**	**Placebo**	
Pavord 2012 (DREAM)	Week 52	0.121 (0.047; 0.195)	0.06 (-0.014; 0.134)	0.061 (-0.039; 0.161)
Ortega 2014 (MENSA)	Week 32	0.185 (0.142; 0.228)	0.086 (0.025; 0.147)	0.099 (0.038; 0.160)
Chupp 2017 (MUSCA)	Week 24	0.176 (0.125; 0.227)	0.056 (0.005; 0.107)	0.12 (0.047; 0.192)

Data from Wenzel 2016 (DRI12544) and Castro 2018 (QUEST) are for the 200 mg dose q2w and respective placebo group only
Source: Table 46, Table 47, Table 55, Table 56, Table 57. If not published, RD (95%) and RR (95% CI) were calculated according to appendix 8.4
CI, confidence interval; FEV1, forced expiratory volume in 1 s; L, litre; LS, least square; q2w, every 2 weeks

FIGURE 3 CHANGE IN FEV1 FROM BASELINE TO WEEK 52 (FROM CASTRO 2018 [8])



No. at Risk

Dupilumab, 300 mg	633	625	614	612	609	598	610	611	593	596	586	579	584	584	570	562	488
Dupilumab, 200 mg	631	610	613	615	604	607	611	605	601	599	589	585	590	577	581	570	477
Placebo, 2.00 ml	321	313	311	313	311	309	313	310	304	296	304	301	301	297	292	290	250
Placebo, 1.14 ml	317	315	307	301	305	301	307	300	303	300	290	286	289	287	288	281	240

Figure 2. Change in the Prebronchodilator FEV_1 from Baseline over the 52-Week Intervention Period in the Intention-to-Treat Population.
Patients received dupilumab at a dose of 200 or 300 mg every 2 weeks or a matched-volume placebo. For the lower dose of dupilumab, the matched placebo had a volume of 1.14 ml. For the higher dose of dupilumab, the matched placebo had a volume of 2.00 ml. P<0.001 for the comparisons of each dupilumab dose with matched placebo at week 12. I bars represent the standard error. FEV_1 denotes forced expiratory volume in 1 second.

Patients with OCS-dependent eosinophilic asthma

In patients with OCS-dependent asthma, a statistically significant LSmean difference of 0.22 L was found between dupilumab 300 mg q2w and placebo in change from baseline to week 24 in FEV1, while no significant difference in change from baseline in FEV1 was found between mepolizumab and placebo in the SIRIUS study (Table 12).

TABLE 12 SUMMARY OF CHANGES FROM BASELINE IN FEV1 –OCS-DEPENDENT EOSINOPHILIC ASTHMA

Study	Timepoint	LSsmeans (95% CI) change from baseline (L)		LSmeans difference (95% CI) (L)
Dupilumab studies		**Dupilumab**	**Placebo**	
Rabe 2018 (VENTURE)	Week 24	0.32 (0.202; 0.438)	0.09 (-0.028; 0.208)	0.22 (0.06; 0.38)
Mepolizumab studies		**Mepolizumab**	**Placebo**	
Bel 2014 (SIRIUS)	Week 24	0.111 (0.003; 0.219)	-0.004 (-0.116; 0.108)	0.114 (-0.042; 0.271)

Source: Table 48, Table 58

CI, confidence interval; FEV1, forced expiratory volume in 1 s; L, litre; LS, least square; OCS, oral corticosteroids

Proportion of patients with an improvement of ≥200 mL in FEV1

Patients with uncontrolled, persistent eosinophilic asthma

The proportion of patients with a clinically relevant improvement of ≥200 mL in FEV1 was only reported in the dupilumab QUEST study where 58.1% (95% CI: 52.8 to 63.3%) of patients in the dupilumab group and 38.3% (31.1 to 45.5%) of patients in the placebo group had an ≥200 mL improvement in FEV1 (Table 47). Compared to placebo, a statistically significantly higher change of having an ≥200 mL improvement in FEV1 after 1 year of treatment with dupilumab was found, with RR (95% CI) of 1.517 (1.231; 1.868) and with 19.78%-points (10.87; 28.68) more patients having an improvement in FEV1 of ≥200 mL.

Patients with OCS-dependent eosinophilic asthma

In patients with OCS-dependent severe eosinophilic asthma, the proportion of patients with an ≥200 mL improvement in FEV1 was only reported in the dupilumab VENTURE study. In the dupilumab group, 55.3% (95% CI: 44.1; 66.4%) of the patients had an improvement of ≥200 mL in FEV1, while the proportion in the placebo group was 33.3% (22.0; 44.7%) (Table 48). Compared to placebo, a statistically significantly higher change of having an ≥200 mL improvement in FEV1 after 24 weeks of treatment with dupilumab was found, with RR (95% CI) of 1.658 (1.115; 2.465) and with 21.93%-points (5.98; 37.88) more patients having an improvement in FEV1 of ≥200 mL.

Asthma control

Patients with uncontrolled, persistent eosinophilic asthma

Asthma control was in all studies assessed by use of the ACQ. In the dupilumab studies, results of the ACQ were reported at week 24 for the increased EOS subgroup, while the 3 mepolizumab studies reported change from baseline to the end of treatment (week 24, 32 and 52, respectively). For both dupilumab and mepolizumab, LSmean differences in change from baseline to week 24 and 32 showed a statistically significant improvement (i.e. reduced score) in the range of 0.4-0.5 compared to placebo, while the LSmean difference in change from baseline to week 52 in the DREAM study was lower and not statistically significant (Table 13).

TABLE 13 SUMMARY OF CHANGES FROM BASELINE IN ASTHMA CONTROL – UNCONTROLLED, PERSISTENT EOSINOPHILIC ASTHMA

Study	Timepoint assessed Tool used	LSmeans (95% CI)		LSmeans difference (95% CI)
Dupilumab studies		**Dupilumab**	**Placebo**	
Wenzel 2016 (DRI12544)	Week 24 ACQ-5	-1.55 (-1.726; -1.374)	-1.07 (-1.246; -0.894)	-0.48 (-0.72; -0.23)
Castro 2018 (QUEST)	Week 24 ACQ-5	-1.51 (-1.608; -1.412)	-1.09 (-1.227; -0.953)	-0.42 (-0.58; -0.26)
Mepolizumab studies		**Mepolizumab**	**Placebo**	
Pavord 2012 (DREAM)	Week 52 ACQ-6	-0.75 (-0.926; -0.574)	-0.59 (-0.766; -0.414)	-0.16 (-0.39; 0.07)
Ortega 2014 (MENSA)	Week 32 ACQ-5	-0.93 (-1.028; -0.832)	-0.5 (-0.637; -0.363)	-0.43 (-0.564; -0.29)
Chupp 2017 (MUSCA)	Week 24 ACQ-5	-0.8 (-0.996; -0.604)	-0.4 (-0.596; -0.204)	-0.4 (-0.6; -0.2)

Data from Wenzel 2016 (DRI12544) and Castro 2018 (QUEST) are for the 200 mg dose q2w and respective placebo group only
For ACQ, the longest reported duration of follow up for the EOS subgroup in the dupilumab QUEST study was 24 weeks
ACQ is a patient-reported measure of the adequacy of asthma control and change in asthma control that occurs either spontaneously or as a result of treatment. Higher scores indicate less control; a global score is calculated ranging from 0 to 6. The MCID is 0.5 [42].
Source: Table 46, Table 47, Table 55, Table 56, Table 57
ACQ, Asthma Control Questionnaire; CI, confidence interval; LS, least square; q2w, every 2 weeks

Patients with OCS-dependent eosinophilic asthma

The results for asthma control were not reported for the increased EOS subgroup in the dupilumab VENTURE study. Instead, the results from the ITT population are presented below. This is considered a conservative estimate for the increased EOS subgroup, since in both the phase 2b study and the QUEST

study, the LSmean differences (95% CI) *vs* placebo in changes from baseline to week 24 in ACQ score were greater in the increased EOS subgroups (-0.48 [-0.72; -0.23] and -0.42 [-0.58; -0.26], respectively) than in the ITT populations (-0.35 [-0.57; -0.14] and -0.35 [-0.48; -0.21], respectively)[43]. Furthermore, since an average of 71.4% of the ITT population (81/103 in the dupilumab group and 69/107 in the placebo group) in the VENTURE study had EOS ≥150 cells/µL [11], the results from the ITT population are considered indicative of the results in the increased EOS subgroup.

For both dupilumab and mepolizumab, LSmean differences in change from baseline to week 24 showed a statistically significant improvement (i.e. reduced score) of approximately 0.5 in ACQ score (Table 14).

TABLE 14 SUMMARY OF CHANGES FROM BASELINE IN ASTHMA CONTROL – OCS-DEPENDENT EOSINOPHILIC ASTHMA

Study	Timepoint assessed Tool used	LSmeans (95% CI)		LSmeans difference (95% CI)
Dupilumab studies		**Dupilumab**	**Placebo**	
Rabe 2018 (VENTURE)	Week 24 ACQ	-1.05 (-1.266; -0.834)	-0.57 (-0.766; -0.374)	-0.47 (-0.76; -0.18)
Mepolizumab studies		**Mepolizumab**	**Placebo**	
Bel 2014 (SIRIUS)	Week 24 ACQ	-0.61 (-0.865; -0.355)	-0.09 (-0.345; 0.165)	-0.52 (-0.87; -0.17)

Data from Rabe 2018 are for the ITT population

ACQ is a patient-reported measure of the adequacy of asthma control and change in asthma control that occurs either spontaneously or as a result of treatment. Higher scores indicate less control; a global score is calculated ranging from 0 to 6. The MCID is 0.5 [42].

Source: Table 48, Table 58

ACQ, Asthma Control Questionnaire; CI, confidence interval; LS, least square; MCID, minimal clinically important difference; OCS, oral corticosteroids

Quality of life

Patients with uncontrolled, persistent eosinophilic asthma

All studies reported QoL; however, by use of different tools. The dupilumab studies and the mepolizumab DREAM study assessed QoL using the AQLQ while the mepolizumab MENSA and MUSCA studies used the SGRQ. QoL results on the original scales are summarised in Table 15.

Compared to placebo, the dupilumab studies showed statistically significant mean improvements (indicated by higher scores on the AQLQ) in QoL of 0.3-0.5 units at week 24, while the mepolizumab DREAM study did not show a noticeable change in QoL at week 52 using the same tool. The mepolizumab MENSA and MUSCA studies showed statistically significant improvements (indicated by lower scores on the SGRQ) in QoL of 7 and 8 units at weeks 32 and 24, respectively, using the SGRQ.

TABLE 15 SUMMARY OF CHANGES FROM BASELINE IN QUALITY OF LIFE – UNCONTROLLED, PERSISTENT EOSINOPHILIC ASTHMA

Study	Timepoint assessed Tool used	LSmeans (95% CI)		LSmeans difference (95% CI)
Dupilumab studies		**Dupilumab**	**Placebo**	
Wenzel 2016 (DRI12544)	Week 24 AQLQ	1.27 (1.074; 1.466)	0.78 (0.584; 0.976)	0.49 (0.24; 0.75)
Castro 2018 (QUEST)	Week 24 AQLQ	1.19 (1.092; 1.288)	0.94 (0.803; 1.077)	0.26 (0.09; 0.42)
Mepolizumab studies		**Mepolizumab**	**Placebo**	
Pavord 2012 (DREAM)	Week 52 AQLQ	0.80 (0.624; 0.976)	0.71 (0.534; 0.886)	0.08 (-0.16; 0.32)
Ortega 2014 (MENSA)	Week 32 SGRQ	-15.7 (-17.293; -14.107)	-9.0 (-11.352; -6.648)	-6.7 (-9.1; -4.4)
Chupp 2017 (MUSCA)	Week 24 SGRQ	-15.6 (-17.560; -13.640)	-7.9 (-9.860; -5.940)	-7.7 (-10.5; -4.9)

Data from Wenzel 2016 (DRI12544) and Castro 2018 (QUEST) are for the 200 mg dose q2w and respective placebo group only
For AQLQ, the longest reported duration of follow up for the EOS subgroup in the dupilumab QUEST study was 24 weeks
AQLQ is a patient-reported measure of asthma-specific health-related quality of life. Higher scores indicate better quality of life; a global score is calculated ranging from 1 to 7. The MCID is 0.5 for all scales [44, 45].
SGRQ is a patient-reported measure of QoL in patients with diseases of airway obstruction. SGRQ scores are based on a scale of 0 to 100, with lower scores indicating better QoL; a change of 4 units is considered clinically relevant [46].
Source: Table 46, Table 47, Table 55, Table 56, Table 57
AQLQ, Asthma Quality of Life Questionnaire; CI, confidence interval; EOS, blood eosinophils; LS, least square; MCID, minimal clinically important difference; q2w, every 2 weeks; SGRQ, St. George's Respiratory Questionnaire

Patients with OCS-dependent eosinophilic asthma

The results for QoL were not reported for the increased EOS subgroup in the dupilumab VENTURE study. Instead, the results from the ITT population are presented below. This is considered a conservative estimate for the increased EOS subgroup, since an average of 71.4% of the ITT population (81/103 in the dupilumab group and 69/107 in the placebo group) in the VENTURE study had EOS ≥150 cells/µL [11]. Furthermore, in both the phase 2b study and the QUEST study, the improvements in QoL were greater in the increased EOS subgroups than in the ITT populations (LSmean differences [95% CI] *vs* placebo in AQLQ were 0.49 [0.24; 0.75] and 0.26 [0.09; 0.42], respectively, in the increased EOS subgroups and 0.31 [0.08; 0.55] and 0.20 [0.06; 0.34], respectively, in the ITT populations [6, 8, 43]).

The dupilumab VENTURE study assessed QoL using the AQLQ while the mepolizumab SIRIUS study used the SGRQ. Compared to placebo, both studies showed statistically significant mean improvements (indicated by higher scores on the AQLQ and lower scores on the SGRQ) in QoL after 24 weeks of treatment (Table 16).

TABLE 16 SUMMARY OF CHANGES FROM BASELINE IN QUALITY OF LIFE – OCS-DEPENDENT EOSINOPHILIC ASTHMA

Study	Timepoint assessed Tool used	LSmeans (95% CI)		LSmeans difference (95% CI)
Dupilumab studies		**Dupilumab**	**Placebo**	
Rabe 2018 (VENTURE)	Week 24 AQLQ	0.89 (0.694; 1.086)	0.54 (0.344; 0.736)	0.35 (0.073;0.627)
Mepolizumab studies		**Mepolizumab**	**Placebo**	
Bel 2014 (SIRIUS)	Week 24 SGRQ	-8.8 (-12.132; -5.468)	-3.1 (-6.432; 0.232)	-5.8 (-10.6; -1.0)

Data from Rabe 2018 are for the ITT population
AQLQ is a patient-reported measure of asthma-specific health-related quality of life. Higher scores indicate better quality of life; a global score is calculated ranging from 1 to 7. The MCID is 0.5 for all scales [44, 45].
SGRQ is a patient-reported measure of QoL in patients with diseases of airway obstruction. SGRQ scores are based on a scale of 0 to 100, with lower scores indicating better QoL; a change of 4 units is considered clinically relevant [46].
Source: Table 48, Table 58. If not published, RD (95%) and RR (95% CI) were calculated according to appendix 8.4
AQLQ, Asthma Quality of Life Questionnaire; CI, confidence interval; ITT, intention-to-treat; LS, least square; MCID, minimal clinically important difference; OCS, oral corticosteroids; SGRQ, St. George's Respiratory Questionnaire

Sick leave

Data on sick leave were not reported for dupilumab in the subgroup of patients with increased EOS. However, in the phase 2b study (DRI12544), the annualised days of sick leave due to severe exacerbation event in the ITT population was 0.613 days/year and 2.238 days/year in the dupilumab 200 mg q2w and placebo groups, respectively (p<0.0001) (Table 46). Since the mean baseline EOS was 361.1 (352.7) cells/µL and 342.3 (300.0) cells/µL in the dupilumab 200 mg q2w and placebo groups, respectively [6], and 80% of the population had EOS ≥150 cells/µL (120/150 patients in the dupilumab 200 mg q2w group and 127/158 patients in the placebo group, see Table 46), these results are considered indicative of the effect of dupilumab on sick leave in a population with uncontrolled, persistent asthma with increased EOS.

No data on sick leave were found for mepolizumab.

Safety results – uncontrolled, persistent eosinophilic asthma

Safety data for dupilumab were only reported for the safety population that included all the patients who received ≥1 dose or part of a dose, and data were analysed according to the intervention received. Thus, it was not possible to retrieve safety data specifically for the increased EOS subgroup, therefore data for the safety population are presented below. For the phase 2b (DRI12544) and QUEST studies, data are for the 200 mg dose q2w and corresponding placebo group only.

Incidence of serious adverse events

In the phase 2b and the QUEST studies with dupilumab, the incidence of serious adverse events (SAEs) was similar between the dupilumab 200 mg and placebo groups (Table 17). In the VENTURE study in OCS-dependent patients, SAEs were reported by 8.7% of patients in the dupilumab 300 mg group and 5.6% of those in the placebo group.

In the mepolizumab studies, the incidence of SAEs was lower in the active treatment group than the placebo group or comparable between groups, depending on the study (Table 17).

TABLE 17 INCIDENCE OF SERIOUS ADVERSE EVENTS IN STUDIES WITH DUPILUMAB AND MEPOLIZUMAB

Study	Patients with events / total N (incidence)		RD (95% CI)	RR (95% CI)
Dupilumab studies	**Dupilumab**	**Placebo**		
Wenzel 2016 (DRI12544)	10 / 148 (6.8%)	9 / 158 (5.7%)	1.06 (-4.36; 6.48)	1.19 (0.50; 2.84)
Castro 2018 (QUEST)	49 / 631 (7.8%)	26 / 313 (8.3%)	-0.54 (-4.24; 3.16)	0.93 (0.59; 1.48)
Rabe 2018 (VENTURE)	9 / 103 (8.7%)	6 / 107 (5.6%)	3.13 (-3.85; 10.11)	1.56 (0.58; 4.22)
Mepolizumab studies	**Mepolizumab**	**Placebo**		
Pavord 2012 (DREAM)	20 / 153 (13.1%)	25 / 155 (16.1%)	-3.06 (-10.93; 4.82)	0.81 (47; 1.40)
Ortega 2014 (MENSA)	30 / 385 (7.8%)	27 / 191 (14.1%)	-6.34 (-11.96; -0.72)	0.55 (0.34; 0.90)
Chupp 2017 (MUSCA)	15 / 273 (5.5%)	22 / 278 (7.9%)	-2.42 (-6.59; 1.75)	0.69 (0.37; 1.31)
Bel 2014 (SIRIUS)	1 / 69 (1.4%)	12 / 66 (18.2%)	-16.73 (-26.46; -7.01)	0.08 (0.01; 0.60)

Data from Wenzel 2016 (DRI12544) and Castro 2018 (QUEST) are for the 200 mg dose q2w and respective placebo group only
Data for the safety population are presented for dupilumab
Source: Table 52, Table 53, Table 54, Table 55, Table 56, Table 57, Table 58. RD (95%) and RR (95% CI) were calculated according to appendix 8.4
CI, confidence interval; N, total number of subjects; q2w, every 2 weeks; RD, risk difference; RR, relative risk

Discontinuation from the study

In the phase 2b (DRI12544) and the QUEST studies with dupilumab, the rate of discontinuation from the study was similar between the dupilumab 200 mg group and placebo group (Table 18). In the VENTURE study in OCS-dependent patients, few patients discontinued: 2 (1.9%) in the dupilumab 300 mg group and 5 (4.7%) in the placebo group.

In the mepolizumab studies, the rate of discontinuation from the studies was generally similar to or less than the discontinuation rate in the placebo group (Table 18).

TABLE 18 DISCONTINUATION FROM STUDIES WITH DUPILUMAB AND MEPOLIZUMAB

Study	Patients with events / total N (incidence)		RD (95% CI)	RR (95% CI)
Dupilumab studies	**Dupilumab**	**Placebo**		
Wenzel 2016 (DRI12544)	11 / 148 (7.4%)	12 / 158 (7.6%)	-0.16 (-6.07; 5.75)	0.98 (0.45; 2.15)
Castro 2018 (QUEST)	70 / 631 (11.1%)	38 / 317 (12.0%)	-0.89 (-5.23; 3.44)	0.93 (0.64; 1.34)
Rabe 2018 (VENTURE)	2 / 103 (1.9%)	5 / 107 (4.7%)	-2.73 (-7.54; 2.07)	0.42 (0.08; 2.09)
Mepolizumab studies	**Mepolizumab**	**Placebo**		
Pavord 2012 (DREAM)	24 / 153 (15.7%)	28 / 155 (18.1%)	-2.38 (-10.74; 5.98)	0.87 (0.53; 1.43)
Ortega 2014 (MENSA)	25 /385 (6.5%)	12 / 191 (6.3%)	0.21 (-4.02; 4.44)	1.03 (0.53; 2.01)
Chupp 2017 (MUSCA)	5 / 274 (1.8%)	14 / 277 (5.1%)	-3.23 (-6.26; -0.20)	0.36 (0.13; 0.99)
Bel 2014 (SIRIUS)	3 / 69 (4.3%)	4 / 66 (6.1%)	-1.71 (-9.22; 5.79)	0.72 (0.17; 3.08)

Data from Wenzel 2016 (DRI12544) and Castro 2018 (QUEST) are for the 200 mg dose q2w and respective placebo group only
Data for the ITT population are presented for dupilumab
Source: Table 52, Table 53, Table 54, Table 55, Table 56, Table 57, Table 58. RD (95%) and RR (95% CI) were calculated according to appendix 8.4
CI, confidence interval; N, total number of subjects; q2w, every 2 weeks; RD, risk difference; RR, relative risk

Anaphylactic reactions

Data for the anaphylactic reactions are presented for the safety pool of dupilumab studies (the phase 2b study and the QUEST study) with data extracted from the EPAR. Additionally, safety data for the VENTURE study are reported separately based on the primary publication [11].

Anaphylactic reactions have been reported very rarely in the dupilumab asthma development program. In the safety pool, 1 serious anaphylactic reaction and 1 serious event of anaphylactic shock (both medically reviewed) were reported in the dupilumab group. No such events were reported in the placebo group and none were reported in the VENTURE study [11, 43]. The low number of anaphylaxis events suggests a low immunogenic potential of dupilumab in the asthma population.

No anaphylactic reactions have been reported in the mepolizumab group in the included studies. In the DREAM study, no serious life-threatening anaphylactic reactions were reported. In the MUSCA study, a single event of anaphylaxis was reported in the placebo group. Events of anaphylaxis were not reported in the MENSA or SIRIUS studies.

5.1.4 Comparative analyses

Efficacy results – uncontrolled, persistent eosinophilic asthma

Reduction in annual number of exacerbation events

The comparative analyses of the annualised rate of severe exacerbations in patients with eosinophilic asthma are summarised in Table 19. Based on comparison between the 2 studies with 24 weeks' duration (DRI12544 and MUSCA), the risk of severe exacerbations was 34.3% lower, and the annualised rate of severe exacerbations was 0.175 events/patient-year lower with dupilumab *vs* mepolizumab; the differences were, however, not statistically significant. In the 2 studies with 1 year duration (QUEST and DREAM), the risk of severe exacerbations was 15.0% lower, and the annualised rate of severe exacerbations was 0.186 events/patient-year lower with dupilumab *vs* mepolizumab; the differences were, however, not statistically significant.

In patients with OCS-dependent eosinophilic asthma, the risk of severe exacerbations was 38.5% lower, and the annualised rate of severe exacerbations was 0.555 events/patient-year lower with dupilumab compared to mepolizumab; however, the differences were not statistically significant.

TABLE 19 SUMMARY OF ANNUALISED SEVERE EXACERBATION RATES – DUPILUMAB *VS* MEPOLIZUMAB

Population	Studies included in the analysis	RD (95% CI)	RR (95% CI)
Uncontrolled, persistent eosinophilic asthma	Wenzel 2016 (DRI12544) *vs* Chupp 2017 (MUSCA)	-0.175 (-0.352; 0.202)	0.657 (0.309; 1.396)
Uncontrolled, persistent eosinophilic asthma	Castro 2018 (QUEST) *vs* Pavord 2012 (DREAM)	-0.186 (-0.530; 0.324)	0.850 (0.573; 1.261)
OCS-dependent eosinophilic asthma	Rabe 2018 (VENTURE) *vs* Bel 2014 (SIRIUS)	-0.555 (-0.965; 0.210)	0.615 (0.330; 1.146)

Data from Castro 2018 (QUEST) are for the 200 mg dose q2w and respective placebo group only
Source: Table 75 and Table 76
CI, confidence interval; OCS, oral corticosteroid; q2w, every 2 weeks; RD, rate difference; RR, rate ratio

Proportion of patients with 0 annual exacerbations

Comparative analysis of the proportion of patients with 0 annual exacerbations could only be performed for patients with uncontrolled, persistent eosinophilic asthma. The chance of having 0 annual exacerbations was 19.6% lower (95% CI: 40.4% lower to 8.4% higher) with dupilumab compared to mepolizumab. In absolute numbers there were 10.6%-points fewer (21.9%-points fewer to 4.5%-points more) patients with 0 annual exacerbations in the dupilumab group *vs* the mepolizumab group (Table 75). The differences between dupilumab and mepolizumab were not statistically significant.

Mean % reduction in daily OCS dose

Since data were reported differently in the VENTURE and SIRIUS studies, it was not possible to perform indirect comparisons of % reduction in daily OCS maintenance dose. The by-study results showed for the dupilumab VENTURE study an LSmean 29.39%-points (15.67 to 43.12%-points) greater reduction in OCS dose with dupilumab *vs* placebo (Table 48). The observed median (interquartile range) % reduction in the OCS dose from baseline to week 24 was 100% (62.5 to 100%) in the dupilumab group, as compared with 50% (0 to 100%) in the placebo group [11]. In the mepolizumab SIRIUS study, the median (95% CI) reduction was 50% (20.0 to 75.0%) and 0% (-20.2 to 33.3%) in the mepolizumab and placebo groups, respectively with a p-value for difference between treatments of 0.007 (Table 58). Thus, in both studies, statistically significant and clinically relevant % reductions in daily OCS maintenance dose were found. With a difference in median % reduction of 50% between active and placebo groups in both studies, the effect of dupilumab and mepolizumab on reduction in maintenance OCS dose are assessed as similar.

Proportion of patients no longer requiring OCS

The comparative analysis of the proportion of patients no longer requiring OCS did not show statistically significant differences between dupilumab and mepolizumab. The chance of no longer requiring OCS at the end of the study was 3.5% lower (67.9% lower to 190.6% higher) with dupilumab compared to mepolizumab. In absolute numbers there was 0.5%-points fewer (9.8%-points fewer to 27.6%-points more) patients no longer requiring OCS in the dupilumab group compared to the mepolizumab group (Table 76).

Proportion of patients with ≥50% reduction in OCS dose

The comparative analysis of the proportion of patients with ≥50% reduction in OCS dose did not show statistically significant differences between dupilumab and mepolizumab. The chance of having a ≥50% reduction in OCS dose was 2.7% lower (39.2% lower to 55.9% higher) with dupilumab compared to mepolizumab. In absolute numbers there was 1.4%-points fewer (21.0%-points fewer to 29.9%-points more) patients with a ≥50% reduction in OCS dose in the dupilumab group compared to the mepolizumab group (Table 76).

Mean change from baseline in lung function

The comparative analyses of changes from baseline in FEV1 in patients with uncontrolled, persistent eosinophilic asthma showed clearly larger improvements in FEV1 with dupilumab compared to mepolizumab of 0.100 L and 0.189 L after 24 and 52 weeks, respectively, which were statistically significant (Table 20). The lower end of the 95% CI did, however not reach the adjusted MCID of 100 mL defined by the Medicines Council [1] and therefore the differences were not assessed as clinically relevant. The analysis of change from baseline in FEV1 in OCS-dependent eosinophilic asthma showed a numerical larger increase in FEV1 with dupilumab compared to mepolizumab of 0.106 L, which was, however, not statistically significant.

TABLE 20 SUMMARY OF CHANGE FROM BASELINE IN FEV1 – DUPILUMAB *VS* MEPOLIZUMAB

Population	Studies included in the analysis	LSmean difference (95% CI) (L)
Uncontrolled, persistent eosinophilic asthma	Castro 2018 (QUEST) (24-wk data) *vs* Ortega 2014 (MENSA) and Chupp 2017 (MUSCA)	0.100 (0.013; 0.188)
Uncontrolled, persistent eosinophilic asthma	Castro 2018 (QUEST) (52-wk data) *vs* Pavord 2012 (DREAM)	0.189 (0.062; 0.316)
OCS-dependent eosinophilic asthma	Rabe 2018 (VENTURE) *vs* Bel 2014 (SIRIUS)	0.106 (-0.122; 0.334)

Data from Castro 2018 (QUEST) are for the 200 mg dose q2w and respective placebo group only
Source: Table 75 and Table 76
CI, confidence interval; FEV1, forced expiratory volume in 1 s; L, litre; LS, least square; OCS, oral corticosteroid; q2w, every 2 weeks

Proportion of patients with an improvement of ≥200 mL in FEV1

No comparative analysis of the proportion of patients with an improvement in FEV1 of ≥200 mL could be performed since the outcome was only reported for the dupilumab studies.

Asthma control

The comparative analyses of changes from baseline to week 24 in ACQ-5 showed minor differences between dupilumab and mepolizumab that were not statistically significant. In patients with uncontrolled, persistent eosinophilic asthma, the difference in change from baseline in ACQ-5 score of -0.017 in favour of dupilumab was not statistically significant (Table 21). In OCS-dependent eosinophilic asthma the corresponding difference in change from baseline in ACQ-5 score of 0.050 in favour of mepolizumab was also not statistically significant (Table 21).

TABLE 21 SUMMARY OF CHANGE FROM BASELINE IN ASTHMA CONTROL – DUPILUMAB *VS* MEPOLIZUMAB

Population	Studies included in the analysis	LSmean difference (95% CI) (ACQ-5 score)
Uncontrolled, persistent eosinophilic asthma	Wenzel 2016 (DRI12544) and Castro 2018 (QUEST) *vs* Ortega 2014 (MENSA) and Chupp 2017 (MUSCA)	-0.017 (-0.218; 0.184)
OCS-dependent eosinophilic asthma	Rabe 2018 (VENTURE) *vs* Bel 2014 (SIRIUS)	0.050 (-0.413; 0.513)

Data from Castro 2018 (QUEST) are for the 200 mg dose q2w and respective placebo group only
ACQ is a patient-reported measure of the adequacy of asthma control and change in asthma control that occurs either spontaneously or as a result of treatment. Higher scores indicate less control; a global score is calculated ranging from 0 to 6. The MCID is 0.5 [42]
Source: Table 75 and Table 76
ACQ-5, 5-item Asthma Control Questionnaire; CI, confidence interval; LS, least square; MCID, minimal clinically important difference; OCS, oral corticosteroid; q2w, every 2 weeks

Quality of life

The comparative analyses of changes from baseline to week 24 in QoL showed no statistically significant or clinically relevant differences in QoL between dupilumab and mepolizumab. In patients with uncontrolled, persistent eosinophilic asthma, the change from baseline in the AQLQ score was 0.129 smaller with dupilumab compared to mepolizumab; the difference was however not statistically significant (Table 22). In OCS-dependent eosinophilic asthma the corresponding difference in change from baseline in the AQLQ score was very close to zero and also not statistically significant (Table 22).

The statistical comparative analysis only includes week 24 and week 32 data, and it should be noted that no benefit of mepolizumab compared to placebo was shown in QoL after 52 weeks of follow up (LSmean difference [95% CI] in AQLQ 0.08 [-0.16; 0.32], see Table 15). This contrasts with what was shown in the

dupilumab QUEST study, where week 52 QoL data are available for the ITT population. In QUEST, a statistically significant improvement in QoL was seen at week 24 with dupilumab compared to placebo (LSmean difference *vs* placebo [95% CI] 0.20 [0.06 to 0.34]), which was even further improved after 52 weeks of follow up (0.29 [0.15 to 0.44]) (see Table 39 and [8]). However, the lower end of the 95% CIs did not meet the adjusted MCID of 0.25 defined by the Medicines Council [1].

TABLE 22 SUMMARY OF CHANGE FROM BASELINE IN QUALITY OF LIFE – DUPILUMAB *VS* MEPOLIZUMAB

Population	Studies included in the analysis	LSmean difference (95% CI) (AQLQ score)
Uncontrolled, persistent eosinophilic asthma	Wenzel 2016 (DRI12544) and Castro 2018 (QUEST) *vs* Ortega 2014 (MENSA) and Chupp 2017 (MUSCA)	-0.129 (-0.319; 0.061)
OCS-dependent eosinophilic asthma	Rabe 2018 (VENTURE) *vs* Bel 2014 (SIRIUS)	-0.006 (-0.411; 0.398)

Data from Castro 2018 (QUEST) are for the 200 mg dose q2w and respective placebo group only
Indirect comparison was performed using the standardised mean difference procedure according to the guideline from the Medicines Council [47] and numbers converted back to the AQLQ scale (see appendix 8.4)
AQLQ is a patient-reported measure of asthma-specific health-related quality of life. Higher scores indicate better quality of life; a global score is calculated ranging from 1 to 7. The MCID is 0.5 for all scales [44, 45].
Source: Table 75 and Table 76
AQLQ, Asthma Quality of Life Questionnaire; CI, confidence interval; LS, least square; MCID, minimal clinically important difference; OCS, oral corticosteroid; q2w, every 2 weeks

Sick leave

No comparative analysis of sick leave could be performed since the outcome was only reported for dupilumab.

Safety results – uncontrolled, persistent eosinophilic asthma

Proportion of patients with serious adverse events

For patients with uncontrolled, persistent eosinophilic asthma, the differences between dupilumab and mepolizumab in the proportion of patients with SAEs were not statistically significant. In the 24 and 32-week studies, the risk of having an SAE was 97.4% higher with dupilumab compared to mepolizumab, and 6.5%-points more patients had an SAEs with dupilumab *vs* mepolizumab (Table 23). In the 52-week studies, the risk of having an SAE was 15.3% higher with dupilumab compared to mepolizumab. and 2.0%-points more patients had an SAEs with dupilumab *vs* mepolizumab.

In patients with OCS-dependent eosinophilic asthma a statistically significantly increased risk of SAEs was found with dupilumab *vs* mepolizumab with a twice as high risk at the lower end of the 95% CI (Table 23). In absolute numbers, 26%-points more patients had SAEs with dupilumab compared to mepolizumab; however, the lower end of the 95% CI was below the adjusted MCID of 2.5%-points defined by the Medicines Council [1], and hence the difference was not assessed as clinically relevant. However, the difference was mainly driven by the SIRIUS study having a very low SAE rate in the mepolizumab group *vs* placebo (1/69 *vs* 12/66), since no noticeable differences between dupilumab (8.7% of patients with an SAE) and placebo (5.6% of patients with an SAE) were observed in the by-study results (see Table 17).

TABLE 23 SUMMARY OF PROPORTION WITH SERIOUS ADVERSE EVENTS – DUPILUMAB *VS* MEPOLIZUMAB

Population	Studies included in the analysis	RD (95% CI)	RR (95% CI)
Uncontrolled, persistent eosinophilic asthma	Wenzel 2016 (DRI12544) *vs* Ortega 2014 (MENSA) and Chupp 2017 (MUSCA)	6.478 (-1.596; 27.451)	1.974 (0.760; 5.128)
Uncontrolled, persistent eosinophilic asthma	Castro 2018 (QUEST) *vs* Pavord 2012 (DREAM)	2.010 (-5.669; 17.624)	1.153 (0.567; 2.345)
OCS-dependent eosinophilic asthma	Rabe 2018 (VENTURE) *vs* Bel 2014 (SIRIUS)	25.969 (1.498; 257.1)	19.549 (2.070; 184.6)

Data from Castro 2018 (QUEST) are for the 200 mg dose q2w and respective placebo group only
Source: Table 75 and Table 76
CI, confidence interval; OCS, oral corticosteroid; q2w, every 2 weeks; RD, risk difference; RR, relative risk

Discontinuation from the study

In the 24 and 32-week studies in uncontrolled, persistent asthma, the risk of discontinuation was 30.4% higher with dupilumab compared to mepolizumab, and 1.3%-points more patients discontinued with dupilumab *vs* mepolizumab (Table 24). In the 52-week studies, the risk of study discontinuation was 6.6% higher with dupilumab compared to mepolizumab, and 1.0%-points more patients discontinued with dupilumab *vs* mepolizumab. None of the differences were, however, statistically significant.

In patients with OCS-dependent eosinophilic asthma, the risk of study discontinuation was 42.1% lower with dupilumab compared to mepolizumab, and 1.8%-points fewer patients discontinued with dupilumab *vs* mepolizumab. These differences were also not statistically significant.

TABLE 24 SUMMARY OF PROPORTION OF PATIENTS DISCONTINUED – DUPILUMAB *VS* MEPOLIZUMAB

Population	Studies included in the analysis	RD (95% CI)	RR (95% CI)
Uncontrolled, persistent eosinophilic asthma	Wenzel 2016 (DRI12544) *vs* Ortega 2014 (MENSA) and Chupp 2017 (MUSCA)	1.261 (-2.085; 10.027)	1.304 (0.498; 3.416)
Uncontrolled, persistent eosinophilic asthma	Castro 2018 (QUEST) *vs* Pavord 2012 (DREAM)	1.032 (-6.704; 15.422)	1.066 (0.573; 1.982)
OCS-dependent eosinophilic asthma	Rabe 2018 (VENTURE) *vs* Bel 2014 (SIRIUS)	-1.809 (-4.018; 17.685)	0.579 (0.066; 5.113)

Data from Castro 2018 (QUEST) are for the 200 mg dose q2w and respective placebo group only
Source: Table 75 and Table 76
CI, confidence interval; OCS, oral corticosteroid; q2w, every 2 weeks; RD, risk difference; RR, relative risk

Anaphylactic reactions

Anaphylactic reactions have been reported very rarely both with dupilumab and mepolizumab and no obvious differences have been observed. In the SmPCs, anaphylactic reactions are listed as a very rare (<1/10,000) adverse reaction for dupilumab based on the asthma development program [48] and as rare (<1/1,000) adverse reaction for mepolizumab, based on spontaneous post marketing reporting [49]. Thus, the immunogenic potential of both dupilumab and mepolizumab seems to be low.

5.2 What is the added clinical value of dupilumab compared with omalizumab in treatment of patients >12 years of age with severe asthma with type 2 inflammation characterised by allergy and concomitant eosinophilia or characterised by allergy and concomitant increased FeNO?

Population

Patients >12 years with severe asthma with type 2-inflammation characterised by allergy and concomitant eosinophilia or characterised by allergy and concomitant increased FeNO.

Eosinophilia is defined as blood EOS ≥150 cells/µL observed within the last month or blood EOS ≥300 cells/µL observed within the last year, or sputum eosinophilia ≥3 % within the last year.

Allergy is defined in the protocol as proven sensibilisation towards a perennial allergen on skin prick test and/or measurement of increased specific IgE antibodies (> 0.35 kU/L) and symptoms on relevant exposure for the allergen.

Increased FeNO is defined as FeNO ≥25 ppb observed within the last month.

Intervention

Dupilumab in a loading dose of 400 mg (two 200 mg SC injections), followed by 200 mg SC injection q2w as add-on to standard treatment.

For patients in maintenance treatment with OCS or for patients with concomitant moderate-to-severe atopic dermatitis: Dupilumab in a loading dose of 600 mg (two 300 mg SC injections), followed by 300 mg SC injection q2w as add-on to standard treatment.

Comparator

Omalizumab (dose and dosing frequency depend on the blood IgE level and body weight) SC injection q2w or q4w in addition to standard treatment.

5.2.1 Presentation of relevant studies

Dupilumab studies

The effect of dupilumab in subgroups of patients with evidence of allergic asthma at baseline was investigated in a *post-hoc* analysis of data from the QUEST study [9]. The QUEST study is described in section 4.3.1 and summaries of main study characteristics and baseline characteristics for the allergic subgroup are presented in appendix 8.2.1 and 8.3.1 , respectively. For this subgroup analysis, allergic asthma was defined according to the most commonly used criteria in clinical practise in the USA, i.e. total serum IgE ≥30 IU/mL and ≥1 positive perennial aeroallergen-specific IgE ≥0.35 kU/L at baseline. The following perennial allergens were included: *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, *Alternaria alternata*, *Cladosporium herbarum*, cat and dog danders, German cockroach, oriental cockroach, and *Aspergillus fumigatus*. Ongoing allergic/atopic conditions were self-reported by the patients and were recorded in >90% of this subgroup of allergic patients [9]. Only data for the treatment arms with the relevant dosage regimen are presented, i.e. the 200 mg dose q2w and matching placebo groups.

No data are available for dupilumab in patients with OCS-dependent allergic asthma.

Omalizumab studies

A total of 16 studies with omalizumab were found. The studies are described in section 4.3.3 and summaries of main study characteristics and baseline characteristics are presented in appendix 8.2.3 and 8.3.3 , respectively.

In all studies, where specified, omalizumab was administered SC at a minimum dose of 0.016 mg/kg IgE (IU/mL) q2w or q4w. Placebo was used as comparator in most (12) of the omalizumab studies [17, 20, 23, 24, 27-29, 32, 33, 36-38], while the comparator in 4 studies was BSC [25], conventional therapy [34], ICS + LABA [35] or optimised asthma therapy [30]. Consequently, these 4 studies were not blinded.

The treatment period varied from 16 to 52 weeks. Most (9) studies had a duration of 20-32 weeks [23, 24, 27, 30, 33, 35-38], 3 studies had a 16-week treatment period [28, 29, 34], and 4 studies were of 48-52 weeks' duration [17, 20, 25, 32]. Of the 4 studies with a duration of approximately 1 year, only 1 study (with 48 weeks' duration) was double-blind, placebo-controlled and with omalizumab as add-on treatment to stable standard of care [32]; while the other 3 studies were either open-label [25] or included a steroid-stable phase followed by first a steroid-reduction phase and subsequently an extension phase where any other asthma medication was allowed and stable dose was not required [17, 20]. Two additional studies (of 32 weeks' duration) had a 16-week steroid-stable phase followed by a phase where the ICS dose was reduced [23, 38]. No studies investigated the potential OCS sparing effect of omalizumab.

Allergy was in most studies defined as positive skin prick test or *in vitro* reactivity to ≥1 aeroallergen and a total serum IgE of 30-700 IU/mL.

According to the manuscripts, the studies by Busse *et al* 2001 [17] and Soler *et al* 2001 [20] were performed in patients with severe and moderate-to-severe allergic asthma, respectively; however, based on the most recent GINA guidelines [50], the asthma severity was assessed as moderate. Since the studies are included in the Medicines Council's guideline for treatment of severe asthma [5], we decided to include the studies in this application although the protocol states that studies not reporting on severe asthma should be excluded [1].

No studies reported data for all outcomes, and some studies only reported results for a single or few outcomes relevant for this application; thus, the by-study results presented are very scattered and a limited amount of data are included in the comparative analyses.

5.2.2 Relevant differences between studies

The allergic subpopulation in the dupilumab QUEST study varied from the populations in the omalizumab studies in some patient inclusion criteria and baseline characteristics (see section 8.3.1 and 8.3.3).

The number of exacerbations in the last year was approximately 2 in the dupilumab study population and in some of the omalizumab studies. Most of the omalizumab studies did not report the exacerbation history, while a higher number of exacerbations in the last year were reported in the Chanez 2010 study (4.0-4.7 exacerbations in previous year) [29], and the OCS-dependent subgroup in the Bousquet 2011 study (2.7-3.3 exacerbations in previous year) [31]. FEV1 was not reported in many of the omalizumab studies, but generally, where reported, FEV1 was better in the omalizumab studies with FEV1 of 2.3-2.8 L compared to the allergic subpopulation in the dupilumab QUEST study where FEV1 was approximately 1.8 L.

Medium-to-high-dose ICS was an inclusion criterion in the QUEST study, and high-dose (according to current standards at the time of the study) was an inclusion criterion in many of the omalizumab studies

but not reported in others. OCS use was not reported for the QUEST study and was either not allowed or used by between 7% and 80% of patients in the omalizumab studies. Use of LABA or another second controller was an inclusion criterion in the QUEST study, while LABA was allowed in some of the omalizumab studies and not in others.

The protocol for this application [1] defined allergy as proven sensibilisation towards a perennial allergen on skin prick test and/or measurement of increased specific IgE antibodies (> 0.35 kU/L) and symptoms on relevant exposure for the allergen. Symptoms on relevant exposure for the antigen(s) were not recorded in the dupilumab study or in any of the omalizumab studies. However, in the QUEST study, ongoing allergic/atopic conditions were self-reported by >90% of the subgroup of allergic patients [9]. The mean IgE level was slightly higher in the allergic subpopulation of the dupilumab QUEST study (304-337 IU/mL) than in the majority of the omalizumab studies (167-281 IU/mL in all studies except for Mukherjee 2019).

5.2.3 Results per study

By-study results extracted from the publications, EPARs and/or SmPCs are summarised in appendix 8.5.1 for the dupilumab studies and appendix 8.5.3 for the omalizumab studies. No discrepancies between published data, the EPARs and/or SmPCs were noted.

Efficacy results – uncontrolled, persistent allergic asthma

Reduction in annual number of exacerbation events

Exacerbation events were defined slightly different in the dupilumab and omalizumab studies. According to the ATS/ERS, the definition of a severe asthma exacerbation for clinical trials should include ≥1 of the following: Use of systemic corticosteroids or an increase from a stable maintenance dose for ≥3 days, or hospitalisation or emergency room visit because of asthma, requiring systemic corticosteroids [51]. In the QUEST study, severe exacerbations were defined in accordance with ATS/ERS, while not all the omalizumab studies defined the number of days required for treatment with systemic corticosteroids, and none included the option of hospitalisation or emergency room visit because of asthma in the definition.

In the QUEST study, annualised rates of severe exacerbation events were reported for 2 allergic subgroups: 1 with allergy and increased EOS (≥150 cells/µL) and 1 with allergy and increased FeNO (≥25 ppb). Five omalizumab studies reported annualised rates of severe or clinically relevant exacerbation rates and 4 omalizumab studies reported exacerbation rates or clinically significant exacerbation rates for the duration of the study.

In the dupilumab QUEST study, the annualised rate of severe exacerbations was 0.357 events/patient-year lower compared to placebo in the subgroup with allergy and increased EOS and 0.553 events/patient-year lower compared to placebo in the subgroup with allergy and increased FeNO (Table 25). The risk of severe exacerbations was statistically significantly reduced with rate ratios of 0.584 and 0.374, respectively, in the 2 subgroups.

A total of 9 omalizumab studies reported the exacerbation rate; however, only 3 of the studies had 1 year of follow up and 1 study had 48 weeks of follow up. All the studies of approximately 1 year duration showed statistically significant differences in rate ratios in the range of 0.41-0.75 for omalizumab compared to the control, while 3 of the studies with shorter duration did not show a statistically significant difference to control treatment (Table 25).

TABLE 25 SUMMARY OF EXACERBATION RATES – UNCONTROLLED, PERSISTENT ALLERGIC ASTHMA

Study (subgroup)	Follow-up	Mean (95% CI) rate		RD	RR
Annualised rates					
Dupilumab studies		**Dupilumab**	**Placebo**		
Castro 2018 (QUEST) (allergy + EOS ≥150 cells/µL)	52 weeks	0.502 (0.392; 0.644)	0.859 (0.642; 1.149)	-0.357	0.584 (0.398; 0.856)
Castro 2018 (QUEST) (allergy + FeNO ≥25 ppb)	52 weeks	0.33 (0.242; 0.450)	0.883 (0.639; 1.219)	-0.553	0.374 (0.239; 0. 585)
Omalizumab studies		**Omalizumab**	**Control**		
Busse 2001	52 weeks[a]	0.468 (NR; NR)	0.842 (NR; NR)	-0.374	0.556 (0.409; 0.756)
Soler 2001	52 weeks[a]	0.376 (NR; NR)	0.898 (NR; NR)	-0.522	0.419 (0.309; 0.568)
Holgate 2004	32 weeks[b]	0.878 (NR; NR)	1.266 (NR; NR)	-0.388	0.694 (0.432; 1.114)
Vignola 2004	28 weeks	0.454 (NR; NR)	0.67 (NR; NR)	-0.216	0.678 (0.432; 1.062)
Ayres 2004 (severe subgroup)	12 months	1.26 (NR; NR)	3.06 (NR; NR)	-1.8	0.41 (0.288; 0.583)
Exacerbation rates for the duration of the study					
Humbert 2005	28 weeks	0.68 (0.53; 0.87)	0.91 (0.73-1.14)	-0.23	0.738 (0.552; 0.998)
Bousquet 2011	32 weeks	0.55 (NR; NR)	0.98 (NR; NR)	-0.43	0.57 (0.417; 0.778)
Hanania 2011	48 weeks	0.66 (NR; NR)	0.88 (NR; NR)	-0.22	0.75 (0.61; 0.92)
Busse 2013	24 weeks	0.21 (NR; NR)	0.26 (NR; NR)	-0.05	0.73 (0.44; 1.24)

Data from Castro 2018 (QUEST) are for the 200 mg dose q2w and respective placebo group only

[a] Extension phase

[b] 16 weeks ICS stable, 16 weeks ICS reduction

Source: Table 49, Table 59, Table 60, Table 61, Table 62, Table 63, Table 64, Table 67, Table 68, Table 72. If not published, RD (95%) and RR (95% CI) were calculated according to appendix 8.4

CI, confidence interval; EOS, blood eosinophils FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroids; q2w, every 2 weeks; RD, risk difference; RR, relative risk

Proportion of patients with 0 annual exacerbations

The proportion of patients with 0 annual exacerbations was not reported for the subgroups with allergy and increased EOS or allergy and increased FeNO, or for the entire allergic subgroup in the dupilumab QUEST study. Instead the results in the broad ITT population are presented. This is considered a more conservative estimate of the effect.

The results in the ITT population for the QUEST study showed statistically significant differences between dupilumab and placebo with 13%-points more patients in the dupilumab group compared to the placebo group having 0 annual exacerbations, while the chance of having 0 annual exacerbations was 23% greater in the dupilumab group compared to the placebo group (Table 26).

A total of 12 omalizumab studies reported the proportion of patients with 0 exacerbations over the duration of the study; in the Ayres 2004 study, the outcome was also reported for the subgroup of patients with severe asthma. By-study results are shown for all studies, regardless of study duration, in Table 26. Only the Ayres 2004 study had a duration of 1 year, while the Hanania 2011 study was of 48 weeks duration, which is assessed as comparable. For the Busse 2001 and Soler 2001 studies, the proportion of patients with 0 exacerbations could only be retrieved for the duration of the steroid-stable phase, i.e. 16 weeks and not for the 52-week extension phase.

In the Ayres 2004 study, 23%-points more patients in the omalizumab group compared to BSC group had 0 annual exacerbations and an 87.4% greater chance of having 0 exacerbations. The differences were statistically significant, while in the severe subgroup of the same study, the effect was smaller and not statistically significant.

In the Hanania 2011 study, statistically significant differences were found between omalizumab and placebo; approximately 7%-points more patients in the omalizumab group compared to placebo had 0 exacerbations and the change of having 0 exacerbations was 12% greater in the omalizumab group than in the placebo group (Table 26).

TABLE 26 SUMMARY OF PROPORTION OF PATIENTS WITH 0 EXACERBATIONS DURING THE TREATMENT PERIOD – UNCONTROLLED, PERSISTENT ALLERGIC ASTHMA

Study	Follow up	Proportion (95% CI)		RD (95% CI)	RR (95% CI)
Dupilumab studies		**Dupilumab**	**Placebo**		
Castro 2018 (QUEST)	52 weeks	70.8 (67.3; 74.4)	57.7 (52.3; 63.2)	13.1 (6.62; 19.6)	1.23 (1.10; 1.37)
Omalizumab studies		**Omalizumab**	**Control**		
Busse 2001	16 weeks[a]	85.4 (81.2; 89.7)	76.7 (71.5; 81.8)	8.79 (2.12; 15.47)	1.115 (1.025; 1.212)
Soler 2001	16 weeks[a]	87.2 (83.3; 91.2)	69.5 (64.0; 75.0)	17.74 (10.99;24.49)	1.255 (1.146; 1.375)
Vignola 2004	28 weeks	81.8 (76.6; 87.0)	74.5 (68.4; 80.6)	7.33 (-0.71; 15.36)	1.098 (0.990; 1.219)
Ayres 2004	12 months	49.5 (42.7; 56.3)	26.4 (18.0; 34.8)	23.10 (12.28; 33.92)	1.874 (1.326; 2.650)
Ayres 2004 (severe subgroup)	12 months	40.0 (31.0; 49.0)	34.7 (21.4; 48.0)	5.31 (-10.75;21.36)	1.153 (0.739; 1.798)
Humbert 2005	28 weeks	56.9 (50.2; 63.7)	51.4 (44.7; 58.2)	5.51 (-4.02; 15.04)	1.107 (0.928; 1.321)
Ohta 2009	16 weeks	96 (92.9; 99.1)	89 (84.2; 93.8)	7.00 (1.29; 12.71)	1.079 (1.013; 1.149)
Chanez 2010	16 weeks	45 (23.2; 66.8)	63.6 (35.2; 92.1)	-18.64 (-54.46; 17.19)	0.707 (0.366; 1.367)
Hanania 2011	48 weeks	64.4 (59.9; 68.9)	57.5 (52.8; 62.2)	6.92 (0.37; 13.47)	1.120 (1.005; 1.249)
Bardelas 2012	24 weeks	89.7 (84.6; 94.8)	82.2 (75.8; 88.7)	7.48 (-0.74; 15.71)	1.091 (0.990; 1.202)
Rubin 2012 (QUALITX, Brazilian)	20 weeks	56.4 (45.4; 67.4)	47.4 (31.5; 63.2)	9.04 (-10.27;28.36)	1.191 (0.808; 1.755)
Busse 2013	24 weeks	84.7 (79.1; 90.3)	80.7 (74.8; 86.6)	4.01 (-4.15; 12.18)	1.050 (0.951; 1.159)
Mukherjee 2019	32 weeks[b]	75 (32.6; 117.4)	20 (0.0; 55.1)	55.00 (-0.04; 100.00)	3.750 (0.594; 23.661)

Data from Castro 2018 (QUEST) are for the ITT population and for the 200 mg dose q2w and respective placebo group only

[a] during the steroid stable phase

[b] during the entire treatment phase including steroid-reduction phase

Source: Table 49, Table 59, Table 60, Table 62, Table 63, Table 64, Table 65, Table 66, Table 68, Table 69, Table 71, Table 72, Table 74. If not published, RD (95%) and RR (95% CI) were calculated according to appendix 8.4

CI, confidence interval; ITT, intention-to-treat; q2w, every 2 weeks; RD, risk difference; RR, relative risk

Mean change from baseline in lung function

For the dupilumab QUEST study, the mean change from baseline in FEV1 was reported at week 12 for the subgroups with allergy and increased EOS, and allergy and increased FeNO, and at weeks 24 and 52 for the entire allergic subgroup. Since the effect of dupilumab on FEV1 was relatively stable from week 12 until the end of the study in the ITT population (see Figure 3), and since the results are comparable across the 3 subgroups, both week 12, 24 and 52 data are shown to provide support for the week 12 data in the subgroups that best match the population for this clinical question.

In the 3 different allergic subgroups and at the 3 different timepoints, the results were similar, with statistically significant improvements in FEV1 from baseline of 0.16-0.19 L compared to placebo (Table 27).

For omalizumab, the change from baseline in FEV1, compared to the control group, ranged from an impairment of 0.085 L to an improvement of 0.31 L (Table 27); however, only few of the studies reported measures of variability for the outcome, therefore the results presented should be interpreted with caution.

TABLE 27 SUMMARY OF CHANGES FROM BASELINE IN FEV1 – UNCONTROLLED, PERSISTENT ALLERGIC ASTHMA

Study	Timepoint assessed	LSsmeans (95% CI) change from baseline (L)		LSmeans difference (95% CI) (L)
Dupilumab studies		**Dupilumab**	**Placebo**	
Castro 2018 (QUEST) (allergy + EOS ≥150)	Week 12	NR	NR	0.16 (0.07; 0.24)
Castro 2018 (QUEST) (allergy +FeNO ≥25)	Week 12	NR	NR	0.19 (0.09; 0.30)
Castro 2018 (QUEST) (allergic subgroup)	Week 24	0.34 (0.301; 0.379)	0.18 (0.121; 0.239)	0.16 (0.089; 0.231)
Castro 2018 (QUEST) (allergic subgroup)	Week 52	0.36 (0.321; 0.399)	0.18 (0.121; 0.239)	0.18 (0.109; 0.251)
Omalizumab studies		**Omalizumab**	**Control**	
Ayres 2004 (severe subgroup)	Week 52	0.16 (NR; NR)	-0.15 (NR; NR)	0.31 (NE; NE)
Humbert 2005	Week 28	0.190 (NR; NR)	0.096 (NR; NR)	0.094 (NE; NE)
Bousquet 2011 (severe subgroup)	Week 32	NR	NR	0.13 (0.03; 0.23)
Bardelas 2012	Week 24	0.08 (NR; NR)	0.16 (NR; NR)	-0.085 (-0.19; 0.02)
Hoshino 2012	Week 16	0.21 (NR; NR)	0.02 (NR; NR)	0.19 (NE; NE)
Rubin 2012 (QUALITX, Brazilian)	Week 20	0.13 (0.052; 0.208)[a]	-0.003 (-0.121; 0.115)[a]	0.133 (NE; NE)
Busse 2013	Week 24	0.055 (0.005; 0.105)[a]	-0.026 (-0.077; 0.025)[a]	0.081 (NE; NE)

Data from Castro 2018 (QUEST) are for the 200 mg dose q2w and respective placebo group only

[a] unadjusted 95% CI

Source: Table 49, Table 63, Table 64, Table 67, Table 69 Table 70, Table 71, Table 72. If not published, RD (95%) and RR (95% CI) were calculated according to appendix 8.4

CI, confidence interval; EOS, blood eosinophils FeNO; fractional exhaled nitric oxide FEV1, forced expiratory volume in 1 s; L, litre; LS, least square; NE, not estimable; NR, not reported; q2w, every 2 weeks

Proportion of patients with an improvement of ≥200 mL in FEV1

The proportion of patients with a clinically relevant improvement of ≥200 mL in FEV1 was not reported for any of the allergic subgroups in the dupilumab QUEST study, or in any of the omalizumab studies.

In the ITT population in the QUEST study, the proportion (95% CI) of patients with ≥200 mL improvement at week 52 was 50.5% (46.0; 55.0%) in the dupilumab group and 37.1% (31.0; 43.2%) in the placebo group (Table 49). Compared to placebo, the RR (95% CI) of having an improvement of ≥200 mL in FEV1 was 1.362 (1.130; 1.643), and in absolute numbers, 13.44 (5.86; 21.02) %-points more patients had an improvement of ≥200 mL in FEV1. Since 57% of the ITT population had allergic asthma according to the criteria used in the *post hoc* analysis [9], the results of the ITT population can be considered indicative of the results on lung function in an allergic subgroup. Furthermore, the LSmean (95% CI) difference in change from baseline in FEV1 in the ITT population (0.14 L [0.08; 0.19]) [8] was smaller than the differences in the

in the 3 allergic subgroups presented in Table 27, supporting that the ITT results are a conservative estimate for the effect on lung function in an allergic population.

Asthma control

In the dupilumab QUEST study, asthma control was assessed by use of the ACQ and reported at weeks 24 and 52 for the entire allergic subgroup; no results were available for the subgroups with allergy and increased EOS, or allergy and increased FeNO.

Three omalizumab studies reported the change from baseline to the end of treatment in asthma control using the ACQ [37], TASS [32] or Asthma Control Test (ACT) [33].

For dupilumab, LSmean differences in change from baseline to weeks 24 and 52 showed statistically significant improvements (i.e. reduced scores) in asthma control in the range of 0.3-0.4 compared to placebo (Table 28). Omalizumab did not result in any statistically significant improvements in asthma control compared to the control groups (Table 28).

TABLE 28 SUMMARY OF CHANGES FROM BASELINE IN ASTHMA CONTROL – UNCONTROLLED, PERSISTENT ALLERGIC ASTHMA

Study	Timepoint assessed Tool used	LSmeans (95% CI)		LSmeans difference (95% CI)
Dupilumab studies		**Dupilumab**	**Placebo**	
Castro 2018 (QUEST) (allergic subgroup)	Week 24 ACQ	-1.39 (-1.488; -1.292)	NR	-0.28 (-0.46; -0.11)
Castro 2018 (QUEST) (allergic subgroup)	Week 52 ACQ	-1.53 (-1.648; -1.412)	-1.10 (-1.276; -0.924)	-0.43 (-0.642;-0.218)
Omalizumab studies		**Omalizumab**	**Control**	
Hanania 2011	Week 48 TASS	-1.9 (NR; NR)	-1.6 (NR; NR)	-0.3 (NE; NE)
Bardelas 2012	Week 24 ACT total score	5.01 (NR; NR)	4.36 (NR; NR)	0.64 (-0.30; 1.59)
Li 2016	Week 24 ACQ	-0.511 (-0.691; -0.331)	-0.342 (-0.516; -0.168)	-0.169 (-0.420; 0.082)

Data from Castro 2018 (QUEST) are for the 200 mg dose q2w and respective placebo group only

ACQ is a patient-reported measure of the adequacy of asthma control and change in asthma control that occurs either spontaneously or as a result of treatment. Higher scores indicate less control; a global score is calculated ranging from 0 to 6. The MCID is 0.5 [42]

ACT is a patient-reported measure including 5 questions which are scored individually on a 5-point Likert scale (total score 5-25) with higher scores indicating better asthma control

TASS is a patient-reported measure including a nocturnal asthma score (0 to 4 scale), morning asthma symptoms (yes or no) and a daytime asthma symptom score (0 to 4 scale). Total score 0-9 with higher TASS scores representing worse symptoms

Source: Table 49, Table 68, Table 69, Table 73. If not published, RD (95%) and RR (95% CI) were calculated according to appendix 8.4

ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; CI, confidence interval; LS, least square; MCID, minimal clinically important difference; NE, not estimable; NR, not reported; q2w, every 2 weeks; TASS, Total Asthma Symptom Severity

Quality of life

In the dupilumab QUEST study, QoL was assessed by use of the AQLQ and reported at weeks 24 and 52 for the ITT population; no results were available for the subgroups with allergy and increased EOS, or allergy and increased FeNO, or for the entire allergic subgroup. Thus, the results in the ITT population are presented. This is considered a conservative estimate.

Four omalizumab studies reported QoL at week 16, 24 or 28. All studies reporting QoL used the AQLQ.

For dupilumab, statistically significant LSmean differences to placebo in change from baseline to weeks 24 and 52 in AQLQ in the range of 0.2-0.3 units were found (Table 29). In the omalizumab studies, improvements of approximately 0.25-0.45 were seen in the omalizumab groups *vs* comparator. The improvement in the Li 2016 study was not statistically significant, and since no measures of variability were reported in the Humbert 2005 study, this result should be interpreted with caution (Table 29).

TABLE 29 SUMMARY OF CHANGES FROM BASELINE IN QUALITY OF LIFE – UNCONTROLLED, PERSISTENT ALLERGIC ASTHMA

Study	Timepoint assessed Tool used	LSmeans (95% CI)		LSmeans difference (95% CI)
Dupilumab studies		**Dupilumab**	**Placebo**	
Castro 2018 (QUEST)	Week 24 AQLQ	1.14 (1.062; 1.218)	0.94 (0.822; 1.058)	0.20 (0.06; 0.34)
Castro 2018 (QUEST)	Week 52 AQLQ	1.28 (1.202; 1.358)	0.99 (0.872; 1.108)	0.29 (0.15; 0.44)
Omalizumab studies		**Omalizumab**	**Control**	
Soler 2001	Week 16 AQLQ	0.883 (0.781; 0.985)	0.592 (0.474; 0.710)	0.291 (0.135; 0.447)
Vignola 2004	Week 28 AQLQ	1.321 (1.186; 1.456)	1.072 (0.931; 1.213)	0.249 (0.054; 0.444)
Humbert 2005	Week 28 AQLQ	0.91 (NR; NR)	0.46 (NR; NR)	0.45 (NE; NE)
Li 2016	Week 24 AQLQ	0.51 (0.210; 0.810)	0.10 (-0.208; 0.408)	0.41 (-0.020; 0.840)

Data from Castro 2018 (QUEST) are for the ITT population and for the 200 mg dose q2w and respective placebo group only
AQLQ is a patient-reported measure of asthma-specific health-related quality of life. Higher scores indicate better quality of life; a global score is calculated ranging from 1 to 7. The MCID is 0.5 for all scales [44, 45].
Source: Table 49, Table 60, Table 62, Table 64, Table 73. If not published, RD (95%) and RR (95% CI) were calculated according to appendix 8.4
AQLQ, Asthma Quality of Life Questionnaire; CI, confidence interval; ITT, intention-to-treat; LS, least square; MCID, minimal clinically important difference; NE, not estimable; NR, not reported; q2w, every 2 weeks

Sick leave

No data on sick leave were reported for the subgroup of patients with allergic asthma treated with dupilumab. However, in the phase 2b study (DRI12544), the annualised days of sick leave due to severe exacerbation event in the ITT population was 0.613 days/year and 2.238 days/year in the dupilumab 200 mg q2w and placebo groups, respectively (p<0.0001) (Table 46). Since 66% of the patients in these treatment groups had allergic rhinitis [6], these results are considered indicative of the effect of dupilumab on sick leave in a population with uncontrolled, persistent allergic asthma.

For omalizumab, sick leave was only reported in the Ayres 2004 study with a median (range) of 14 (1-365) days and 28 (1-259) days of absenteeism in the omalizumab and control groups, respectively. In the subgroup of patients with severe asthma in the same study, the corresponding numbers were 15.5 (1-365) days and 46 (3-186) days, respectively (Table 63).

Safety results – uncontrolled, persistent allergic asthma

Safety data for dupilumab were only reported for the safety population that included all the patients who received ≥1 dose or part of a dose, and data were analysed according to the intervention received. Thus, it

was not possible to retrieve safety data specifically for the allergic subgroups, therefore data for the safety population are presented below. For the phase 2b (DRI12544) and QUEST studies, data are only included for the 200 mg dose q2w and respective placebo group.

Incidence of serious adverse events

In the phase 2b (DRI12544) and the QUEST studies with dupilumab, the incidence of SAEs was similar between the dupilumab 200 mg and placebo groups (Table 30). In the VENTURE study in OCS-dependent patients, SAEs were reported by 8.7% of patients in the dupilumab 300 mg group and 5.6% of those in the placebo group.

In the omalizumab studies, the incidence of SAEs ranged from 0 to 16.5% in the omalizumab treatment group and from 0 to 16.4% in the placebo group across studies (Table 30).

TABLE 30 INCIDENCE OF SERIOUS ADVERSE EVENTS IN STUDIES WITH DUPILUMAB AND OMALIZUMAB

Study	Patients with events / total N (incidence)		RD (95% CI)	RR (95% CI)
Dupilumab studies	**Dupilumab**	**Placebo**		
Wenzel 2016 (DRI12544)	10 / 148 (6.8%)	9 / 158 (5.7%)	1.06 (-4.36; 6.48)	1.19 (0.50; 2.84)
Castro 2018 (QUEST)	49 / 631 (7.8%)	26 / 313 (8.3%)	-0.54 (-4.24; 3.16)	0.93 (0.59; 1.48)
Rabe 2018 (VENTURE)	9 / 103 (8.7%)	6 / 107 (5.6%)	3.13 (-3.85; 10.11)	1.56 (0.58; 4.22)
Omalizumab studies	**Omalizumab**	**Placebo**		
Busse 2001	11 / 268 (4.1%)	12 / 257 (4.7%)	-0.56 (-4.07; 2.94)	0.88 (0.40; 1.96)
Soler 2001	18 / 274 (6.6%)	19 / 272 (7.0%)	-0.42 (-4.63; 3.80)	0.94 (0.51; 1.75)
Holgate 2004	1 / 126 (0.8%)	5 / 120 (4.2%)	-3.37 (-7.27; 0.52)	0.19 (0.02; 1.61)
Vignola 2004 (SOLAR)	3 / 209 (1.4%)	3 / 196 (1.5%)	-0.10 (-2.45; 2.26)	0.94 (0.19; 4.59)
Ayres 2004	34 / 206 (16.5%)	14 / 106 (13.2%)	-3.30 (-11.50; 4.90)	0.80 (0.45; 1.42)
Humbert 2005 (INNOVATE)	29 / 245 (11.8%)	37 / 237 (15.6%)	-3.78 (-9.92; 2.37)	0.76 (0.48; 1.19)
Ohta 2009 (Japanese)	6 / 151 (4.0%)	11 / 164 (6.7%)	-2.73 (-7.67; 2.20)	0.59 (0.23; 1.56)
Chanez 2010	0 / 20 (0.0%)	1 / 11 (9.1%)	-10.84 (-32.30; 10.62)	0.30 (0.03; 2.95)
Bousquet 2011	33 / 274 (12.0%)	21 / 128 (16.4%)	-4.36 (-11.85; 3.12)	0.73 (0.44; 1.22)
Hanania 2011	40 / 428 (9.3%)	44 / 420 (10.5%)	-1.13 (-5.15; 2.89)	0.89 (0.59; 1.34)
Rubin 2012 (QUALITX, Brazilian)	3 / 78 (3.8%)	0 / 38 (0.0%)	2.50 (-4.30; 9.30)	2.00 (0.23;17.31)
Busse 2013	4 / 157 (2.5%)	6 / 171 (3.5%)	-0.96 (-4.66; 2.74)	0.73 (0.21; 2.53)
Li 2016 (Chinese)	6 / 310 (1.9%)	9 / 299 (3.0%)	-1.07 (-3.54; 1.40)	0.64 (0.23; 1.78)

Data from Wenzel 2016 (DRI12544) and Castro 2018 (QUEST) are for the 200 mg dose q2w and respective placebo group only
Source: Table 52, Table 53, Table 54, Table 59, Table 60, Table 61, Table 62, Table 63, Table 64, Table 65, Table 66, Table 67, Table 68, Table 71, Table 72, Table 73. RD (95%) and RR (95% CI) were calculated according to appendix 8.4
CI, confidence interval; N, total number of subjects; q2w, every 2 weeks; RD, risk difference; RR, relative risk

Discontinuation from the study

In the phase 2b (DRI12544) and the QUEST studies with dupilumab, the rate of discontinuation from the study was similar between the dupilumab 200 mg group and placebo group (Table 31). In the VENTURE study in OCS-dependent patients, few patients discontinued: 2 (1.9%) in the dupilumab 300 mg group and 5 (4.7%) in the placebo group.

In the omalizumab studies, the rate of discontinuation from the studies ranged from 2.4% to 20.0% in the omalizumab group and from 0 to 27.3% in the placebo group across studies (Table 31).

TABLE 31 DISCONTINUATION FROM STUDIES WITH DUPILUMAB AND OMALIZUMAB

Study	Patients with events / total N (incidence)		RD (95% CI)	RR (95% CI)
Dupilumab studies	**Dupilumab**	**Placebo**		
Wenzel 2016 (DRI12544)	11 / 148 (7.4%)	12 / 158 (7.6%)	-0.16 (-6.07; 5.75)	0.98 (0.45; 2.15)
Castro 2018 (QUEST)	70 / 631 (11.1%)	38 / 317 (12.0%)	-0.89 (-5.23; 3.44)	0.93 (0.64; 1.34)
Rabe 2018 (VENTURE)	2 / 103 (1.9%)	5 / 107 (4.7%)	-2.73 (-7.54; 2.07)	0.42 (0.08; 2.09)
Omalizumab studies	**Omalizumab**	**Placebo**		
Busse 2001	31 / 268 (11.6%)	42 / 257 (16.3%)	-4.78 (-10.70; 1.15)	0.71 (0.46; 1.09)
Soler 2001	29 / 274 (10.6%)	66 / 272 (24.3%)	-13.68 (-19.94; -7.42)	0.44 (0.29; 0.65)
Holgate 2004	11 / 126 (8.7%)	11 / 120 (9.2%)	-0.44 (-7.57; 6.70)	0.95 (0.43; 2.11)
Vignola 2004 (SOLAR)	5 / 209 (2.4%)	15 / 196 (7.7%)	-5.26 (-9.52; -1.00)	0.31 (0.12; 0.84)
Ayres 2004[a]	15 / 206 (7.3%)	0 / 106 (0.0%)	6.77 (2.72; 10.81)	8.31 (1.12; 61.81)
Humbert 2005 (INNOVATE)	30 / 245 (12.2%)	22 / 237 (9.3%)	2.96 (-2.56; 8.48)	1.32 (0.78; 2.22)
Ohta 2009 (Japanese)	13 / 151 (8.6%)	28 / 164 (17.1%)	-8.46 (-15.76; -1.17)	0.50 (0.27; 0.94)
Chanez 2010	3 / 20 (15.0%)	3 / 11 (27.3%)	-12.27 (-42.89; 18.35)	0.55 (0.13; 2.28)
Bousquet 2011	22 / 275 (8.0%)	25 / 131 (19.1%)	-11.08 (-18.54; -3.63)	0.42 (0.25; 0.72)
Hanania 2011	83 / 427 (19.4%)	94 / 421 (22.3%)	-2.89 (-8.36; 2.58)	0.87 (0.67; 1.13)
Bardelas 2012	16 / 136 (11.8%)	13 / 135 (9.6%)	2.14 (-5.22; 9.49)	1.22 (0.61; 2.44)
Rubin 2012 (QUALITX, Brazilian)	8 / 78 (10.3%)	4 / 38 (10.5%)	-0.27 (-12.12; 11.59)	0.97 (0.31; 3.03)
Busse 2013	24 / 157 (15.3%)	20 / 171 (11.7%)	3.59 (-3.82; 11.00)	1.31 (0.75; 2.27)
Li 2016 (Chinese)	11 / 308 (3.6%)	16 / 308 (5.2%)	-1.62 (-4.85; 1.61)	0.69 (0.32; 1.46)
Mukherjee 2019	1 / 5 (20.0%)	1 / 6 (16.7%)	3.33 (-42.69; 49.36)	1.20 (0.10; 14.7)

Data from Wenzel 2016 (DRI12544) and Castro 2018 (QUEST) are for the 200 mg dose q2w and respective placebo group only

[a] discontinued due to AE/SAE

Ayres 2004, Bousquet 2011 and Rubin 2012 were open-label studies

Source: Table 52, Table 53, Table 54, Table 59, Table 60, Table 61, Table 62, Table 63, Table 64, Table 65, Table 66, Table 67, Table 68, Table 69, Table 71, Table 72, Table 73, Table 74. RD (95%) and RR (95% CI) were calculated according to appendix 8.4

AE, adverse event; CI, confidence interval; N, total number of subjects; q2w, every 2 weeks; RD, risk difference; RR, relative risk; SAE, serious adverse event

Anaphylactic reactions

Anaphylactic reactions have been reported very rarely in the dupilumab asthma development program. In the safety pool, 1 serious anaphylactic reaction and 1 serious event of anaphylactic shock (both medically reviewed) were reported in the dupilumab group. No such events were reported in the placebo group and none were reported in the VENTURE study [11, 43]. The low number of anaphylaxis events suggests a low immunogenic potential of dupilumab in the asthma population.

In the omalizumab studies, anaphylactic reactions were rare in the clinical trials. There were no reports of anaphylaxis in the Bousquet 2011 study, Bardelas 2012 study or in the Busse 2013 study. In the Hanania 2011 study, 1 patient (0.23%) in the omalizumab group and 2 in the placebo group (0.48%) experienced anaphylaxis events. Post marketing data has suggested a reporting rate of approximately 0.20% [52].

5.2.4 Comparative analyses

Efficacy results – uncontrolled, persistent allergic asthma

Reduction in annual number of exacerbation events

The comparative analyses of the annualised rate of exacerbations in patients with allergic asthma included the dupilumab QUEST study and 4 omalizumab studies of approximately 1 year duration (Busse 2001, Soler 2001, Ayres 2004 and Hanania 2011). The risk of severe exacerbations was 15.5% lower (95% CI: 38.8% lower to 16.5% higher), and the annualised rate of severe exacerbations was 0.107 events/patient-year lower (0.268 events lower to 0.114 events higher) in the dupilumab group *vs* the omalizumab group (Table 77). The differences were, however, not statistically significant.

Proportion of patients with 0 annual exacerbations

The comparative analysis of the proportion of patients with allergic asthma having 0 annual exacerbations included the dupilumab QUEST study and 2 omalizumab studies of approximately 1 year duration (Ayres 2004 and Hanania 2011). The chance of having 0 annual exacerbations was 4.6% higher (95% CI: 9.8% lower to 21.4% higher) with dupilumab compared to omalizumab. In absolute numbers there were 2.6%-points more patients (5.6%-points fewer to 12.2%-points more) with 0 annual exacerbations in the dupilumab group *vs* the omalizumab group (Table 77). The differences were, however, not statistically significant.

Mean change from baseline in lung function

The indirect comparative analysis of changes from baseline in FEV1 in patients with uncontrolled, persistent allergic asthma was based on 5 studies: 24-week data from the dupilumab QUEST study and 4 omalizumab studies (Bousquet 2011, Bardelas 2012, Rubin2012 and Busse2013). The analysis showed a 0.096 L larger increase from baseline in FEV1 with dupilumab compared to omalizumab, and with a 95% CI of 0.011 to 0.182 L, the difference was statistically significant (Table 77). Since the lower end of the 95% CI did not reach the adjusted MCID of 100 mL defined by the Medicines Council [1], the difference was, however, not assessed as clinically relevant.

Proportion of patients with an improvement of ≥200 mL in FEV1

No comparative analysis of the proportion of patients with an improvement in FEV1 of ≥200 mL could be performed since the outcome was only reported for the dupilumab studies.

Asthma control

The comparative analysis of changes from baseline in asthma control in patients with uncontrolled, persistent allergic asthma was based on only 2 studies: 24-week data from the dupilumab QUEST study and the 24-week Li 2016 study in Chinese patients. The small difference in change from baseline in ACQ score of -0.111 in favour of dupilumab compared to omalizumab was not statistically significant (95% CI: -0.417 to 0.195) (Table 77).

Quality of life

The comparative analysis of changes from baseline in QoL in patients with uncontrolled, persistent allergic asthma was based on 3 studies: 24-week data from the dupilumab QUEST study, the 28-week Vignola 2004 study and the 24-week Li 2016 study in Chinese patients. The small difference in change from baseline in AQLQ score of -0.077 in favour of omalizumab was not statistically significant (95% CI: -0.304 to 0.151) (Table 77).

Sick leave

It was not possible to perform indirect comparisons of sick leave; however, no obvious differences between dupilumab and omalizumab were noted in the by-study results. In the dupilumab phase 2b study (DRI12544) the annualised rate of sick leave due to severe exacerbation events in the ITT population (which were considered indicative of the effect in an allergic subpopulation) was 0.613 days/year and 2.238 days/year in the dupilumab 200 mg q2w and placebo groups, respectively (p<0.0001) (Table 46). For omalizumab, sick leave was reported in the Ayres 2004 study with a median (range) of 14 (1-365) days and 28 (1-259) days of absenteeism in the omalizumab and control groups, respectively. In the subgroup of patients with severe asthma in the same study, the corresponding numbers were 15.5 (1-365) days and 46 (3-186) days, respectively (Table 63).

Safety results – uncontrolled, persistent allergic asthma

Proportion of patients with serious adverse events

In the studies with a duration of 20 to 32 weeks, the risk of having an SAE was 61.0% higher with dupilumab compared to omalizumab. In absolute numbers, 3.0%-points more patients had SAEs with dupilumab *vs* omalizumab (Table 32). In the 48 to 52-week studies, the risk of having an SAE was 3.6% higher with dupilumab compared to omalizumab, and in absolute numbers 0.24%-points more patients had SAEs with dupilumab *vs* omalizumab (Table 32). However, none of the differences between dupilumab and omalizumab were statistically significant.

TABLE 32 SUMMARY OF PROPORTION WITH SERIOUS ADVERSE EVENTS – DUPILUMAB *VS* OMALIZUMAB

Studies included in the analysis	Duration of studies	RD (95% CI)	RR (95% CI)
Wenzel 206 (DRI12544) Holgate 2004 Vignola 2004 Humbert 2005 Bousquet 2011 Rubin 2012 (QUALITX, Brazilian) Busse 2013 Li 2016	20-32 weeks	2.981 (-1.756; 14.890)	1.610 (0.641; 4.048)
Castro 2018 (QUEST) Busse 2001 Soler 2001 Hanania 2011	48-52 weeks	0.242 (-2.693; 5.345)	1.036 (0.596; 1.802)

Data from Wenzel 2016 (DRI12544) and Castro 2018 (QUEST) are for the 200 mg dose q2w and respective placebo group only
Source: Table 77
CI, confidence interval; OCS, oral corticosteroid; q2w, every 2 weeks; RD, risk difference; RR, relative risk

Discontinuation from the study

In the studies with a duration of 20 to 32 weeks, the risk of discontinuation was 5.2% lower with dupilumab compared to omalizumab and in absolute numbers, 0.5%-points fewer patients discontinued with dupilumab *vs* omalizumab (Table 33). In the 48 to 52-week studies, the risk of discontinuation was 30.6% higher with dupilumab compared to omalizumab, and 4.25%-points more patients discontinued with dupilumab *vs* omalizumab (Table 33). None of the differences between dupilumab and omalizumab were statistically significant.

TABLE 33 SUMMARY OF PROPORTION OF PATIENTS DISCONTINUED – DUPILUMAB *VS* OMALIZUMAB

Studies included in the analysis	Duration of studies	RD (95% CI)	RR (95% CI)
Wenzel 206 (DRI12544) Holgate 2004 Vignola 2004 Humbert 2005 Bardelas 2012 Busse 2013 Li 2016 Mukherjee 2019	20-32 weeks	-0.547 (-6.210; 12.471)	0.948 (0.413; 2.180)
Castro 2018 (QUEST) Busse 2001 Soler 2001 Hanania 2011	48-52 weeks	4.250 (-1.961; 13.699)	1.306 (0.859; 1.988)

Data from Wenzel 2016 (DRI12544) and Castro 2018 (QUEST) are for the 200 mg dose q2w and respective placebo group only
Data from the open-label studies Ayres 2004 (52 weeks), Bousquet 2011 (32 weeks) and Rubin 2012 (20 weeks) were not included in the indirect comparisons of discontinuations
Source: Table 77
CI, confidence interval; OCS, oral corticosteroid; q2w, every 2 weeks; RD, risk difference; RR, relative risk

Anaphylactic reactions

Anaphylactic reactions have been reported very rarely both with dupilumab and omalizumab and no obvious differences have been observed. In the SmPCs, anaphylactic adverse reactions based on clinical studies are listed as a very rare (<1/10,000) for dupilumab [48] and as rare (<1/1,000) for omalizumab [52]. Thus, the immunogenic potential of both dupilumab and omalizumab seems to be low.

5.3 What is the added clinical value of dupilumab compared with placebo in treatment of patients >12 years of age with severe asthma with type 2 inflammation characterised by increased FeNO with no concomitant eosinophilia and without concomitant allergy?

Population

The protocol provided by the Medicines Council defines this population as patients >12 years with severe asthma with type 2-inflammation characterised by increased FeNO *without* concomitant eosinophilia and *without* concomitant allergy. However, since data for this subgroup are not reported, we provide instead the available data for the subgroup of patients with baseline FeNO ≥25 ppb regardless of EOS and allergy status (see also section 4.3.1).

Increased FeNO is defined as FeNO ≥25 ppb observed within the last month.

Intervention

Dupilumab in a loading dose of 400 mg (two 200 mg SC injections), followed by 200 mg SC injection q2w as add-on to standard treatment.

For patients in maintenance treatment with OCS or for patients with co-morbid moderate-to-severe atopic dermatitis: Dupilumab in a loading dose of 600 mg (two 300 mg SC injections), followed by 300 mg SC injection q2w as add-on to standard treatment.

Comparator

Placebo in addition to standard treatment.

5.3.1 Presentation of relevant studies

Results for the increased FeNO subgroup have been reported from the dupilumab QUEST and VENTURE studies in a population with moderate-to-severe uncontrolled persistent asthma and in a population with OCS-dependent asthma, respectively. The studies are presented in section 4.3.1. and summaries of main study characteristics and baseline characteristics for the ITT population are presented in appendix 8.2.1 and 8.3.1 , respectively.

In both studies, dupilumab was compared with placebo. Therefore, this clinical question can be answered exclusively using the data from these 2 studies and direct comparisons. The by-study results and the comparative analyses are identical and presented as one below.

5.3.2 Comparative analyses

Efficacy results – uncontrolled, persistent asthma with increased FeNO

Reduction in annual number of exacerbation events

In patients with moderate-to-severe uncontrolled persistent asthma and increased FeNO, a 65% lower annual risk of a severe exacerbation was seen in the dupilumab group compared to the placebo group. The difference between dupilumab and placebo was statistically significant. In absolute terms, the rate of severe exacerbations was 0.65 events/patient-year lower in the dupilumab group compared to the placebo group (Table 34), and clinically relevant since the upper end of the 95% CI met the adjusted MCID of 0.5 annual exacerbation defined by the Medicines Council [1].

In patients with OCS-dependent asthma and increased FeNO, the risk of severe exacerbations was 67.4% lower in the dupilumab group compared to the placebo group. The rate of severe exacerbations was 0.948 events/patient-year lower with dupilumab compared to placebo. The analysis only included 114 patients, so while the results are statistically significant, the 95% CIs are wide and do not meet the MCID criteria for being clinically relevant (Table 34).

TABLE 34 SUMMARY OF ANNUALISED EXACERBATION RATES – UNCONTROLLED, PERSISTENT ASTHMA AND INCREASED FENO AND OCS-DEPENDENT ASTHMA AND INCREASED FENO

Study	Subgroup	N DUP/PBO	LSmean (95% CI)		RD (95% CI)	RR (95% CI)
			Dupilumab	Placebo		
Uncontrolled, persistent asthma; follow up 52 weeks						
Castro 2018 (QUEST)	FeNO ≥25ppb	299/162	0.35 (0.27; 0.45)	1.00 (0.78; 1.30)	-0.65 (-0.750; -0.500)	0.35 (0.25; 0.50)[a]
OCS-dependent asthma, follow up 24 weeks						
Rabe 2018 (VENTURE)	FeNO ≥25ppb	57/57	0.459 (0.130; 0.788)	1.407 (0.778; 2.036)	-0.948 (-1.242; -0.133)	0.326 (0.117; 0.905)

Data from Castro 2018 (QUEST) are for the 200 mg dose q2w and respective placebo group only

[a] p-value <0.0001

Source: Table 50, Table 51, Table 78, Table 79

CI, confidence interval; DUP, dupilumab; FeNO, fractional exhaled nitric oxide; LS, least square; N, number of subjects; OCS, oral corticosteroid; PBO, placebo; ppb, parts per billion; q2w, every 2 weeks; RD, rate difference; RR, rate ratio

Proportion of patients with 0 annual exacerbations

In patients with moderate-to-severe uncontrolled persistent asthma and increased FeNO, the chance of having 0 annual exacerbations was 37% higher in the dupilumab group compared to the placebo group. In absolute numbers there were 20.8%-points more patients with 0 annual exacerbations in the dupilumab group compared to placebo (Table 35). Both results were statistically significant, and since the lower end of the 95% CI for the absolute difference was well above the adjusted MCID of 5%-points defined by the Medicines Council [1], also clinically relevant.

In patients with OCS-dependent asthma and increased FeNO, the chance of having 0 annual exacerbations was 84% higher in the dupilumab group compared to the placebo group, and 36.8%-points more patients had 0 annual exacerbations in the dupilumab group compared to placebo (Table 35). Since the lower end of the 95% CI for the absolute difference was well above the adjusted MCID of 5%-points defined by the Medicines Council [1], the difference was also clinically relevant.

TABLE 35 SUMMARY OF PROPORTION OF PATIENTS WITH 0 EXACERBATIONS DURING THE TREATMENT PERIOD – UNCONTROLLED, PERSISTENT ASTHMA AND INCREASED FENO AND OCS-DEPENDENT ASTHMA AND INCREASED FENO

Study	Subgroup	N DUP/PBO	Proportion (95% CI)		RD (95% CI)	RR (95% CI)
			Dupilumab	Placebo		
Uncontrolled, persistent asthma; follow up 52 weeks						
Castro 2018 (QUEST)	FeNO ≥25ppb	299/162	76.9 (72.1; 81.7)	56.2 (48.5;63.8)	20.75 (11.74; 29.76)	1.37 (1.179; 1.590)
OCS-dependent asthma, follow up 24 weeks						
Rabe 2018 (VENTURE)	FeNO ≥25ppb	57/57	80.7 (70.5; 90.9)	43.9 (31.0; 56.7)	36.84 (20.38; 53.30)	1.84 (1.336; 2.534)

Data from Castro 2018 (QUEST) are for the 200 mg dose q2w and respective placebo group only

[a] p-value <0.0001

Source: Table 50, Table 51, Table 78, Table 79

CI, confidence interval; DUP, dupilumab; FeNO, fractional exhaled nitric oxide; N, number of subjects; OCS, oral corticosteroid; PBO, placebo; ppb, parts per billion; q2w, every 2 weeks; RD, risk difference; RR, relative risk

Mean % reduction in daily OCS dose

The mean % reduction in maintenance OCS dose was reported for the VENTURE study in a subgroup with FeNO ≥25 ppb at baseline. The LSmean % reduction (95% CI) in OCS dose was 78.01 (64.96; 91.06) and 43.26 (31.30; 55.22) in the dupilumab 300 mg group and placebo group, respectively (Table 51). Compared to placebo, a 34.75%-points larger reduction was found in the dupilumab group, which was statistically significant with a 95% CI of 18.66 to 54.05%-points (Table 79). The mean (standard deviation [SD]) OCS dose before the adjustment phase was 11.81 (6.20) mg/day in the ITT population [11]; thus, the difference in % reduction in dose is equivalent to ≥2.2 mg/day prednisone/prednisolone equivalent. Thus, the difference between dupilumab and placebo meets both of the criteria for adjusted MCID defined by the Medicines Council (i.e. 10%-points and minimum 1.25 mg prednisolone equivalent) [1], and are clinically relevant.

Proportion of patients no longer requiring OCS

The proportion of patients who no longer required OCS at the end of the study was reported for the ITT population in the VENTURE study. The proportion (95% CI) of patients with no OCS use at the end of the study was 48.0% (36.0; 59.0) and 25.0% (17.0; 35.0) in the dupilumab 300 mg and placebo groups, respectively (Table 51). The change of no longer requiring maintenance OCS was 80.95% greater (27.6 to 156.6% greater) in the dupilumab group compared to the placebo group. In absolute numbers, 23.46%

more patients in the dupilumab group no longer required maintenance OCS, and with a 95% CI of 10.54 to 36.37%-points more patients no longer requiring maintenance OCS, the result was statistically significant (Table 79). Since the lower end of the 95% CI is well above the adjusted MCID of 2.5%-points defined by the Medicines Council [1], the difference between dupilumab and placebo is also clinically relevant.

Proportion of patients with ≥50% reduction in OCS dose

The proportion of patients with ≥50% reduction in OCS dose at the end of the study was reported for the ITT population in the VENTURE study. The proportion (95% CI) of patients with ≥50% reduction in OCS dose at the end of the study was 80.0% (70.0; 87.0) and 50.0% (40.0; 61.0) in the dupilumab 300 mg and placebo groups, respectively (Table 51). The change of no longer requiring maintenance OCS was 49.4% greater (22.0 to 83.0% greater) in the dupilumab group compared to placebo, and with 26.34% more (14.10 to 38.58%-points more) patients in the dupilumab group with ≥50% reduction in maintenance OCS dose (Table 79). The differences are statistically significant and clinically relevant, since the lower end of the 95% CI for the absolute difference is well above the adjusted MCID of 5%-points defined by the Medicines Council [1].

Mean change from baseline in lung function

In patients with moderate-to-severe uncontrolled persistent asthma and increased FeNO, a statistically significant improvement in FEV1 of 0.3 L was shown in the dupilumab group compared to the placebo group (Table 36). The difference is also clinically relevant, since the lower end of the 95% CI is well above the MCID of 100 mL defined by the Medicines Council [1].

In patients with OCS-dependent asthma and increased FeNO, an improvement in FEV1 of 0.25 L was shown in the dupilumab group compared to the placebo group. The analysis only included 109 patients, so while the result is statistically significant, the CI is wide (Table 36) and the lower end of the 95% CI does not meet the MCID of 100 mL [1].

TABLE 36 SUMMARY OF CHANGES FROM BASELINE IN FEV1 – UNCONTROLLED, PERSISTENT ASTHMA AND INCREASED FENO AND OCS-DEPENDENT ASTHMA AND INCREASED FENO

Study	Subgroup	N DUP/PBO	Timepoint	LSmeans (95% CI) (L)		LSmeans difference (95% CI) (L)
				Dupilumab	Placebo	
Uncontrolled, persistent asthma						
Castro 2018 (QUEST)	FeNO ≥25ppb	224/124	Week 52	0.49 (0.431; 0.549)	0.18 (0.102; 0.258)	0.3 (0.22; 0.39)[a]
OCS-dependent asthma						
Rabe 2018 (VENTURE)	FeNO ≥25ppb	54/55	Week 24	0.24 (0.091; 0.389)	0.0 (-0.137; 0.137)	0.25 (0.04 ; 0.45)

Data from Castro 2018 (QUEST) are for the 200 mg dose q2w and respective placebo group only

[a] p-value <0.0001

Source: Table 50, Table 51, Table 78, Table 79

CI, confidence interval; DUP, dupilumab; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 s; L, litre; LS, least square; N, number of subjects; OCS, oral corticosteroid; PBO, placebo; q2w, every 2 weeks; ppb, parts per billion

Proportion of patients with an improvement of ≥200 mL in FEV1

In patients with moderate-to-severe uncontrolled persistent asthma and increased FeNO, the chance of having an improvement of ≥200 mL in FEV1 after 52 weeks of treatment was 55.6% higher in the dupilumab group compared to the placebo group. In absolute numbers there was 23.8%-points more patients with an improvement of ≥200 mL in FEV1 in the dupilumab group compared to placebo (Table 37). In addition to

being statistically significant, the difference is clinically relevant, since the lower end of the 95% CI is well above the MCID of 7.5%-points defined by the Medicines Council [1].

In patients with OCS-dependent asthma and increased FeNO, the chance of having an improvement of ≥200 mL in FEV1 after 24 weeks was 52.8% higher in the dupilumab group compared to the placebo group. The absolute difference was 19.19%-points more patients with an improvement of ≥200 mL in FEV1 in the dupilumab group compared to placebo (Table 37). The analysis only included 109 patients, so while the result is statistically significant, the CI is wide and the lower end of the 95% CI does not meet the MCID of 7.5%-points [1].

TABLE 37 SUMMARY OF PROPORTION OF PATIENTS WITH AN IMPROVEMENT OF ≥200 ML IN FEV1 – UNCONTROLLED, PERSISTENT ASTHMA AND INCREASED FENO AND OCS-DEPENDENT ASTHMA AND INCREASED FENO

Study	Subgroup	N DUP/PBO	Proportion (95% CI)		RD (95% CI)	RR (95% CI)
			Dupilumab	Placebo		
Uncontrolled, persistent asthma; assessment at week 52						
Castro 2018 (QUEST)	FeNO ≥25ppb	224/124	66.5 (60.3; 72.7)	42.7 (34.0; 51.4)	23.78 (13.10; 34.45)	1.556 1.244; 1.947
OCS-dependent asthma, assessment at week 24						
Rabe 2018 (VENTURE)	FeNO ≥25ppb	54/55	55.6 (42.3; 68.8)	36.4 (23.7; 49.1)	19.19 (0.83; 37.56)	1.528 (1.001; 2.333)

Data from Castro 2018 (QUEST) are for the 200 mg dose q2w and respective placebo group only

Source: Table 50, Table 51, Table 78, Table 79

CI, confidence interval; DUP, dupilumab; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 s; N, number of subjects; OCS, oral corticosteroid; PBO, placebo; ppb, parts per billion; q2w, every 2 weeks; RD, risk difference; RR, relative risk

Asthma control

Results for asthma control are not available in patients with increased FeNO for any of the dupilumab studies. Instead the results in the ITT populations are presented below as a conservative estimate. In the QUEST study, the mean (SD) baseline FeNO was 34.45 (34.91) ppb and 34.47 (28.54) ppb in the dupilumab 200 mg q2w and placebo groups, respectively [6], and an average of 49% of the population had FeNO ≥25 ppb (299/631 patients in the dupilumab 200 mg q2w group and 162/317 patients in the placebo group, see Table 50). In the VENTURE study [11], the mean (SD) FeNO level at baseline was 35.55 (28.34) and 39.62 (34.12) in the dupilumab and placebo groups, respectively, and an average of 54% of the population had FeNO ≥25 ppb (57/103 patients in the dupilumab group and 57/107 patients in the placebo group, see Table 51). Thus, the results in the ITT group are considered indicative of the effect of dupilumab in a population with severe asthma with increased FeNO.

In patients with moderate-to-severe uncontrolled persistent asthma, a statistically significant improvement (i.e. reduced score) in ACQ score of 0.39 was shown at week 52 in the dupilumab group compared to the placebo group (Table 38). Since the upper end of the 95% CI meets the adjusted MCID of 0.25 in ACQ score defined by the Medicines Council [1], the difference is clinically relevant.

In patients with OCS-dependent asthma, an improvement in ACQ score of 0.47 was shown at week 24 in the dupilumab group compared to the placebo group (Table 38). While being statistically significant, the upper end of the 95% CI did not meet the adjusted MCID of 0.25, and therefore the result is not assessed as clinically relevant.

TABLE 38 SUMMARY OF CHANGES FROM BASELINE IN ASTHMA CONTROL – UNCONTROLLED, PERSISTENT ASTHMA AND OCS-DEPENDENT ASTHMA

Study	N DUP/PBO	Timepoint Tool	LSmeans (95% CI)		LSmeans difference (95% CI)
			Dupilumab	Placebo	
Uncontrolled, persistent asthma					
Castro 2018 (QUEST)	631/317	Week 52 ACQ-5	-1.54 (-1.618; -1.462)	-1.15 (-1.268; -1.032)	-0.39 (-0.53; -0.25)
OCS-dependent asthma					
Rabe 2018 (VENTURE)	96/99	Week 24 ACQ-5	-1.05 (-1.266; -0.834)	-0.57 (-0.766; -0.374)	-0.47 (-0.76; -0.18)

Data from Castro 2018 (QUEST) are for the 200 mg dose q2w and respective placebo group only
Data from Castro 2018 (QUEST) and Rabe 2018 (VENTURE) are for ITT population
ACQ is a patient-reported measure of the adequacy of asthma control and change in asthma control that occurs either spontaneously or as a result of treatment. Higher scores indicate less control; a global score is calculated ranging from 0 to 6. The MCID is 0.5 [42].
Source: Table 50, Table 51, Table 78, Table 79
ACQ-5, 5-item Asthma Control Questionnaire; CI, confidence interval; DUP, dupilumab; ITT, intention-to-treat; LS, least square; MCID, minimal clinically important difference; N, number of subjects; OCS, oral corticosteroid; PBO, placebo; q2w, every 2 weeks

Quality of life

Results for QoL are not available in patients with increased FeNO for any of the dupilumab studies. Instead the results in the ITT populations are presented below. Based on the same rationale as presented in the above section on asthma control, the results in the ITT group are considered a conservative estimate, indicative of the effect of dupilumab on QoL in a population with severe asthma with increased FeNO.

In patients with moderate-to-severe uncontrolled persistent asthma, a statistically significant improvement (i.e. increased score) in AQLQ score of 0.29 was shown at week 52 in the dupilumab group compared to the placebo group (Table 39). Since the lower end of the 95% CI did not meet the adjusted MCID of 0.25 defined by the Medicines Council [1], the difference is, however, not assessed as clinically relevant.

In patients with OCS-dependent asthma, a statistically significant improvement in AQLQ score of 0.35 was shown at week 24 in the dupilumab group compared to the placebo group (Table 39). Since the lower end of the 95% CI did not meet the adjusted MCID of 0.25 defined by the Medicines Council [1], the difference is not assessed as clinically relevant.

TABLE 39 SUMMARY OF CHANGES FROM BASELINE IN QUALITY OF LIFE – UNCONTROLLED, PERSISTENT ASTHMA AND OCS-DEPENDENT ASTHMA

Study	N DUP/PBO	Timepoint Tool	LSmeans (95% CI)		LSmeans difference (95% CI)
			Dupilumab	Placebo	
Uncontrolled, persistent asthma					
Castro 2018 (QUEST)	631/317	Week 52 AQLQ	1.28 (1.202; 1.358)	0.99 (0.872; 1.108)	0.29 (0.15; 0.44)
OCS-dependent asthma					
Rabe 2018 (VENTURE)	98/100	Week 24 AQLQ	0.89 (0.694; 1.086)	0.54 (0.344; 0.736)	0.35 (0.073; 0.627)

Data from Castro 2018 (QUEST) are for the 200 mg dose q2w and respective placebo group only
Data from Castro 2018 (QUEST) and Rabe 2018 (VENTURE) are for ITT population
AQLQ is a patient-reported measure of asthma-specific health-related quality of life. Higher scores indicate better quality of life; a global score is calculated ranging from 1 to 7. The MCID is 0.5 for all scales [44, 45].
Source: Table 50, Table 51, Table 78, Table 79
AQLQ, Asthma Quality of Life Questionnaire; CI, confidence interval; DUP, dupilumab; ITT, intention-to-treat; LS, least square; MCID, minimal clinically important difference; N, number of subjects; OCS, oral corticosteroid; PBO, placebo; q2w, every 2 weeks

Sick leave

No data were reported for sick leave in the subgroup with increased FeNO. However, in the phase 2b study (DRI12544), the annualised days of sick leave due to severe exacerbation event in the ITT population was 0.613 days/year and 2.238 days/year in the dupilumab 200 mg q2w and placebo groups, respectively (p<0.0001) (Table 46). In the phase 2b study, the mean (SD) FeNO at baseline was 39.25 (36.67) ppb and 38.95 (34.79) pbb in the dupilumab 200 mg q2w and placebo groups, respectively [6], therefore the results can be indicative of the effect of dupilumab on sick leave in a population with increased FeNO.

Safety results

Proportion of patients with serious adverse events

In the phase 2b (DRI12544) and the QUEST studies with dupilumab, the incidence of SAEs was similar between the dupilumab 200 mg and placebo groups (Table 40). In the phase 2b study, the risk of an SAE was 19% higher in the dupilumab group *vs* the placebo group, and 1.06%-points more patients in the dupilumab group had an SAE compared to the placebo group. In the QUEST study, the risk of an SAE was 7% lower and 0.54%-points fewer patients had an SAE in the dupilumab group compared to placebo. None of the differences between dupilumab 200 mg and placebo were statistically significant.

In the VENTURE study in OCS-dependent patients, SAEs were reported by 8.7% of patients in the dupilumab 300 mg group and 5.6% of those in the placebo group (Table 40). Compared to placebo, the risk of an SAE was 56% higher in the dupilumab group and 3.13%-points more patients in the dupilumab group had an SAE. The differences between dupilumab 300 mg and placebo were not statistically significant.

TABLE 40 INCIDENCE OF SERIOUS ADVERSE EVENTS IN STUDIES WITH DUPILUMAB *VS* PLACEBO

Study	Patients with events / total N (incidence)		RD (95% CI)	RR (95% CI)
Dupilumab studies	**Dupilumab**	**Placebo**		
Wenzel 2016 (DRI12544)	10 / 148 (6.8%)	9 / 158 (5.7%)	1.06 (-4.36; 6.48)	1.19 (0.50; 2.84)
Castro 2018 (QUEST)	49 / 631 (7.8%)	26 / 313 (8.3%)	-0.54 (-4.24; 3.16)	0.93 (0.59; 1.48)
Rabe 2018 (VENTURE)	9 / 103 (8.7%)	6 / 107 (5.6%)	3.13 (-3.85; 10.11)	1.56 (0.58; 4.22)

Data from Wenzel 2016 (DRI12544) and Castro 2018 (QUEST) are for the 200 mg dose q2w and respective placebo group only
Source: Table 52, Table 53, Table 54, Table 78, Table 79
CI, confidence interval; N, total number of subjects; q2w, every 2 weeks; RD, risk difference; RR, relative risk

Discontinuation from the study

In the phase 2b (DRI12544) and the QUEST studies with dupilumab, the rate of discontinuation from the study was similar between the dupilumab 200 mg group and placebo group (Table 41). In the phase 2b study, the risk of discontinuation was 2% lower in the dupilumab group *vs* the placebo group. The absolute difference was close to zero with 0.16%-points fewer patients in the dupilumab group discontinued from the study compared to placebo. In the QUEST study, the risk of discontinuation was 7% lower, and 0.89%-points fewer patients in the dupilumab group discontinued from the study (Table 41). No statistically significant differences between dupilumab 200 mg and placebo were found.

In the VENTURE study in OCS-dependent patients, few patients discontinued: 2 (1.9%) in the dupilumab 300 mg group and 5 (4.7%) in the placebo group. Compared to placebo, the risk of discontinuation was 58% lower in the dupilumab group, and 2.73%-points fewer patients in the dupilumab group discontinued (Table 41). No statistically significant differences between dupilumab 300 mg and placebo were found.

TABLE 41 DISCONTINUATION FROM STUDIES WITH DUPILUMAB *VS* PLACEBO

Study	Patients with events / total N (incidence)		RD (95% CI)	RR (95% CI)
Dupilumab studies	**Dupilumab**	**Placebo**		
Wenzel 2016 (DRI12544)	11 / 148 (7.4%)	12 / 158 (7.6%)	-0.16 (-6.07; 5.75)	0.98 (0.45; 2.15)
Castro 2018 (QUEST)	70 / 631 (11.1%)	38 / 317 (12.0%)	-0.89 (-5.23; 3.44)	0.93 (0.64; 1.34)
Rabe 2018 (VENTURE)	2 / 103 (1.9%)	5 / 107 (4.7%)	-2.73 (-7.54; 2.07)	0.42 (0.08; 2.09)

Data from Wenzel 2016 (DRI12544) and Castro 2018 (QUEST) are for the 200 mg dose q2w and respective placebo group only
Source: Table 52, Table 53, Table 54, Table 78, Table 79
CI, confidence interval; N, total number of subjects; q2w, every 2 weeks; RD, risk difference; RR, relative risk

Anaphylactic reactions

Anaphylactic reactions have been reported very rarely in the dupilumab asthma development program. In the safety pool, 1 serious anaphylactic reaction and 1 serious event of anaphylactic shock (both medically reviewed) were reported in the dupilumab group. No such events were reported in the placebo group and none were reported in the VENTURE study [11, 43]. The low number of anaphylaxis events suggests a low immunogenic potential of dupilumab in the asthma population.

6 Other considerations

6.1 Efficacy and safety in adolescents

Adolescents were enrolled in the QUEST and VENTURE studies, while the phase 2b study (DRI12544) did not allow enrolment of adolescents. The adolescents formed part of the ITT population and the different subgroups for which results are presented in this application. The limited number of results that are available for adolescents separately are described below and show that the efficacy of dupilumab in adolescents is similar to the efficacy in adults.

In the QUEST study, a total of 107 adolescent patients were enrolled across all treatment groups. The mean age of the adolescent population was 14.2 years with a range of 12 to 17 years. Approximately one-third of the patients (35.5%) were females, and most of the patients (90.7%) were white. Most of the adolescent patients (96.3%) had an ongoing atopic medical condition [43].

The rate of severe exacerbations in the adolescent population was generally lower than that observed in the adult population. The adjusted annualised event rate of severe exacerbations in the 107 adolescent patients during the 52-week treatment period was lower in the dupilumab 200 mg q2w group compared with the matching placebo group (0.191 for the dupilumab 200 mg q2w compared with 0.356 for the matching placebo group), indicating a 46.4% reduced risk of severe exacerbation events [43].

In addition, a greater increase in pre-bronchodilator FEV1 from baseline to week 12 for the adolescent population was observed in the 200 mg q2w group (LSmean 0.40 L) compared with the matching placebo group (0.03 L) [43].

In the VENTURE study only 3 adolescent patients were enrolled and did hence not allow for any between group comparisons.

Overall, the AE profile of dupilumab in adolescent patients with asthma was similar to the AE profile seen in adults. Of the 3 adolescents randomised in the VENTURE study, 2 were assigned to placebo. The single adolescent who received dupilumab did not experience any AEs.

6.2 Eosinophilia

Across all dupilumab studies for the treatment of asthma, dupilumab-treated patients had a greater mean initial increase from baseline in EOS compared to those treated with placebo. Eosinophil counts declined to near baseline levels by the end of the studies. This transient rise in EOS seen across these studies is consistent with the current understanding of the mechanism of action of dupilumab.

In the pooled safety population, a greater proportion of patients in the combined dupilumab treatment group experienced transient blood eosinophilia to greater than 5 Giga/L (1.1%) compared with placebo-treated patients (0.4%) [43]. In the VENTURE study, in which patients on dupilumab had greater OCS reductions than patients on placebo, 2.9% of patients in the dupilumab group and 0.9% of those in the placebo group had blood eosinophilia counts >5 Giga/L. This increase in EOS was typically transient and generally not associated with clinically relevant AEs and, in fact, was associated with greater efficacy on FEV1 and exacerbations when compared with the treatment group as a whole. There were rare cases of patients treated with dupilumab who experienced blood eosinophilia associated with clinical symptoms such as eosinophilic granulomatosis with polyangiitis (EGPA; 2 patients with EGPA, otherwise known as Churg Strauss) and 2 with eosinophilic pneumonia [43].

In the pooled safety population, a total of 57 patients experienced “eosinophilia TEAEs”, which occurred at a higher frequency in the dupilumab group compared with the placebo group: 53 (3.4%) in the dupilumab combined group *vs* 4 (0.5%) in the placebo group [43]. In the VENTURE study, a total of 15 patients experienced “eosinophilia TEAEs”, which occurred at a higher frequency in the dupilumab group compared with the placebo group: 14 (13.6%) patients in the dupilumab group *vs* 1 (0.9%) in the placebo group [43]. The higher frequency of increase in EOS reported in this study compared to other dupilumab asthma studies, is likely due to the fact that steroid tapering is a known trigger for eosinophilia and patients on dupilumab had a more extensive taper than those on placebo.

6.3 Effects on other atopic medical conditions

IL-4 and IL-13 cytokines are the key drivers of other type 2 inflammatory diseases, including diseases such as atopic dermatitis, allergic rhinitis and chronic rhinosinusitis with nasal polyps. By blocking of the shared receptor component for IL-4 and IL-13, dupilumab treatment results in beneficial effects of dupilumab on other type-2 inflammatory diseases which are prevalent in asthma patients. These include atopic dermatitis [53], allergic rhinitis [54], chronic rhinosinusitis [55], and nasal polyps [56]. In the QUEST study, more than 20% of the patients suffered from co-morbid chronic rhinosinusitis with or without nasal polyps and more than 80% of the patients had some sort of ongoing atopic medical condition, such as atopic dermatitis, allergic conjunctivitis or allergic rhinitis. Hence, patients that are treated with dupilumab for their asthma disease may also experience improvements in potential additional co-morbid conditions. As an example, significant and sustained improvements in upper airway symptoms and quality of life measurements were observed in patients in the QUEST study who in addition to their asthma also suffered from co-morbid chronic rhinosinusitis and nasal polyps [57].

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8 Appendices

8.1 Literature search

TABLE 42 PUBMED SEARCH

Search performed 01 July 2019

Search	Add to builder	Query	Items found
#12	Add	Search **(#10 NOT #11)**	203
#11	Add	Search **(Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR News[pt] OR Review[pt] OR Systematic Review[pt])**	5715859
#10	Add	Search **(#8 AND #9)**	379
#9	Add	Search **(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti])**	1268161
#8	Add	Search **(#6 NOT #7)**	1499
#7	Add	Search **(Animals[mh] NOT Humans [mh])**	4594519
#6	Add	Search **(#1 AND #5)**	1503
#5	Add	Search **(#2 OR #3 OR #4)**	2786
#4	Add	Search **(Omalizumab[mh] OR omalizumab[tiab] OR xolair*[tiab])**	2262
#3	Add	Search **(mepolizumab[nm] OR SB-240563[tiab] OR SB240563[tiab] OR nucala*[tiab])**	252
#2	Add	Search **(SAR231893[nm] OR dupilumab[tiab] OR REGN668[tiab] OR REGN-668[tiab] OR SAR-231893[tiab] OR SAR23189[tiab] OR dupixent*[tiab])**	358
#1	Add	Search **(Asthma[mh] OR asthma*[tiab])**	170968

TABLE 43 CENTRAL SEARCH

Performed on 01 July 2019.

#1	asthma:kw OR asthma*:ti,ab	Limits	32415
#2	(SAR231893 OR dupilumab or REGN668 OR "REGN 668" OR dupixent*):ti,ab,kw	Limits	229
#3	(mepolizumab OR "SB 240563" OR SB240563 OR nucala*):ti,ab,kw	Limits	235
#4	(omalizumab OR olizumab OR xolair* OR "hu 901" OR HU901):ti,ab,kw	Limits	820
#5	#2 OR #3 OR #4	Limits	1247
#6	#1 and #5	Limits	771
#7	conference abstract:pt	Limits	148973
#8	review:pt	Limits	26232
#9	NCT*:au	Limits	139230
#10	("clinicaltrials gov" OR trialsearch):so	Limits	256664
#11	#7 OR #8 OR #9 OR #10	Limits	431931
#12	#6 NOT #11	Limits	392
#13	pubmed:an	Limits	648391
#14	#12 NOT #13	Limits	234

Of the 234 results, 230 were in “Trials”.

TABLE 44 INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria	**Population:** Patients ≥12 years old with severe asthma with type-2 inflammation characterised by eosinophilia; allergy and eosinophilia or allergy and increased FeNO; or increased FeNO **Intervention:** Dupilumab 200 mg or 300 mg q2w **Comparators:** Mepolizumab 100 mg SC q4w or 75 mg IV q4w, omalizumab SC q2w or q4w (dose and frequency according to IgE level and body weight) **Outcomes:** exacerbations, OCS reduction, lung function (FEV1), asthma control (ACQ or other questionnaire), QoL (AQLQ or other questionnaire), SAEs, discontinuations, sick leave **Settings (if applicable):** No restrictions **Study design:** Randomised trials, open-label studies acceptable **Language restrictions:** English or Scandinavian language **Other search limits or restrictions applied:** None
Exclusion criteria	**Population:** Not including patients with severe asthma **Intervention:** Other doses or dosing frequencies than defined in the inclusion criteria **Comparators:** Other doses or dosing frequencies than defined in the inclusion criteria **Outcomes:** Not reporting at least one of the critical or important outcomes **Settings (if applicable):** NA **Study design:** Non-randomised **Language restrictions:** Other than English or Scandinavian languages excluded **Other search limits or restrictions applied:** None

ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1; sIgE, immunoglobulin E; IV, intravenously; NA, not applicable; OCS, oral corticosteroids; q2w, every 2 weeks; q4w, every 4 weeks; QoL, quality of life; SAE, serious adverse event; SC, subcutaneously

TABLE 45 LIST OF STUDIES EXCLUDED BASED ON FULL-TEXT READ

Reference	Reason for exclusion
Luskin AT, Kosinski M, Bresnahan BW, Ashby M, Wong DA. Symptom control and improved functioning: the effect of omalizumab on asthma-related quality of life (ARQL). J Asthma. 2005;42(10):823-7.	Data from Soler 2001 and Busse 2001 which are published elsewhere (Buhl 2002a and Finn 2003).
Haldar P, Brightling CE, Hargadon B, Gupta S, Monteiro W, Sousa A, Marshall RP, Bradding P, Green RH, Wardlaw AJ, Pavord ID. Mepolizumab and exacerbations of refractory eosinophilic asthma. NEJM. 2009;360(10):973-84.	Not the correct dose (750 mg/month) and not severe asthma.
Trojan TD, Andrew Bird J. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. Pediatrics. 2013;132(SUPPL.1):S48.	Summary of the DREAM study (Pavord 2012) in "Best articles relevant to pediatric allergy and immunology".
Prazma CM, Wenzel S, Barnes N, Douglass JA, Hartley BF, Ortega H. Characterisation of an OCS-dependent severe asthma population treated with mepolizumab. Thorax. 2014;69(12):1141-2.	Includes data on an OCS dependent subgroup, but the data include subjects on all doses tested, i.e. 75 mg, 250 mg and 750 mg IV /month
Busse WW, Maspero JF, Rabe KF, Papi A, Wenzel SE, Ford LB, Pavord ID, Zhang B, Staudinger H, Pirozzi G, Amin N, Akinlade B, Eckert L, Chao J, Graham NMH, Teper A. Liberty Asthma QUEST: Phase 3 Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate Dupilumab Efficacy/Safety in Patients with Uncontrolled, Moderate-to-Severe Asthma. Advances in therapy. 2018;35(5):737-48.	Study protocol.

8.2 Main characteristics of included studies

8.2.1 Dupilumab studies

Reference and NCT number	Study design	Follow-up	Age (years)	Relevant outcomes	Asthma diagnosis before or at randomisation documented by	Asthma severity	Refractory asthma (e.g. exacerbations, symptoms, FEV1)	Reduced lung function	EOS (cells/µL)	ICS dose	2nd controller	OCS	# patients randomised per group
Wenzel 2016 (main) (DRI12544) 01854047 *Corren 2019a (QoL)*	Randomised, double-blind, placebo-controlled trial	24 weeks	≥18	Exacerbations FEV1 ACQ-5 AQLQ Symptom score SAE Discontinuations	Airway reversibility (FEV1 ≥12% and 200 mL)	Moderate-to-severe	Experienced in prior year: hospitalisation, emergency/urgent care visit or systemic CS treatment for worsening asthma	FEV1 40-80% of predicted	Not inclusion criterion. Randomisation stratified by EOS at screening (≥300 cells/µL, 200–299 cells/µL and <200 cells/µL)	Medium-to-high (≥250 µg FT or equivalent)	Additional LABA required	Allowed but not required	776: DUP 200 mg/q4w (N=154), DUP 300 mg/q4w (N=157), DUP 200 mg/q2w (N=150), DUP 300 mg/q2w (N=157), PBO (N=158) all SC
Castro 2018 (main) (QUEST) 02414854 *Castro 2019 (lung function)* *Corren 2019b (allergic subgroups)*	Randomised, double-blind, placebo-controlled trial	52 weeks	≥12	Exacerbations FEV1 ACQ-5 AQLQ Symptom score EQ-5D-5L SAE Discontinuations	Airway reversibility (FEV1 ≥12% and 200 mL) *Allergic asthma was defined as total serum IgE ≥30 IU/mL and ≥1 positive perennial aeroallergen-specific IgE value (≥0.35 kU/L) at baseline[a]*	Moderate-to-severe	Asthma worsening in the previous year leading to hospitalisation, emergency medical care or treatment with systemic CS for ≥3 days	FEV1 ≤80% for adults; ≤90% for adolescents	Not inclusion criterion. Randomisation stratified by EOS at screening (≥300 cells/µL, <300 cells/µL)	Medium-to-high (≥500 µg FT or equivalent)	Additional controller drugs required	Not specified	1902 (randomised 2:1, DUP *vs* PBO): DUP 200 mg (N=631), PBO (N=317), DUP 300 mg (N=633), PBO (N=321) all SC and q2w
Rabe 2018 (main) (VENTURE) 02528214 *Rabe 2019 (lung function)*	Randomised, double-blind, placebo-controlled trial	24 weeks	≥12	Exacerbations OCS reduction FEV1 ACQ-5 AQLQ SAE Discontinuations	Airway reversibility (FEV1 ≥12% and 200 mL) or airway hyperresponsiveness (methacholine: PC20 of ≤8 mg/mL)	Severe	Not specified	FEV1 ≤80% for adults; ≤90% for adolescents	Not inclusion or stratification criteria. Subgroup analysis (≥300 cells/µL or <300 cells/µL; ≥150 cells/µL or <150 cells/µL)	High (>500 µg FT or equivalent)	Additional controller drugs required	All OCS dependent (5-35 mg/day prednisone / prednisolone or equivalent)	210: DUP 300 mg (N=103), PBO (N=107) all SC and q2w

References in italics are secondary publications of the primary reference above.

[a] The following perennial allergens were included: *Dermatophagoides farinae, Dermatophagoides pteronyssinus, Alternaria alternata, Cladosporium herbarum*, cat and dog danders, German cockroach, oriental cockroach and *Aspergillus fumigatus*

ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; CS, corticosteroids; DUP, dupilumab; EOS, blood eosinophils; EQ-5D-5L, European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels; FEV1, forced expiratory volume in 1 s; FT, fluticasone propionate; ICS, inhaled corticosteroids; IgE, immunoglobulin E; LABA, long-acting beta agonist; OCS, oral corticosteroids; PBO, placebo; PC20, provocative concentration of inhaled methacholine needed to reduce FEV1 by 20%; QoL, quality of life; q2w, every 2 weeks; q4w, every 4 weeks; SAE, serious adverse event; SC, subcutaneously

8.2.2 Mepolizumab studies

Reference and NCT number	Study design	Follow-up	Age (years)	Relevant outcomes	Asthma diagnosis before or at randomisation documented by	Asthma severity	Refractory asthma (e.g. exacerbations, symptoms, FEV1)	Reduced lung function	EOS (cells/µL)	ICS dose	2nd controller	OCS	# patients randomised per group
Pavord 2012 (DREAM) 01000506	Randomised, double-blind, placebo-controlled trial	52 weeks	≥12	Exacerbations FEV1 ACQ-6 AQLQ SAE Discontinuations	Airway reversibility (FEV1 >12% and 200 mL); hyperresponsiveness (methacholine: PC20 of ≤8 mg/mL, histamine: PD20 of <7.8 µmol); or airflow variability (diurnal PEF >20% for ≥3 days in 2-week run-in period, or FEV1 >20% between 2 clinic visits)	Severe	≥2 exacerbations requiring systemic corticosteroid treatment in the previous year Met ATS criteria	FEV1 <80% of predicted	At least one of: sputum eosinophils ≥3%, FeNO ≥50 ppb, peripheral EOS ≥300 cells/µL, or deterioration of asthma control ≤25% reduction in ICS or OCS	High (≥880 µg FT)	Additional controller drugs required	Allowed but not required	616 (mITT): MEP 75 mg (N=153), MEP 250 mg (N=152), MEP 750 mg (N=156), PBO (N=155) all IV and q4w
Ortega 2014 (MENSA) 01691521	Randomised, double-blind, placebo-controlled trial	32 weeks	≥12	Exacerbations FEV1 ACQ-5 SGRQ SAE Discontinuations	Airway reversibility (FEV1 >12%); hyperresponsiveness (positive methacholine or mannitol challenge); or airway variability (FEV1 ≥20% between 2 clinic visits)	Severe	≥2 exacerbations requiring systemic corticosteroid treatment in the previous year	FEV1 <80% for adults; <90% for adolescents or FEV1/FVC <0.8	EOS ≥150 cells/µL at screening or ≥300 cells/µL some time during the previous year	High (≥880 µg FT)	Additional controller drugs required	Allowed but not required	576: MEP 75 mg IV (N=191), MEP 100 mg SC (N=194), PBO (N=191) all q4w
Bel 2014 (SIRIUS) 01691508	Randomised, double-blind, placebo-controlled trial	24 weeks	≥12	Exacerbations OCS reduction FEV1 ACQ-5 SGRQ SAE Discontinuations	Airway reversibility, hyperresponsiveness or airway variability (details not specified)	Severe	Not specified	FEV1 <80% of predicted	EOS ≥300 cells/µL in the 12-month period before screening or ≥150 cells/µL in the optimisation phase	High (≥880 µg FT)	Additional controller drugs required	All OCS (5-35 mg/day prednisone or equivalent)	135: MEP 100 mg (N=69), PBO (N=66) both SC and q4w
Chupp 2017 (MUSCA) 02281318	Randomised, double-blind, placebo-controlled trial	24 weeks	≥12	Exacerbations FEV1 ACQ-5 SGRQ SAE Discontinuations	Airway reversibility (FEV1 ≥12% and 200 mL); hyperresponsiveness (methacholine: PC20 of <8 mg/mL, histamine: PD20 of <7.8 µmol, mannitol: decrease in FEV1 as per label); or airway variability (diurnal PEF >20% for ≥3 days in 4-week run-in period, or FEV1 ≥20% between 2 clinic visits)	Severe	≥ 2 exacerbations requiring systemic corticosteroid treatment in the previous year	FEV1 <80% for adults; <90% for adolescents or FEV1/FVC <0.8	EOS ≥300 cells/µL in the 12 months before screening, or ≥150 cells/µL at screening	High (details not given)	Additional controller drugs required	Allowed but not required	551 (mITT): MEP 100 mg (N=274), PBO (N=277) both SC and q4w

ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; ATS, American Thoracic Society; EOS, blood eosinophils; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 s; FT, fluticasone propionate; FVC, forced vital capacity; ICS, inhaled corticosteroids; IV, intravenously; MEP, mepolizumab; mITT, modified intention-to-treat (5 were randomised in both trials but did not receive treatment); OCS, oral corticosteroids; PC20, provocative concentration of inhaled methacholine needed to reduce FEV1 by 20%; PD20, provocative dose of histamine needed to reduce FEV1 by 20%; PEF, peak expiratory flow; PBO, placebo; ppb, parts per billion; q4w, every 4 weeks; SAE, serious adverse event; SC, subcutaneously; SGRQ, St. George's Respiratory Questionnaire

8.2.3 Omalizumab studies

Reference and NCT number	Study design	Follow-up	Age (years)	Relevant outcomes	Asthma diagnosis before or at randomisation documented by	Asthma severity	Refractory asthma (e.g. exacerbations, symptoms, FEV1)	Reduced lung function	ICS dose	2nd controller	OCS	# patients randomised per group
Busse 2001 (main) NCT not found *Finn 2003 (QoL)* *Lanier 2003 (extension)*	Randomised, double-blind, placebo-controlled trial	52 weeks: 16 weeks ICS stable, 12 weeks ICS reduction, 24 weeks extension	12-75	Exacerbations FEV1 Symptom score AQLQ SAE Discontinuations	Airway reversibility (FEV1 ≥12%) Allergic asthma was defined as positive skin prick test to ≥1 common allergen (*Dermatophagoides farinae*, *D. pteronyssinus*, cockroach (whole body), dog, cat); total serum IgE 30-700 IU/mL	Moderate[a]	Symptoms, no further information provided	FEV1 40-80% of predicted	Medium-to-high (420-840 µg BDP)	Not allowed	Not allowed	525 (main): OMA (N=268), PBO (N=257) 460 (extension): OMA (N=245), PBO (N= 215)
Soler 2001 (main) NCT not found *Buhl 2002a (QoL)* *Buhl 2002b (extension)*	Randomised, double-blind, placebo-controlled trial	52 weeks: 16 weeks ICS stable, 12 weeks ICS reduction, 24 weeks extension	12-75	Exacerbations FEV1 Symptom score AQLQ SAE Discontinuations	Airway reversibility (FEV1 ≥12 %) Allergic asthma was defined as positive skin prick test to ≥1 common allergen (*Dermatophagoides farinae*, *D. pteronyssinus*, dog, cat); total serum IgE 30-700 IU/mL	Moderate[a]	Symptom score	FEV1 40-80% of predicted	High (500-1200 µg BDP)	Not allowed in main study but additional controller drugs allowed in extension	Not allowed	546 (main): OMA (N=274), PBO (N=272) 483 (extension): OMA (N=254), PBO (N=229)
Holgate 2004 NCT not found	Randomised, double-blind, placebo-controlled trial	32 weeks: 16 weeks ICS stable, 16 weeks ICS reduction	12-75	Exacerbations FEV1 Symptom score AQLQ SAE Discontinuations	Not specified Allergic asthma was defined as positive skin prick test to aeroallergen/s; total serum IgE 30-700 IU/mL	Moderate-to-severe[a]	Not specified	FEV1 not mentioned in eligibility criteria; mean 63% (active) and 66% (PBO) at baseline	High (≥ 1000 µg fluticasone)	LABA allowed but not required	Allowed but not reported	246: OMA (N=126), PBO (N=120)
Vignola 2004 (SOLAR) NCT not found	Randomised, double-blind, placebo-controlled trial	28 weeks	12-75	Exacerbations FEV1 Symptom score (Wasserfallen) AQLQ SAE Discontinuations	Airway reversibility (FEV1 ≥12 %) Allergic asthma was defined as positive skin prick test to ≥1 indoor allergen that the patient would be exposed to daily during the study; IgE 30-1300 IU/mL	Moderate-to-severe with persistent allergic rhinitis	≥2 unscheduled medical visits for asthma during the past year or ≥ 3 in the past 2 years	FEV1 not mentioned in eligibility criteria; mean 77% (active) and 79% (PBO) at baseline	Medium-to-high (400-2400 µg budesonide)	LABA allowed but not required	Not allowed	405: OMA (N=209), PBO (N=196)

Reference and NCT number	Study design	Follow-up	Age (years)	Relevant outcomes	Asthma diagnosis before or at randomisation documented by	Asthma severity	Refractory asthma (e.g. exacerbations, symptoms, FEV1)	Reduced lung function	ICS dose	2nd controller	OCS	# patients randomised per group
Ayres 2004 (main) NCT not found *Niven 2008 (severe subgroup)*	Randomised, open-label trial omalizumab *vs* BSC	12 months	12-75	Exacerbations FEV1 Symptom score (Wasserfallen) Mini-AQLQ SAE Discontinuations Sick leave	Airway reversibility (FEV1 ≥12 %) Allergic asthma was defined as positive skin prick test to ≥2 clinically relevant antigens; total serum IgE 30-700 IU/mL	Moderate-to-severe Severe in subgroup analysis	≥1 emergency room visit/hospitalization and ≥1 additional course of OCS due to asthma in the past year	FEV1 not mentioned in eligibility criteria; median 71% (active) and 72% (BSC) at baseline	Medium-to-high (≥400 µg BDP [adolescents] ≥800 µg [adults])	LABA allowed but not required	Allowed but not required	312 randomised 2:1: OMA (N=206), BSC (N=106) 164 in severe subgroup: OMA (N=115), BSC (N=49)
Humbert 2005 (INNOVATE) 00046748	Randomised, double-blind, placebo-controlled trial	28 weeks	12-75	Exacerbations FEV1 Asthma symptoms AQLQ SAE Discontinuations	Airway reversibility (FEV1 ≥12 %) Allergic asthma was defined as positive skin prick test to ≥1 perennial aeroallergen, to which they were likely to be exposed during the study; total serum IgE 30-700 IU/mL	Severe	≥2 exacerbations requiring systemic corticosteroids, or 1 severe exacerbation resulting in hospitalisation or emergency room treatment in the past year	FEV1 ≥40% and <80% of predicted	High (≥800 µg BDP or ≥400 µg FT)	Additional LABA required	Allowed up to 20 mg/day	482, but 419 in efficacy population due to protocol amendment, OMA (N=209), PBO (N=210)
Ohta 2009 (Japanese) 00232050	Randomised, double-blind, placebo-controlled trial	16 weeks	20-75	Exacerbations FEV1 Asthma symptoms SAE Discontinuations	Airway variability (diurnal PEF ≥20% for ≥1 day/week) Allergic asthma was defined as positive skin prick test or in vitro reactivity to a perennial aeroallergen; total serum IgE 30-700 IU/mL	Moderate-to-severe	Symptoms interfering with night-time sleep ≥1 day/week or restricting daily activities Clinically significant exacerbation was withdrawal criterion	FEV1 or mean PEF 40-80% of predicted	High (≥800 µg BDP or equivalent)	Additional controller drugs required	Allowed but chronic use (>10 mg/day prednisolone) prohibited	315 (mITT[b]): OMA (N=151), PBO (N=164)
Chanez 2010 00454051	Randomised, double-blind, placebo-controlled trial	16 weeks	≥18	Exacerbations Asthma symptoms SAE Discontinuations Sick leave	Not specified Allergic asthma was defined as positive skin prick test or in vitro reactivity to a perennial aeroallergen; total serum IgE 30-700 IU/mL	Severe	Frequent daily symptoms or nocturnal awakening ≥2 severe exacerbations or exacerbations requiring medical intervention with OCS in the past year, or hospitalisation/ER for an exacerbation in the past year	FEV1 <80% of predicted	High (>1000 µg BDP or equivalent)	Additional LABA required	Allowed but not required	31 randomised 2:1: OMA (N=20), PBO (N=11)

Reference and NCT number	Study design	Follow-up	Age (years)	Relevant outcomes	Asthma diagnosis before or at randomisation documented by	Asthma severity	Refractory asthma (e.g. exacerbations, symptoms, FEV1)	Reduced lung function	ICS dose	2nd controller	OCS	# patients randomised per group
Bousquet 2011 (main) 00264849 *Siergiejko 2011 (OCS subgroup)*	Randomised, open-label trial omalizumab *vs* OAT	32 weeks	12-75	Exacerbations FEV1 OCS reduction ACQ SAE Discontinuations	Airway reversibility (FEV1 ≥12 %) Allergic asthma was defined as positive skin prick or radioallergosorbent test to ≥1 perennial allergen; total serum IgE 30-700 IU/mL	Severe	≥2 severe asthma exacerbations (requiring treatment with OCS) in past 2 years, ≥1 severe exacerbation in previous year Inadequate control defined according to GINA 2004 Step 3 or 4 clinical features	FEV1 40-80% of predicted	High (>1000 µg BDP or equivalent)	Additional LABA required Others allowed if established >4 weeks before randomisation	Allowed if established >4 weeks before randomisation	400 (mITT[c]) randomised 2:1: OMA (N=272), OAT (N=128) 82 (OCS subgroup): OMA (N=59), OAT (N=23)
Hanania 2011 00314574	Randomised, double-blind, placebo-controlled trial	48 weeks	12-75	Exacerbations Symptom score TASS AQLQ SAE Discontinuations	Based on criteria specified by the NAEPP guidelines Allergic asthma was defined as positive skin prick test or in vitro response (radioallergosorbent test) to dog, cat, cockroach, *Dermatophagoides farinae* or *D. pteronyssinus* in the 12 months before screening; total serum IgE 30-700 IU/mL	Severe	≥1 night-time awakening and daytime symptoms requiring rescue medication ≥1 exacerbation in the past year	FEV1 40-80% of predicted	High (≥500 µg fluticasone or equivalent)	Additional LABA required Other additional controllers allowed	Allowed but not required	848 (mITT[d]): OMA (N=427), PBO (N=421)
Bardelas 2012 00267202	Randomised, double-blind, placebo-controlled trial	24 weeks	≥12	Exacerbations FEV1 Asthma control ACT Discontinuations Sick leave	Not specified Allergic asthma was defined as positive skin prick test or radioallergosorbent test to ≥1 perennial aeroallergens in the prior 12 months; total serum IgE 30-700 IU/mL	Moderate-to-severe	ACT total score ≤19 plus ≥1 of: symptoms >2 days/week, night-time awakenings ≥once/week, use of SABA >2 days/week, or FEV1 ≤80% of predicted	Not required; mean 75% (active) and 77% (PBO) at baseline	Medium as a minimum	Additional controller drugs required	Not allowed	271: OMA (N=136), PBO (N=135)
Hoshino 2012 (Japanese) NCT not found	Randomised, open-label, omalizumab *vs* conventional therapy	16 weeks	20-75	FEV1 AQLQ	Airway reversibility (FEV1 >12 %) or hyperresponsiveness (methacholine: PC20 of <8 mg/mL) Allergic asthma was defined as positive skin prick test to ≥1 common allergen (*Dermatophagoides pteronyssinus*, *D. farinae*, cat, dog); total serum IgE 30-700 IU/mL	Severe	≥1 night-time awakenings/week and daytime asthma symptoms requiring use of rescue medication for ≥2 days/week	FEV1 not mentioned in eligibility criteria; mean 65% (active) and 68% (CT) at baseline	High (≥ 400 µg FT or equivalent)	Additional LABA required Others allowed if established >8 weeks before randomisation	Allowed up to 20 mg/day	30: OMA (N=14), CT (N=16)

Reference and NCT number	Study design	Follow-up	Age (years)	Relevant outcomes	Asthma diagnosis before or at randomisation documented by	Asthma severity	Refractory asthma (e.g. exacerbations, symptoms, FEV1)	Reduced lung function	ICS dose	2nd controller	OCS	# patients randomised per group
Rubin 2012 (QUALITX) (Brazilian) 00567476	Randomised, open-label, omalizumab+ LABA+ICS *vs* LABA+ICS	20 weeks	12-75	Exacerbations FEV1 AQLQ SAE Discontinuations	Airway reversibility (FEV1 >12 %) Allergic asthma was defined as positive skin prick test (diameter of wheal 23 mm) for ≥1 perennial aeroallergen; total serum IgE 30-700 IU/mL	Severe	Daily or persistent asthma symptoms Night symptoms at least once a week ≥2 exacerbations treated with OCS or ≥1 severe exacerbation treated with OCS and hospitalisation/ ER in last year	FEV1 >40% and <80% of predicted	High (≥500 µg fluticasone or equivalent)	Additional LABA required	Possibly allowed; OCS for any reason other than asthma is exclusionary	116 randomised 2:1: OMA (N=78), control (N=38)
Busse 2013 NCT not found	Randomised, double-blind, placebo-controlled trial	24 weeks	12-75 y	Exacerbations FEV1 SAE Discontinuations	Not specified Allergic asthma was defined as total serum IgE 30-1300 IU/mL	Moderate-to-severe	Daytime asthma symptom score ≥ 1 on ≥20 days and a mean symptom score of ≥1.5, or night-time awakening due to asthma symptoms >4 times in the 4-week run-in period	>80%, i.e. normal lung function	Medium-to-high (most likely) (mean dose 489 µg active, 528 µg PBO; ICS unspecified)	Additional controller drugs allowed but not required	Not allowed	328 (mITT[e]): OMA (N=157), PBO (N=171)
Li 2016 (Chinese) 01202903	Randomised, double-blind, placebo-controlled trial	24 weeks	18-75	Exacerbations FEV1 ACQ AQLQ SAE Discontinuations	Airway reversibility (FEV1 ≥12 %) Allergic asthma was defined as positive reaction to ≥1 perennial aeroallergen; total serum IgE 30-700 IU/mL	Moderate-to-severe	Uncontrolled based on GINA step 4 ≥2 or ≥3 exacerbations in previous 12 or 24 months	FEV1 40-80% of predicted	Medium-to-high (>500 µg BDP or equivalent)	Additional LABA required	Not specified	609 (mITT[f]): OMA (N=310), PBO (N=299)
Mukherjee 2019 02049294	Randomised, double-blind, placebo-controlled trial	32 weeks: 16 weeks ICS stable, 16 weeks ICS reduction	18-75	Exacerbations FEV1 ACQ-5 SAE Discontinuations	Airway reversibility (FEV1 ≥12 %) or hyperresponsiveness (methacholine: PC20 of <8 mg/mL) Allergic asthma was defined as positive skin prick test to common aeroallergens; elevated serum IgE levels (range not specified)	Severe	Not specified	FEV1 not mentioned in eligibility criteria; mean 60% (active) and 52% (PBO) at baseline	High (<1500 µg FT or equivalent)	Not allowed	Prednisone allowed but not required	9 (mITT[g]): OMA (N=4), PBO (N=5)

Omalizumab was generally administered SC at a dose approximately ≥0.016 mg/kg IgE (IU/mL) every 2 or 4 weeks, based on the patient's body weight and baseline total serum IgE level. In Mukherjee 2019, the dose was not specified. References in italics are secondary publications of the primary reference above. [a] Definition of asthma severity according to most recent GINA guidelines not as reported in manuscript. [b] 12 patients were randomised but did not receive treatment. [c] 4 patients were randomised but did not receive treatment. [d] 2 patients were randomised but did not receive treatment. [e] 5 patients were found to be ineligible after enrolment [f] 7 patients were randomised in error as were screen failures. [g] 2 patients were randomised but not included in analyses

ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; AQLQ, Asthma Quality of Life Questionnaire; BDP, beclomethasone dipropionate; $beta_2$-AR, $beta_2$-adrenoceptors; BSC, best standard care; CT, conventional therapy; ER, emergency room; FEV1, forced expiratory volume in 1 s; FT, fluticasone propionate; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroids; IgE, immunoglobulin E; LABA, long-acting beta agonist; mITT, modified intention-to-treat; NAEPP, National Asthma Education and Prevention Program Expert Panel Report; OAT, optimised asthma therapy; OCS, oral corticosteroids; OMA, omalizumab; PBO, placebo; PC20, provocative concentration of inhaled methacholine needed to reduce FEV1 by 20%; PEF, peak expiratory flow; QoL, quality of life; SABA, short-acting bronchodilator; SAE, serious adverse event; SC, subcutaneously; TASS, Total Asthma Symptom Severity

8.3 Baseline characteristics

8.3.1 Dupilumab studies

Reference	n		Female (%)		Race White (%)		Mean age (years)		# exacerbations in last year		FEV1 (L)		FEV1 % predicted		Mean ACQ score		LABA use[a] (%)		High dose ICS use (%)		OCS use %, daily dose		FeNO (ppb)		EOS (cells/µL)		IgE (IU/mL)	
	DUP	PBO	DUP	PBO	DUP	PBO	DUP	PBO	DUP	PBO	DUP	PBO	DUP	PBO	DUP	PBO	DUP	PBO	DUP	PBO	DUP	PBO	DUP	PBO	DUP	PBO	DUP	PBO
Wenzel 2016 (main) (DRI12544) *Corren 2019a (QoL)*	150	158	64	66	76	75	51.0	49.0	1.9	2.3	1.79	1.82	61.2	61.0	2.7	2.7	LABA required		52	50	Not reported		39.3	39.0	361	342	416	419
Castro 2018 (main) (QUEST) *Castro 2019 (lung function)*	631	317	61	63	Not reported		47.9	48.2	2.1	2.1	1.78	1.76	58.4	58.4	2.8	2.7	LABA or other second controller required		50	54	Not reported		34.5	34.5	349	370	461	394
Corren 2019b (allergic subgroup)	360	183	54	55	Not reported		45.5	44.0	2.0	1.9	1.85	1.84	Not reported		2.7	2.7	LABA or other second controller required		Not reported; medium-to-high-dose inclusion criterion		Not reported		25	27	240	290	304	337
Rabe 2018 (main) (VENTURE) *Rabe 2019 (lung function)*	103	107	60	61	94	93	51.9	50.7	2.0	2.2	1.53	1.63	51.6	52.7	2.4	2.6	LABA or other second controller required		Inclusion criterion		Inclusion criterion; Dose 10.00 (5.0 to 35.0)[b]		35.6	39.6	370	325	Not reported	

Data are presented for 200 mg dupilumab q2w *vs* placebo, except for the VENTURE study (300 mg dupilumab q2w *vs* placebo). References in italics are secondary publications of the primary reference above.

Severe asthma was an inclusion criterion for the VENTURE study (Rabe 2018); the proportion of subjects with severe asthma was not reported in the other studies

[a] or equivalent 2nd controller; [b] median (range) in both the dupilumab and placebo groups

ACQ, Asthma Control Questionnaire; DUP, dupilumab; EOS, blood eosinophils; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 s; ICS, inhaled corticosteroids; IgE; immunoglobulin E; IU, international unit; LABA, long-acting beta agonist; n, number of subjects in the treatment group; OCS, oral corticosteroids; PBO, placebo; ppb, parts per billion; q2w, every 2 weeks

8.3.2 Mepolizumab studies

Reference	n		Female (%)		Race White (%)		Mean age (years)		# exacerbations in last year		FEV1 (L)		FEV1 % predicted		Mean ACQ score		LABA use[a] (%)		High dose ICS use (%)		OCS use (%, daily dose)		FeNO (ppb)		EOS (cells/µL)		IgE (IU/mL)	
	MEP	PBO	MEP	PBO	MEP	PBO	MEP	PBO	MEP	PBO	MEP	PBO	MEP	PBO	MEP	PBO	MEP	PBO	MEP	PBO	MEP	PBO	MEP	PBO	MEP	PBO	MEP	PBO
Pavord 2012 (DREAM)	153	155	68	63	91	90	50.2	46.4	3.7	3.7	1.81	1.90	60	59	2.2	2.5	93	97	Inclusion criterion		30 10 mg	29 10 mg	29.2	33.7	250	280	Not reported	
Ortega 2014 (MENSA) SC	194	191	60	56	Not reported		51	49	3.8	3.6	1.73	1.86	59.3	62.4	2.3	2.3	Not reported		Inclusion criterion		27 12.6 mg	23 15.1 mg	Not reported		290	320	150	150
Ortega 2014 (MENSA) IV	191	191	55	56	Not reported		50	49	3.5	3.6	1.86	1.86	61.4	62.4	2.1	2.3	Not reported		Inclusion criterion		25 12.0	23 15.1 m	Not reported		280	320	180	150
Bel 2014 (SIRIUS)	69	66	64	45	Not reported		50	50	3.3	2.9	1.90	2.00	59.6	57.8	2.2	2.0	Not reported		Inclusion criterion		Incl. 12.5 mg	Incl. 15.0 mg	Not reported		250	230	117	114
Chupp 2017 (MUSCA)	274	277	54	64	Not reported		49.8	52.1	2.9	2.7	1.8	1.7	55.5	55.2	2.2	2.2	>99	99	Inclusion criterion		23 12.6 mg	24 13.4 mg	Not reported		300	350	Not reported	

Data are presented for 100 mg mepolizumab administered SC q4w *vs* placebo, except for the DREAM study (Pavord 2012), where data for 75mg mepolizumab administered IV q4w *vs* placebo are presented, and the MENSA study (Ortega 2014), where both 100 mg SC and 75 mg IV doses are presented. Severe asthma was an inclusion criterion for each of the studies.

[a] Or equivalent 2nd controller

ACQ, Asthma Control Questionnaire; EOS, blood eosinophils; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 s; ICS, inhaled corticosteroids; IgE, immunoglobulin E; IU, international unit; IV, intravenously; LABA, long-acting beta agonist; MEP, mepolizumab; n, number of subjects in the treatment group; OCS, oral corticosteroids; PBO, placebo; ppb, parts per billion; SC, subcutaneously; q4w, every 4 weeks

8.3.3 Omalizumab studies

Reference	n		Female (%)		Race White (%)		Mean age (years)		Severe asthma (%)		# exacerbations in last year		FEV1 (L)		FEV1 % predicted		Mean ACQ score		LABA use[a] (%)		High dose ICS use (%)		OCS use (%, daily dose)		IgE (IU/mL)	
	OMA	PBO	OMA	PBO	OMA	PBO	OMA	PBO	OMA	PBO	OMA	PBO	OMA	PBO	OMA	PBO	OMA	PBO	OMA	PBO	OMA	PBO	OMA	PBO	OMA	PBO
Busse 2001 (main) *Finn 2003 (QoL)*	268	257	61	57	89	89	39.3	39.0	99.3	99.6	Not reported		2.3	2.4	68.2	67.7	4.0[b]	4.2[b]	Not allowed		Not reported		Not allowed		173	186
Lanier 2003 (extension)	245	215	61	55	Not reported		39.6	38.6	99	100	Not reported		Not reported		68.8	68.2	Not reported		Not allowed		Not reported		Not allowed		173	186
Soler 2001 (main) *Buhl 2002a (QoL)*	274	272	49	53	93	89	40.0	39.0	22	22	Not reported		2.5	2.5	69.8	69.9	4.4[b]	4.4[b]	Not allowed in main study		Inclusion criterion		Not allowed		223	206
Buhl 2002b (extension)	254	229	49	52	94	89	41	40	22	23	Not reported		Not reported		70.0	70.4	Not reported		11	17	Inclusion criterion		Not allowed		220	204
Holgate 2004	126	120	64	58	Not reported		41.1	40.5	Inclusion criterion		Not reported		Not reported		62.9	66.0	Not reported		49	43	Inclusion criterion		Not reported		267	266
Vignola 2004 (SOLAR)	209	196	52	58	Not reported		38.3	38.5	89	91	2.1	2.1	2.7	2.8	76.9	79.4	4.0[b]	4.0[b]	41	36	Not reported		Not allowed		Not reported	

Reference	n		Female (%)		Race White (%)		Mean age (years)		Severe asthma (%)		# exacerbations in last year		FEV1 (L)		FEV1 % predicted		Mean ACQ score		LABA use[a] (%)		High dose ICS use (%)		OCS use (%, daily dose)		IgE (IU/mL)	
	OMA	PBO	OMA	PBO	OMA	PBO	OMA	PBO	OMA	PBO	OMA	PBO	OMA	PBO	OMA	PBO	OMA	PBO	OMA	PBO	OMA	PBO	OMA	PBO	OMA	PBO
Ayres 2004 (main)	206	106	72	68	Not reported		37.5	39.3	56	46	Not reported		Not reported		70.5	72.3	17.4[c]	17.0[c]	78	78	Not reported		23, dnr	18 dnr	167	ND
Niven 2008 (severe subgroup)	115	49	75	69	Not reported		38.7	39.3	100	100	Not reported		Not reported		65.6	64.1	19.1[c]	17.5[c]	97	100	100	100	65 dnr	80 dnr	Not reported	
Humbert 2005 (INNOVATE)	209	210	67	66	78	78	43.4	43.3	Inclusion criterion		2.6[d]	2.4[d]	Not reported		61.0	61.6	3.9[b]	3.9[b]	LABA required		Inclusion criterion		24 dnr	21; dnr	198	190
Ohta 2009 (Japanese)	151	164	51	57	All Japanese		48.8	49.2	96	95	Not reported		Not reported		74.1	75.8	Not reported		50	52	Inclusion criterion		13, dnr	7, dnr	261	247
Chanez 2010	20	11	70	45	Not reported		45.7	50.6	Inclusion criterion		4.7	4.0	Not reported		61.3	66.6	Not reported		LABA required		Inclusion criterion		15 dnr	36 dnr	202	253
Bousquet 2011 (main)	272	128	67	59	Not reported		45.6	45.7	Inclusion criterion		2.1 between groups		Not reported		63.0	61.1	Not reported		LABA required		Inclusion criterion		22 dnr	18 dnr	233	231
Siergiejko 2011 (OCS subgroup)	59	23	68	61	100	100	45.2	45.6	Inclusion criterion		2.7	3.3	Not reported		61.3	60.7	Not reported		LABA required		Inclusion criterion		100, 13.1 mg	100, 12.8 mg	207	275
Hanania 2011	427	421	61	70	73	76	43.7	45.3	Inclusion criterion		2.0	1.9	Not reported		65.4	64.4	4.0[b]	3.9[b]	LABA required		Inclusion criterion		17 10.0 mg	17 13.4 mg	179	175
Bardelas 2012	136	135	68	64	75	76	41.9	40.7	Not reported		Not reported		2.4	2.5	74.5	76.5	13.9[e]	13.7[e]	85	77	Not reported		Not allowed		184	181
Hoshino 2012 (Japanese)	14	16	79	75	All Japanese		59.2	51.2	Inclusion criterion		Not reported		1.3	1.4	65.3	68.4	Not reported		LABA required		Inclusion criterion		29	31	248	282
Rubin 2012 (QUALITX) (Brazilian)	78	38	77	76	69	58	43.8	45.2	Inclusion criterion		Not reported		Not reported		Not reported		3.1[b]	3.1[b]	LABA required		Inclusion criterion		Not reported		Not reported	
Busse 2013	157	171	70	68	72	69	36.0	38.1	Not reported		Not reported		2.8	2.8	85.7	85.9	Not reported		79	80	Not reported		Not allowed		196	200
Li 2016 (Chinese)	310	299	55	52	All Chinese		45.8	47.1	Not reported		2.3	2.2	Not reported		63.5	63.0	1.7	1.6	LABA required		Not reported		Not reported		272	279
Mukherjee 2019	4	5	25	20	Not reported		54.5	58.8	Not reported		Not reported		Not reported		60.0	51.6	1.8	2.2	Not allowed		Inclusion criterion		25, 12.5 mg	0	965	482

Data are presented for omalizumab administered SC at a dose approximately equal to 0.016 mg/kg IgE (IU/mL) q4w *vs* placebo, except for Ayres 2004 and Niven 2008 (comparator was best standard care), Bousquet 2011 (comparator was optimised asthma therapy), Hoshino 2012 (comparator was conventional therapy), and Rubin 2012 (comparator was standard care (LABA+OCS)). References in italics are secondary publications of the primary reference above. FeNO and EOS baseline data were not available, except for the Hanania 2011 study (baseline FeNO values of 28.5 and 29.2 ppb for omalizumab *vs*. placebo) and the Mukherjee 2019 study (baseline EOS values of 350 *vs* 620 cells/µL).

[a] Or equivalent 2nd controller; [b] Mean AQLQ score; [c] Mean Wasserfallen asthma symptom score; [d] In previous 14 months; [e] Mean Asthma Control Test

ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; dnr, dose not reported; EOS, blood eosinophils; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 s; ICS, inhaled corticosteroids; IU, international unit; IV, intravenously; LABA, long-acting beta agonist; ND, not determined; OCS, oral corticosteroids; OMA, omalizumab; PBO, placebo; ppb, parts per billion; SC, subcutaneously; q4w, every 4 weeks.

8.4 Statistical considerations

All available data were extracted from the included publications. The by-study tables in section 9.4 include the extracted data by treatment arm and, if reported, the absolute and relative differences. For the binary outcomes, the proportions and CIs were calculated, if not published, based on the number of events and total number of patients. For continuous outcomes, the CIs to the LSmeans were calculated, if not published, based on SD or standard error (SE), if available. In few cases where LSmean values were not published, the mean values were extracted.

The statistical principles used followed specifications in the protocol [1].

The endpoints requested by the protocol were of three types:

- binary (fractions)
- rates (events per person time)
- continuous outcomes

The 4 treatments involved (dupilumab, mepolizumab, omalizumab and placebo) were in every case reported in parallel group studies, each including the relevant treatment and dosage regimen as one study arm and placebo as another study arm.

Direct comparisons were thus only possible for dupilumab *vs* placebo. For the comparisons of dupilumab *vs* either of the active arms, in selected patient subgroups and timeframes, the main approach was the same in every case. The amount of data for comparative analyses were limited by timeframes and study design as follows.

The duration of the included studies varied from 16 to 52 weeks. Since the incidence of the binary outcomes was expected to vary across the duration of a study, and since the magnitude of effect of the continuous outcomes were not necessarily stable from week 16 to 52, it was not considered appropriate to try to standardise to a common duration across studies and therefore comparisons have only been performed between studies and outcomes with approximately the same duration. This means that for mepolizumab, week 24 and 32 data were pooled and compared with dupilumab week 24 data. For omalizumab, week 20, 24, 28 and 32 data were pooled and/or compared with dupilumab week 24 data, and week 48 and 52 data were pooled and compared with dupilumab week 52 data.

Four of the omalizumab studies were open-label studies. In accordance with the approach of the Medicines Council's background for the treatment guideline for biological treatment of severe asthma [5], we did not include data from open-label studies in the comparative analyses of discontinuations. Since knowledge about treatment assignment may also impact patient-reported outcomes [58, 59], we also excluded data from open-label studies from the comparative analyses of the 2 patient-reported outcomes asthma control and QoL.

For a given endpoint in the relevant selection of studies (considering time frame and subgroup of patients), the following steps were performed:

1) a meta-analysis of dupilumab *vs* placebo studies
2) a meta-analysis of the relevant active comparator *vs* placebo studies
3) a direct comparison of
    a. the meta-pools of dupilumab *vs* placebo and

b. active comparator *vs* placebo

In general, some simple pre-processing imputation was done on published data in cases where no doubt existed as to the relevant procedure: missing SEs were derived from reported SDs and the number of patients, and missing proportions (and 95% CI) were derived from the number of events and patients. In cases with 0 counts, a Poisson approximation was used. For fractions, a missing risk-ratio could then be derived in almost every case, including a CI. For rates however, a missing rate-ratio could in most cases not be imputed due to a general lack of reported number of events.

Whenever adjusted values with a corresponding CI was published this value was used for direct and indirect comparisons. But since the number of studies available per clinical question and outcome was limited, typically only 1 or 2 studies, it was considered reasonable to blend adjusted and unadjusted results, with the proviso that adjusted results (with a CI) should take precedence over unadjusted results, if both were available. There was in general not enough information to contrast adjusted and un-adjusted results.

For the within-study analyses of fractions, the incidences and 95% CIs were found as exact Clopper-Pearson intervals, whereas RDs were derived directly as Newcombe intervals, since the general principle of finding the absolute difference as $(RR - 1)*P_0$ where RR is the risk/effect ratio and P_0 is the normal comparator level in Danish setting for the given endpoint, could not be used in the present setup. It has not been possible for the applicant to establish the P_0 values.

Note that in some case 1 or 2 compared fractions were 0. In this case the procedure of Agresti and Caffo [60], see above, was followed (the method of 4 ghosts in their terminology).

For the reporting of single study results, the adjusted values were used when available (assuming that the corresponding SE / CI was also available). To a large extent, the reported p-values for adjusted mean differences (or RRs) were missing or reported in an imprecise form. Since all derived CIs are approximative, it seemed most reasonable to refrain from using the p-values at all, as they would just be an equivalent way of describing the CIs.

The between-study comparisons of dupilumab and active treatments (i.e. mepolizumab and omalizumab) were performed using Bucher's method [61]. For the comparative analysis of QoL outcomes (where the tools AQLQ and SGRQ were used; having comparable reliability and validity [62]) a standardisation was performed using observed active and placebo arm SDs according to the methods described by the Medicines Council [47]. The preferred scale was AQLQ. A standardisation was necessary in 1 case: the pooling of mepolizumab 24 week and 32 week data using SGRQ as compared with pools of the dupilumab phase 2b (DRI12544) and QUEST week 24 data using AQLQ. Here, the observed SDs in change from baseline in AQLQ were very close to 1, in placebo as well as dupilumab arms. The parallel SDs in the mepolizumab and corresponding placebo arms were likewise very close to 16 in every case. Consequently, an immediate standardisation (bringing the SGRQ results on the AQLQ scale) could be achieved by dividing mepolizumab-placebo differences and SDs with 16 and proceeding with Bucher's method.

The asthma control ACT score was only represented in 1 study (Bardelas, 2012; omalizumab *vs* placebo) and the reported information was furthermore scanty. Therefore, it was deemed most reasonable to refrain from using this in a standardised comparison with the ACQ-5 in dupilumab *vs* placebo studies.

The statistical evaluations were performed on the log-transformed scale for rates and fractions, and then back transformed in order to present estimates and CIs as ratios. For the calculation of absolute risk differences, the expression $(RR - 1)*P_0$ was used again. The mean active comparator rates from the

relevant studies of a given indirect comparison were used as the P_0 used above. The corresponding absolute CIs were calculated heuristically by inserting the CI limits instead of RR in the above equation.

The statistical analyses utilised for indirect comparisons were entirely built on post-processing of single-study results using simple weighted normal-approximation synthesis. In most cases a detailed model for proportion outcomes could have been implemented as an alternative, using raw counts. But it was considered more appropriate to build the synthesis of proportion outcomes on the same principle as for rates and continuous outcomes.

The number of dupilumab *vs* placebo studies and comparator *vs* placebo studies used for a given indirect comparison were in most cases just 1 or 2 of each kind. It is thus not possible on purely statistical grounds to assess the degree of homogeneity. The amount of homogeneity was instead assessed qualitatively at the selection process leading to the specification of a given indirect comparison.

8.5 Results per study

8.5.1 Dupilumab studies

TABLE 46 RESULTS OF DUPILUMAB STUDY DRI12544 (WENZEL 2016) – UNCONTROLLED, PERSISTENT ASTHMA – SUBGROUP WITH INCREASED EOS

Trial name:	A randomized, double-blind, placebo-controlled, dose-ranging study to evaluate dupilumab in patients with moderate to severe uncontrolled asthma										
NCT number:	01854047										
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome (population/subgroup)	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**	**RR**	**95% CI**	**P value**		
Annualised rate of severe exacerbations (EOS ≥150 cells/µL)	Dupilumab	120	0.290 (0.159; 0.529)	-0.762	-1.218; -0.306	NR	0.276	0.138; 0.552	0.0003	A negative binomial regression model, including the total number of events occurring during the double-blind treatment period as the response variable; treatment group, baseline blood EOS strata, pooled countries or regions, and number of asthma events in the year before the study as covariates; and log-transformed treatment duration as the offset variable[a]	EPAR p97
	Placebo	127	1.052 (0.693; 1.598)								
Proportion of patients with 0 exacerbations in the 24-week treatment period (ITT)	Dupilumab	148	91.2 (86.7; 95.8)	NR	NR	NR	NR	NR	NR	-	Wenzel 2016 table 2
	Placebo	158	74.1 (67.2; 80.9)								
Change from baseline to wk 12 in FEV1 (L) (EOS ≥150 cells/µL)	Dupilumab	120	0.32 (0.242; 0.398)	0.23	0.13; 0.33	<0.0001	-	-	-	A mixed-effects model with a repeated-measures approach. The model included change from baseline to week 12 as response variables, factors (fixed effects) for treatment, baseline blood EOS strata, pooled countries or regions, visit, treatment-by-visit interaction, baseline value, and baseline-by-visit interaction[b]	EPAR p97 and SmPC p22
	Placebo	127	0.09 (0.012; 0.168)								
Change from baseline to wk 24 in asthma control (ACQ-5) (EOS ≥150 cells/µL)	Dupilumab	108	-1.55 (-1.726; -1.374)	-0.48	-0.72; -0.23	0.0001	-	-	-	A mixed-effects model with a repeated-measures approach. The model included change from baseline to week 12 as response variables, factors (fixed effects)	EPAR p100
	Placebo	100	-1.07 (-1.246; -0.894)								

Trial name:	A randomized, double-blind, placebo-controlled, dose-ranging study to evaluate dupilumab in patients with moderate to severe uncontrolled asthma										
NCT number:	01854047										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome (population/subgroup)	Study arm	N	Result (CI)	Difference	95% CI	P value	RR	95% CI	P value		
Change from baseline to wk 24 in quality of life (AQLQ) (EOS ≥150 cells/µL)	Dupilumab	106	1.27 (1.074; 1.466)	0.49	0.24; 0.75	0.0002	-	-	-	for treatment, baseline blood EOS strata, pooled countries or regions, visit, treatment-by-visit interaction, baseline value, and baseline-by-visit interaction	EPAR p100
	Placebo	100	0.78 (0.584; 0.976)								
Annualised days of sick leave due to severe exacerbation event (days/year) (ITT)	Dupilumab	150	0.613[c]	NR	NR	<0.0001	NR	NR	NR	Poisson model with the total number of events onset between first dose date and last dose date +14 days as the response variable, treatment, pooled countries/regions, and number of asthma events because of the study as covariates, and log-transformed standardised (in years) treatment duration as an offset variable	Corren 2019a table 3
	Placebo	158	2.238[c]								

[a] For patients who prematurely discontinued the study drug, events occurring during the treatment period were included and the analysis adjusted for the treatment duration; [b] FEV1 measurements collected from systemic corticosteroid start date to systemic corticosteroid end date plus 30 days for each exacerbation episode were excluded from the primary analysis to reduce the confounding effect of systemic corticosteroids. For patients discontinuing treatment before week 12, off -treatment FEV1 values were excluded in the primary analysis; [c] No measures of variability reported

Proportion of patients with ≥200 mL improvement in FEV1 was not reported. Safety results (including discontinuations) are reported in Table 52 for the safety population

-, not applicable; ACQ-5, 5-item Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; CI, confidence interval; EOS, blood eosinophils; EPAR, European Public Assessment Report; FEV1, forced expiratory volume in 1 s; ITT, intention-to-treat; L, litre; NR, not reported; RR, relative risk or rate ratio

TABLE 47 RESULTS OF THE DUPILUMAB QUEST STUDY (CASTRO 2018) – UNCONTROLLED, PERSISTENT ASTHMA – SUBGROUP WITH INCREASED EOS

Trial name:	A randomised, double blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of dupilumab in patients with persistent asthma LIBERTY ASTHMA QUEST										
NCT number:	02414854										
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome (population/subgroup)[a]	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**	**RR**	**95% CI**	**P value**		
Annualised rate of severe exacerbations	Dupilumab	437	0.445 (0.368; 0.538)	-0.561	-0.785; -0.338	NR	0.442	0.337; 0.581	<0.0001	A negative binomial regression model, including the 4 intervention groups, age, geographic region, baseline EOS strata, baseline dose of ICS, and number of exacerbations in the previous year as covariates[b]	EPAR p97
	Placebo	232	1.007 (0.814; 1.245)								
Proportion of patients with 0 exacerbations in the 52-week treatment period (%)	Dupilumab	437	71.4 (67.2; 75.6)	NR	NR	NR	NR	NR	NR	-	Castro 2019 table S7
	Placebo	232	53.9 (47.5; 60.3)								
Change from baseline to wk 12 in FEV1 (L)	Dupilumab	425	0.36 (0.321; 0.399)	0.17	0.11; 0.23	<0.0001	-	-	-	A mixed-effects model with repeated measures, including assigned intervention, age, sex, height, baseline EOS strata, baseline ICS dose, visit, intervention-by-visit interaction, the corresponding baseline value, and baseline-by-visit interaction as covariates[b]	Castro 2019 table S1
	Placebo	224	0.19 (0.131; 0.249)								
Change from baseline to wk 24 in FEV1 (L)	Dupilumab	419	0.38 (0.341; 0.419)	0.21	0.15; 0.28	<0.0001	-	-	-		Castro 2019 table S1
	Placebo	217	0.16 (0.101; 0.219)								
Change from baseline to wk 52 in FEV1 (L)	Dupilumab	341	0.40 (0.361; 0.439)	0.25	0.18; 0.32	<0.0001	-	-	-		Castro 2019 table S1
	Placebo	175	0.15 (0.091; 0.209)								
Proportion of patients with ≥200 mL improvement in FEV1 (%)	Dupilumab	341	58.1 (52.8; 63.3)	NR	NR	NR	NR	NR	NR	-	Castro 2019 table S6
	Placebo	175	38.3 (31.1; 45.5)								

Trial name:	A randomised, double blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of dupilumab in patients with persistent asthma LIBERTY ASTHMA QUEST										
NCT number:	02414854										
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome (population/subgroup)[a]	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**	**RR**	**95% CI**	**P value**		
Change from baseline to wk 24 in asthma control (ACQ-5)	Dupilumab	412	-1.51 (-1.608; -1.412)	-0.42	-0.58; -0.26	<0.0001	-	-	-	A mixed-effects model with repeated measures, including assigned intervention, age, baseline EOS strata, baseline ICS dose, visit, intervention-by-visit interaction, the corresponding baseline value, and baseline-by-visit interaction as covariates[b]	EPAR p100
	Placebo	214	-1.09 (-1.227; -0.953)								
Change from baseline to wk 24 in quality of life (AQLQ)	Dupilumab	394	1.19 (1.092; 1.288)	0.26	0.09; 0.42	0.0022	-	-	-		EPAR p100
	Placebo	202	0.94 (0.803; 1.077)								

[a] Results for all outcomes in the subgroup with EOS ≥150 cells/µL; [b] For patients who discontinued the assigned intervention and remained in the study, severe exacerbations/measurements after the intervention was discontinued were included in the analyses

Sick leave was not reported in this study. Safety results (including discontinuations) are reported in Table 53 for the safety population

-, not applicable; ACQ-5, 5-item Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; CI, confidence interval; EOS, blood eosinophils; EPAR, European Public Assessment Report; FEV1, forced expiratory volume in 1 s; ICS, inhaled corticosteroids; L, litre; NR, not reported; RR, relative risk or rate ratio

TABLE 48 RESULTS OF THE DUPILUMAB VENTURE STUDY (RABE 2018) – OCS-DEPENDENT ASTHMA – SUBGROUP WITH INCREASED EOS

Trial name:	A randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of dupilumab in patients with severe steroid dependent asthma LIBERTY ASTHMA VENTURE										
NCT number:	02528214										
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome (population/subgroup)	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**	**RR**	**95% CI**	**P value**		
Annualised rate of severe exacerbations (EOS ≥150 cells/µL)	Dupilumab	81	0.642 (0.425; 0.971)	-0.894	-1.414; -0.374	NR	0.418	0.254; 0.689	0.0007	A negative binomial regression model was used	Rabe 2018 table S6
	Placebo	69	1.536 (1.139; 2.071)								
Proportion of patients with 0 exacerbations in the 24-wk treatment period (%) (EOS ≥150 cells/µL)	Dupilumab	81	77.8 (68.7; 86.8)	NR	NR	NR	NR	NR	NR	-	Rabe 2019 table A3
	Placebo	69	53.6 (41.9; 65.4)								
Mean % reduction in daily OCS maintenance dose (EOS ≥150 cells/µL)	Dupilumab	81	75.91 (66.58; 85.24)	29.39	15.67; 43.12	NR	-	-	-	An analysis of covariance model including % reduction in OCS dose at week 24 as the response variable, with trial group, adjusted OCS dose at baseline, geographic region, and baseline EOS subgroups (≥150 or <150 cells/µL) as covariates. Missing data were handled with the use of a pattern-mixture model by multiple imputations	Rabe 2018 table S5
	Placebo	69	46.51 (36.30; 56.72)								
Proportion of patients with no OCS use (%) (EOS ≥150 cells/µL)	Dupilumab	81	54 (42; 66)	NR	NR	NR	OR: 2.73	1.31; 5.70	NR	NR	Rabe 2018 table S5
	Placebo	68	30 (19; 43)								
Proportion of patients with ≥50% reduction in OCS use (%) (EOS ≥150 cells/µL)	Dupilumab	81	84 (74; 90)	NR	NR	NR	OR: 4.49	2.04; 9.85	NR	NR	Rabe 2018 table S5
	Placebo	69	53 (41; 65)								
Change from baseline to wk 24 in FEV1 (L) (EOS ≥150 cells/µL)	Dupilumab	76	0.32 (0.202; 0.438)	0.22	0.06; 0.38	NR	-	-	-	A mixed effects model with a repeated-measures approach was used	Rabe 2018 table S6
	Placebo	66	0.09 (-0.028; 0.208)								

Trial name:	A randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of dupilumab in patients with severe steroid dependent asthma LIBERTY ASTHMA VENTURE										
NCT number:	02528214										
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome (population/subgroup)	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**	**RR**	**95% CI**	**P value**		
Proportion of patients with ≥200 mL improvement in FEV1 (%) (EOS ≥150 cells/µL)	Dupilumab	76	55.3 (44.1; 66.4)	NR	NR	NR	NR	NR	NR	-	Rabe 2019 table A1
	Placebo	66	33.3 (22.0; 44.7)								
Change from baseline to wk 24 in asthma control (ACQ-5) (ITT)	Dupilumab	96	-1.05 (-1.266; -0.834)	-0.47	-0.76; -0.18	NR	-	-	-	A mixed effects model with a repeated-measures approach	Rabe 2018 p2482 (difference) Ford 2019 poster figure 3 (means)
	Placebo	99	-0.57 (-0.766; -0.374)								
Change from baseline to wk 24 in quality of life (AQLQ) (ITT)	Dupilumab	98	0.89 (0.694; 1.086)	NR	NR	NR	-	-	-	-	Ford 2019 poster, figure 3
	Placebo	100	0.54 (0.344; 0.736)								

Sick leave was not reported in this study. Safety results (including discontinuations) are reported in Table 54 for the safety population

-, not applicable; ACQ-5, 5-item Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; CI, confidence interval; EOS, blood eosinophils; FEV1, forced expiratory volume in 1 s; ITT, intention-to-treat; L, litre; NR, not reported; OCS, oral corticosteroids; RR, relative risk or rate ratio

TABLE 49 RESULTS OF THE DUPILUMAB QUEST STUDY (CASTRO 2018) – UNCONTROLLED, PERSISTENT ASTHMA – ALLERGIC SUBGROUP

Trial name:	A randomised, double blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of dupilumab in patients with persistent asthma LIBERTY ASTHMA QUEST										
NCT number:	02414854										
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome (population/subgroup)	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**	**RR**	**95% CI**	**P value**		
Annualised rate of severe exacerbations (Allergy + EOS ≥150 cells/µL)	Dupilumab	246	0.502 (0.392; 0.644)	NR	NR	<0.01	NR	NR	NR	A negative binomial regression model, which included as covariates the assigned intervention groups, age, geographic region, baseline EOS strata, baseline dose of ICS, and number of severe exacerbations in the previous year[a]	Corren JACI 2019 figure 1B and line 246
	Placebo	138	0.859 (0.642; 1.149)								
Annualised rate of severe exacerbations (Allergy + FeNO ≥25 ppb)	Dupilumab	185	0.330 (0.242; 0.450)	NR	NR	<0.01	NR	NR	NR		Corren JACI 2019 figure 1D and line 246
	Placebo	99	0.883 (0.639; 1.219)								
Proportion of patients with 0 exacerbations in the 52 wk treatment period (%) (ITT)	Dupilumab	631	70.8 (67.3; 74.4)	NR	NR	NR	NR	NR	NR	-	Castro 2019 table S7
	Placebo	317	57.7 (52.3; 63.2)								
Change from baseline to wk 12 in FEV1 (L) (Allergy + EOS ≥150 cells/µL)	Dupilumab	NR	NR	0.16	0.07; 0.24	<0.001	-	-	-	Mixed-effect models with repeated measures, including as covariates the 4 assigned intervention groups, age, sex, height, geographic region, baseline EOS strata, baseline dose of ICS, visit, visit-by-intervention interaction, corresponding baseline value, and baseline-by-visit interaction	Corren JACI 2019 figure 2B
	Placebo	NR	NR								
Change from baseline to wk 12 in FEV1 (L) (Allergy + FeNO ≥25 ppb)	Dupilumab	NR	NR	0.19	0.09; 0.30	<0.001	-	-	-		Corren JACI 2019 figure 2B
	Placebo	NR	NR								
Change from baseline to wk 24 in FEV1 (L) (Allergic subgroup)	Dupilumab	343	0.34 (0.301; 0.379)	NR	NR	<0.001	-	-	-		Corren JACI 2019 figure 2A
	Placebo	173	0.18 (0.121; 0.239)								
Change from baseline to wk 52 in FEV1 (L) (Allergic subgroup)	Dupilumab	275	0.36 (0.321; 0.399)	NR	NR	<0.001	-	-	-		Corren JACI 2019 figure 2A
	Placebo	146	0.18 (0.121; 0.239)								

Trial name:	A randomised, double blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of dupilumab in patients with persistent asthma LIBERTY ASTHMA QUEST										
NCT number:	02414854										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome (population/subgroup)	Study arm	N	Result (CI)	Difference	95% CI	P value	RR	95% CI	P value		
Proportion of patients with ≥200 mL improvement in FEV1 (%) (ITT)	Dupilumab	477	50.5 (46.0; 55.0)	NR	NR	NR	NR	NR	NR	-	Castro 2019 table S6
	Placebo	240	37.1 (31.0; 43.2)								
Change from baseline to wk 24 in asthma control (ACQ-5) (Allergic subgroup)	Dupilumab	339	-1.39 (-1.488; -1.292)	-0.28	-0.46; -0.11	<0.01	-	-	-	Mixed-effect models with repeated measures, including as covariates the 4 assigned intervention groups, age, geographic region, baseline EOS strata, baseline dose of ICS, visit, visit-by-intervention interaction, corresponding baseline value, and baseline-by-visit interaction	Corren JACI 2019 line 273-275
	Placebo	171	NR								
Change from baseline to wk 52 in asthma control (ACQ-5) (Allergic subgroup)	Dupilumab	272	-1.53 (-1.648; -1.412)	NR	NR	NR	-	-	-		Corren JACI 2019 figure 3
	Placebo	145	-1.10 (-1.276; -0.924)								
Change from baseline to wk 24 in quality of life (AQLQ) (ITT)	Dupilumab	631	1.14 (1.062; 1.218)	0.20	0.06; 0.34	NR	-	-	-	A mixed-effects model with repeated measures, including assigned intervention, age, baseline EOS strata, baseline ICS dose, visit, intervention-by-visit interaction, the corresponding baseline value, and baseline-by-visit interaction as covariates	Castro 2018 table S6
	Placebo	317	0.94 (0.822; 1.058)								
Change from baseline to wk 52 in quality of life (AQLQ) (ITT)	Dupilumab	631	1.28 (1.202; 1.358)	0.29	0.15; 0.44	NR	-	-	-		Castro 2018 table S6
	Placebo	317	0.99 (0.872; 1.108)								

[a] All severe exacerbations that occurred during the 52-week treatment period were included regardless of whether the patient remained on treatment

No results were reported for sick leave in this study. Safety results (including discontinuations) are reported in Table 53 for the safety population

-, not applicable; ACQ-5, 5-item Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; CI, confidence interval; EOS, blood eosinophils; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 s; ICS, inhaled corticosteroids; ITT, intention-to-treat; L, litre; NR, not reported; RR, relative risk or rate ratio

TABLE 50 EFFICACY RESULTS OF THE DUPILUMAB QUEST STUDY (CASTRO 2018) – UNCONTROLLED, PERSISTENT ASTHMA – SUBGROUP WITH INCREASED FENO

Trial name:	A randomised, double blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of dupilumab in patients with persistent asthma LIBERTY ASTHMA QUEST										
NCT number:	02414854										
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome (population/subgroup)	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**	**RR**	**95% CI**	**P value**		
Annualised rate of severe exacerbations (FeNO ≥25 ppb)	Dupilumab	299	0.35 (0.27; 0.45)	NR	NR	NR	0.35[a]	0.25; 0.50	<0.0001	A negative binomial regression model, including the 4 intervention groups, age, geographic region, baseline EOS strata, baseline dose of ICS, and number of exacerbations in the previous year as covariates[b]	SmPC p21
	Placebo	162	1.00 (0.78; 1.30)								
Proportion of patients with 0 exacerbations in the 52-wk treatment period (%) (FeNO ≥25 ppb)	Dupilumab	299	76.9 (72.1; 81.7)	NR	NR	NR	NR	NR	NR	-	Castro 2019 table S7
	Placebo	162	56.2 (48.5; 63.8)								
Change from baseline to wk 52 in FEV1 (L) (FeNO ≥25 ppb)	Dupilumab	224	0.49 (0.431; 0.549)	0.3	0.22; 0.39	<0.0001	-	-	-	A mixed-effects model with repeated measures, including assigned intervention, age, sex, height, baseline EOS strata, baseline ICS dose, visit, intervention-by-visit interaction, the corresponding baseline value, and baseline-by-visit interaction as covariates	Castro 2019 table S1
	Placebo	124	0.18 (0.102; 0.258)								
Proportion of patients with ≥200 mL improvement in FEV1 (%) (FeNO ≥25 ppb)	Dupilumab	224	66.5 (60.3; 72.7)	NR	NR	NR	NR	NR	NR	-	Castro 2019 table S6
	Placebo	124	42.7 (34.0; 51.4)								

Trial name:	A randomised, double blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of dupilumab in patients with persistent asthma LIBERTY ASTHMA QUEST										
NCT number:	02414854										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome (population/subgroup)	Study arm	N	Result (CI)	Difference	95% CI	P value	RR	95% CI	P value		
Change from baseline to wk 52 in asthma control (ACQ-5) (ITT)	Dupilumab	631	-1.54 (-1.618; -1.462)	-0.39	-0.53; -0.25	NR	-	-	-	A mixed-effects model with repeated measures, including assigned intervention, age, baseline EOS strata, baseline ICS dose, visit, intervention-by-visit interaction, the corresponding baseline value, and baseline-by-visit interaction as covariates	Castro 2018, table S6
	Placebo	317	-1.15 (-1.268; -1.032)								
Change from baseline to wk 52 in quality of life (AQLQ) (ITT)	Dupilumab	631	1.28 (1.202; 1.358)	0.29	0.15; 0.44	NR	-	-	-		Castro 2018, table S6
	Placebo	317	0.99 (0.872; 1.108)								

[a] Rate ratio; [b] All severe exacerbations that occurred during the 52-week treatment period were included regardless of whether the patient remained on treatment

No results were reported for sick leave in this study. Safety results (including discontinuations) are reported in Table 53 for the safety population

-, not applicable; ACQ-5, 5-item Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; CI, confidence interval; EOS, blood eosinophils; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 s; ICS, inhaled corticosteroids; ITT, intention-to-treat; L, litre; NR, not reported; RR, relative risk or rate ratio

TABLE 51 RESULTS OF THE DUPILUMAB VENTURE STUDY (RABE 2018) – OCS-DEPENDENT ASTHMA – SUBGROUP WITH INCREASED FENO

Trial name:	A randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of dupilumab in patients with severe steroid dependent asthma LIBERTY ASTHMA VENTURE										
NCT number:	02528214										
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**	**RR**	**95% CI**	**P value**		
Annualised rate of severe exacerbations (FeNO ≥25 ppb)[a]	Dupilumab	57	0.459 (0.130; 0.788)	NR	NR	NR	0.326	0.117; 0.905	NR	A negative binomial regression model was used	Rabe 2018 table S7
	Placebo	57	1.407 (0.778; 2.036)								
Proportion of patients with 0 exacerbations in the 24-wk treatment period (%) (FeNO ≥25 ppb)	Dupilumab	57	80.7 (70.5; 90.9)	NR	NR	NR	NR	NR	NR	-	Rabe 2019 table A3
	Placebo	57	43.9 (31.0; 56.7)								
Mean % reduction in daily OCS maintenance dose (FeNO ≥25 ppb)[a]	Dupilumab	55	78.01 (64.96; 91.06)	34.75	18.66; 54.05	NR	-	-	-	An analysis of covariance model including % reduction in OCS dose at wk 24 as the response variable, with treatment group, optimised OCS dose at baseline, geographic region, and baseline EOS subgroup as covariates[b]	Rabe 2018 table S7
	Placebo	57	43.26 (31.30; 55.22)								
Proportion of patients with no OCS use (%) (ITT)	Dupilumab	103	48.0 (36.0; 59.0)	NR	NR	NR	OR: 2.74	1.47; 5.10	0.002	NR	Rabe 2018 table S3
	Placebo	107	25.0 (17.0; 35.0)								
Proportion of patients with ≥50% reduction in OCS use (%) (ITT)	Dupilumab	103	80.0 (70.0; 87.0)	NR	NR	NR	OR: 3.98	2.06; 7.67	<0.001	NR	Rabe 2018 table S3
	Placebo	107	50.0 (40.0; 61.0)								
Change from baseline to wk 24 in FEV1 (L) (FeNO ≥25 ppb)[a]	Dupilumab	54	0.24 (0.091; 0.389)	0.25	0.04; 0.45	NR	-	-	-	Mixed-effects models with repeated measures including treatment group, age, gender, height, baseline optimised OCS dose strata, geographic region, baseline EOS level, number of visits, treatment-by-visit interaction, baseline lung function measurement, and baseline-by-visit interaction as covariates	Rabe 2018 table S7
	Placebo	55	0.0 (-0.137; 0.137)								

Trial name:	A randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of dupilumab in patients with severe steroid dependent asthma LIBERTY ASTHMA VENTURE										
NCT number:	02528214										
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**	**RR**	**95% CI**	**P value**		
Proportion of patients with ≥200 mL improvement in FEV1 (%) (FeNO ≥25 ppb)	Dupilumab	54	55.6 (42.3; 68.8)	NR	NR	NR	NR	NR	NR	-	Rabe 2019 table A1
	Placebo	55	36.4 (23.7; 49.1)								
Change from baseline to wk 24 in asthma control (ACQ-5) (ITT)	Dupilumab	96	-1.05 (-1.266; -0.834)	-0.47	-0.76; -0.18	NR	-	-	-	A mixed effects model with a repeated-measures approach was used	Rabe 2018 p2482 (difference) Ford 2019 poster figure 2 (means)
	Placebo	99	-0.57 (-0.766; -0.374)								
Change from baseline to wk 24 in quality of life (AQLQ) (ITT)	Dupilumab	98	0.89 (0.694; 1.086)	NR	NR	NR	-	-	-	-	Ford 2019 poster figure 3
	Placebo	100	0.54 (0.344; 0.736)								

[a] Results were pooled for the 2 subgroups reported: FeNO≥25 to 50 ppb and FeNO≥50ppb; [b] For patients who discontinued the study or had missing data regarding the OCS dose at week 24 in the primary analysis, the missing data were handled with the use of a pattern-mixture model by multiple imputations

Sick leave was not reported in this study. Safety results (including discontinuations) are reported in Table 54 for the safety population

-, not applicable; ACQ-5, 5-item Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; CI, confidence interval; EOS, blood eosinophils; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 s; ITT, intention-to-treat; L, litre; NR, not reported; OCS, oral corticosteroids; RR, relative risk or rate ratio

TABLE 52 SAFETY RESULTS OF DUPILUMAB STUDY DRI12544 (WENZEL 2016) – UNCONTROLLED, PERSISTENT ASTHMA

Trial names:	A randomized, double-blind, placebo-controlled, dose-ranging study to evaluate dupilumab in patients with moderate to severe uncontrolled asthma										
NCT numbers:	01854047										
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**	**RR**	**95% CI**	**P value**		
Proportion of patients with SAE (total) (%)	Dupilumab	148	6.8 (2.7; 10.8)	NR	NR	NR	NR	NR	NR	-	Wenzel 2016 table 4
	Placebo	158	5.7 (2.1; 9.3)								
Proportion of patients discontinued from the study (%)	Dupilumab	148	7.4 (3.2; 11.7)	NR	NR	NR	NR	NR	NR	-	Wenzel 2016 figure 1
	Placebo	158	7.6 (3.5; 11.7)								

-, not applicable; CI, confidence interval; NR, not reported; RR, relative risk; SAE, serious adverse event

TABLE 53 SAFETY RESULTS OF DUPILUMAB STUDY QUEST (CASTRO 2018) – UNCONTROLLED, PERSISTENT ASTHMA

Trial names:	A randomised, double blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of dupilumab in patients with persistent asthma LIBERTY ASTHMA QUEST										
NCT numbers:	02414854										
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**	**RR**	**95% CI**	**P value**		
Proportion of patients with SAE (total) (%)	Dupilumab	631	7.8 (5.7;9.9)	NR	NR	NR	NR	NR	NR	-	Castro 2018 table 2
	Placebo	313	8.3 (5.2;11.4)								
Proportion of patients discontinued from the study (%)	Dupilumab	631	11.1 (8.6; 13.5)	NR	NR	NR	NR	NR	NR	-	Castro 2018 figure S2
	Placebo	317	12.0 (8.4; 15.6)								

-, not applicable; CI, confidence interval; NR, not reported; RR, relative risk; SAE, serious adverse event

TABLE 54 SAFETY RESULTS OF THE DUPILUMAB VENTURE STUDY (RABE 2018) – OCS-DEPENDENT ASTHMA

Trial names:	A randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of dupilumab in patients with severe steroid dependent asthma LIBERTY ASTHMA VENTURE										
NCT numbers:	02528214										
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**	**RR**	**95% CI**	**P value**		
Proportion of patients with SAE (total) (%)	Dupilumab	103	8.7 (3.3; 14.2)	NR	NR	NR	NR	NR	NR	-	Rabe 2018 table 2
	Placebo	107	5.6 (1.2; 10.0)								
Proportion of patients discontinued from the study (%)	Dupilumab	103	1.9 (0.0; 4.6)	NR	NR	NR	NR	NR	NR	-	Rabe 2018 table 2
	Placebo	107	4.7 (0.7; 8.7)								

CI, confidence interval; NR, not reported; RR, relative risk; SAE, serious adverse event

8.5.2 Mepolizumab studies

TABLE 55 RESULTS OF THE MEPOLIZUMAB DREAM STUDY (PAVORD 2012) – UNCONTROLLED, REFRACTORY ASTHMA

Trial name:	A multicenter, randomised, double-blind, placebo-controlled, parallel group, dose ranging study to determine the effect of mepolizumab on exacerbation rates in subjects with severe uncontrolled refractory asthma. DREAM										
NCT number:	01000506										
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**	**RR**	**95% CI**	**P value**		
Annualised rate of clinically significant exacerbations	Mepolizumab	153	1.24[a]	NR	NR	NR	0.52[b]	0.39; 0.69	NR	A negative binomial model including covariates for treatment group, use of maintenance OCS, region, number of exacerbations in the year before the study and baseline % of predicted FEV	Pavord 2012 table 2
	Placebo	155	2.4[a]								
Proportion of patients with 0 exacerbations in the 52-week treatment period (%)	Mepolizumab	153	54.2 (46.4; 62.1)	NR	NR	NR	NR	NR	NR	-	Pavord 2012 figure 2B
	Placebo	155	32.9 (25.5; 40.3)								
Change from baseline to wk 52 in FEV1 (L)	Mepolizumab	153	0.121 (0.047; 0.195)	0.061	-0.039; 0.161	NR	-	-	-	Mixed model repeated measures methods (including covariates plus baseline value), visit and interaction terms for visit by baseline, and visit by treatment group	Pavord 2012 table 2
	Placebo	155	0.060 (-0.014; 0.134)								
Change from baseline to wk 52 in asthma control (ACQ-6)	Mepolizumab	153	-0.75 (-0.926; -0.574)	-0.16	-0.39; 0.07	NR	-	-	-		Pavord 2012 table 2
	Placebo	155	-0.59 (-0.766; -0.414)								
Change from baseline to wk 52 in quality of life (AQLQ)	Mepolizumab	153	0.80 (0.624; 0.976)	0.08	-0.16; 0.32	NR	-	-	-		Pavord 2012 table 2
	Placebo	155	0.71 (0.534; 0.886)								
Proportion of patients with SAEs (%)	Mepolizumab	153	13.1 (7.7; 18.4)	NR	NR	NR	NR	NR	NR	-	Pavord 2012 table 3
	Placebo	155	16.1 (10.3; 21.9)								
Proportion of patients discontinued from the study (%)	Mepolizumab	153	15.7 (9.9; 21.4)	NR	NR	NR	NR	NR	NR	-	Pavord 2012 figure 1
	Placebo	155	18.1 (12.0; 24.1)								

[a] No measures of variability reported; [b] Rate ratio

All data up to the time of study discontinuation were included for patients who withdrew prematurely.

Proportion of patients with ≥200 mL improvement in FEV1 and sick leave were not reported in this study

-, not applicable; ACQ-6, 6-item Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; CI, confidence interval; FEV1, forced expiratory volume in 1 s; L, litre; NR, not reported; OCS, oral corticosteroids; RR, relative risk or rate ratio; SAE, serious adverse event

TABLE 56 RESULTS OF THE MEPOLIZUMAB MENSA STUDY (ORTEGA 2014) – UNCONTROLLED, REFRACTORY ASTHMA

Trial name:	MEA115588 A randomised, double-blind, double-dummy, placebo-controlled, parallel-group, multi-centre study of the efficacy and safety of mepolizumab adjunctive therapy in subjects with severe uncontrolled refractory asthma. MENSA										
NCT number:	01691521										
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**	**RR**	**95% CI**	**P value**		
Annualised rate of clinically significant exacerbations[a]	Mepolizumab	385	0.88	NR	NR	<0.001	NR	NR	NR	A negative binomial model that included covariates for treatment, use of maintenance OCS, geographic region, number of exacerbations in the previous year, and baseline percentage of the predicted FEV1	Ortega 2014 table 2
	Placebo	191	1.74								
Change from baseline to wk 32 in FEV1 (L)[a]	Mepolizumab	385	0.185 (0.142; 0.228)	0.099	0.038; 0.160	NR	-	-	-	A mixed-model, repeated-measures method that included covariates for treatment, use of maintenance OCS, geographic region, number of exacerbations in the previous year, baseline percentage of the predicted FEV1, baseline value, visit, and terms for the interaction of visit with baseline value and of visit with treatment group	Ortega 2014 table 2
	Placebo	191	0.086 (0.025; 0.147)								
Change from baseline to wk 32 in asthma control (ACQ-5)[a]	Mepolizumab	385	-0.93 (-1.028; -0.832)	-0.43	-0.564; -0.29	<0.001	-	-	-		Ortega 2014 table 2
	Placebo	191	-0.5 (-0.637; -0.363)								
Change from baseline to wk 32 in quality of life (SGRQ)[a]	Mepolizumab	385	-15.7 (-17.293;-14.107)	-6.7	-9.1; -4.4	<0.001	-	-	-		Ortega 2014 table 2
	Placebo	191	-9.0 (-11.352; -6.648)								
Proportion of patients with SAEs (%)	Mepolizumab	385	7.8 (5.1; 10.5)	NR	NR	NR	NR	NR	NR	-	Ortega 2014 table 3
	Placebo	191	14.1 (9.2; 19.1)								
Proportion of patients discontinued from the study (%)	Mepolizumab	385	6.5 (4.0; 9.0)	NR	NR	NR	NR	NR	NR	-	Ortega 2014 figure 1B
	Placebo	191	6.3 (2.8; 9.7)								

[a] Results pooled for the 75 mg IV and 100 mg SC groups

Proportion of patients with 0 exacerbations, proportion of patients with ≥200 mL improvement in FEV1 and sick leave were not reported in this study

-, not applicable; ACQ-5, 5-item Asthma Control Questionnaire; CI, confidence interval; FEV1, forced expiratory volume in 1 s; IV, intravenous; L, litre; NR, not reported; OCS, oral corticosteroids; RR, relative risk or rate ratio; SAE, serious adverse event; SC, subcutaneous; SGRQ, St. George's Respiratory Questionnaire

TABLE 57 RESULTS OF THE MEPOLIZUMAB MUSCA STUDY (CHUPP 2017) – UNCONTROLLED, REFRACTORY ASTHMA

Trial name:	A randomised, double-blind, placebo-controlled, parallel-group, multi-centre 24-week study to evaluate the efficacy and safety of mepolizumab adjunctive therapy in subjects with severe eosinophilic asthma on markers of asthma control										
NCT number:	02281318										
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**	**RR**	**95% CI**	**P value**		
Annualised rate of clinically significant exacerbations	Mepolizumab	274	0.51[a]	NR	NR	NR	0.42[b]	0.31; 0.56	0.0001	Negative binomial regression with region, baseline maintenance OCS therapy, exacerbations in the year before the study, and baseline percentage of predicted FEV1 as covariates	Chupp 2017 table 3
	Placebo	277	1.21[a]								
Change from baseline to wk 24 in FEV1 (L)	Mepolizumab	264	0.176 (0.125; 0.227)	0.120	0.047; 0.192	0.001	-	-	-	Mixed-effect model repeat measures adjusting for baseline values, region, baseline maintenance OCS therapy, exacerbations in the 12 months before the study, baseline percentage of predicted FEV1 (excluding lung function endpoints), and interaction terms for visit by baseline and visit by treatment group as covariates	Chupp 2017 table 3
	Placebo	259	0.056 (0.005; 0.107)								
Change from baseline to wk 24 in asthma control (ACQ-5)	Mepolizumab	266	-0.8 (-0.996; -0.604)	-0.4	-0.6; -0.2	<0.0001	-	-	-		Chupp 2017 table 2
	Placebo	261	-0.4 (-0.596; -0.204)								
Change from baseline to wk 24 in quality of life (SGRQ)	Mepolizumab	265	-15.6 (-17.560;-13.640)	-7.7	-10.5; -4.9	<0.0001	-	-	-		Chupp 2017 table 2
	Placebo	260	-7.9 (-9.860; -5.940)								
Proportion of patients with SAEs (total) (%)	Mepolizumab	273[c]	5.5 (2.8; 8.2)	NR	NR	NR	NR	NR	NR	-	Chupp 2017 table 4
	Placebo	278[c]	7.9 (4.7; 11.1)								
Proportion of patients discontinued from the study (%)	Mepolizumab	274	1.8 (0.2; 3.4)	NR	NR	NR	NR	NR	NR	-	Chupp 2017 figure 2
	Placebo	277	5.1 (2.5; 7.6)								

[a] No measures of variability reported; [b] Rate ratio; [c] 1 patient assigned to mepolizumab received placebo in error. Therefore, 273 patients were included in the mepolizumab safety population and 278 in the placebo safety population

Proportion of patients with 0 exacerbations, proportion of patients with ≥200 mL improvement in FEV1 and sick leave were not reported in this study

-, not applicable; ACQ-5, 5-item Asthma Control Questionnaire; CI, confidence interval; FEV1, forced expiratory volume in 1 s; L, litre; NR, not reported; OCS, oral corticosteroids; RR, relative risk or rate ratio; SAE, serious adverse event; SGRQ, St. George's Respiratory Questionnaire

TABLE 58 RESULTS OF THE MEPOLIZUMAB SIRIUS STUDY (BEL 2014) – OCS-DEPENDENT ASTHMA

Trial name:	MEA115575: A randomised, double-blind, placebo-controlled, parallel-group, multicenter study of mepolizumab adjunctive therapy to reduce steroid use in subjects with severe refractory asthma										
NCT number:	01691508										
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**	**RR**	**95% CI**	**P value**		
Annualised rate of clinically significant exacerbations	Mepolizumab	69	1.44[a]	NR	NR	NR	0.68[b]	0.47; 0.99	0.04	A negative binomial generalized linear model with a log-link function with adjustment for covariates (region, duration of use of OCS (<5 years *vs* ≥5 years) and baseline OCS dose)	Bel 2014 p1194-1195
	Placebo	66	2.12[a]								
Median % reduction in daily OCS maintenance dose	Mepolizumab	69	50 (20.0; 75.0)	NR	NR	0.007	NR	NR	NR	The Wilcoxon test	Bel 2014 table 2
	Placebo	66	0 (-20.2; 33.3)								
Proportion of patients with no OCS use (%)	Mepolizumab	69	14.5 (6.2; 22.8)	NR	NR	NR	OR: 1.67	0.49; 5.75	0.41	A binary logistic-regression model with adjustment for covariates (region, duration of use of OCS (<5 years *vs* ≥5 years) and baseline OCS dose). For patients who withdrew from the study before the maintenance phase, a value equal to the minimum percent reduction in oral glucocorticoid use for all patients was imputed for the analysis	Bel 2014 table 2
	Placebo	66	7.6 (1.2; 14.0)								
Proportion of patients with ≥50% reduction in OCS use (%)	Mepolizumab	69	53.6 (41.9; 65.4)	NR	NR	NR	OR: 2.26	1.10; 4.65	0.03		Bel 2014 table 2
	Placebo	66	33.3 (22.0; 44.7)								
Change from baseline to wk 24 in FEV1 (L)	Mepolizumab	69	0.111 (0.003; 0.219)	0.114	-0.042; 0.271	0.15	-	-	-		EPAR p60-61
	Placebo	66	-0.004 (-0.116; 0.108)								
Change from baseline to wk 24 in asthma control (ACQ-5)	Mepolizumab	69	-0.61 (-0.865; -0.355)	-0.52	-0.87; -0.17	0.004	-	-	-	A mixed-model, repeated-measures analysis with adjustment for covariates (region, duration of use of OCS (<5 years *vs* ≥5 years) and baseline OCS dose)	EPAR p60-61 and Bel 2014 p1195
	Placebo	66	-0.09 (-0.345; 0.165)								
Change from baseline to wk 24 in quality of life (SGRQ)	Mepolizumab	69	-8.8 (-12.132; -5.468)	-5.8	-10.6; -1.0	0.02					EPAR p60-61 and Bel 2014 p1195
	Placebo	66	-3.1 (-6.432; 0.232)								

Trial name:	MEA115575: A randomised, double-blind, placebo-controlled, parallel-group, multicenter study of mepolizumab adjunctive therapy to reduce steroid use in subjects with severe refractory asthma										
NCT number:	01691508										
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**	**RR**	**95% CI**	**P value**		
Proportion of patients with SAEs (%)	Mepolizumab	69	1.4 (0.0; 4.3)	NR	NR	NR	NR	NR	NR	-	Bel 2014 table 3
	Placebo	66	18.2 (8.9; 27.5)								
Proportion of patients discontinued from the study (%)	Mepolizumab	69	4.3 (0.0; 9.2)	NR	NR	NR	NR	NR	NR	-	Bel 2014 figure 1
	Placebo	66	6.1 (0.3; 11.8)								

[a] No measures of variability reported; [b] Rate ratio

Proportion of patients with 0 exacerbations, proportion of patients with ≥200 mL improvement in FEV1 and sick leave were not reported in this study

-, not applicable; ACQ-5, 5-item Asthma Control Questionnaire; CI, confidence interval; FEV1, forced expiratory volume in 1 s; L, litre; NR, not reported; OCS, oral corticosteroids; RR, relative risk or rate ratio; SAE, serious adverse event; SGRQ, St. George's Respiratory Questionnaire

8.5.3 Omalizumab studies

TABLE 59 RESULTS OF THE OMALIZUMAB BUSSE 2001 STUDY

Trial name:	Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma										
NCT number:	Not found Study numbered 008C/E in the EPAR										
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**	**RR**	**95% CI**	**P value**		
Annualised rate of clinically significant exacerbations	Omalizumab	268	0.468[a]	-0.374[b]	NR	NR	0.556[c]	0.409; 0.756	<0.001	Poisson regression. Imputed values were used for discontinued patients	EPAR p20
	Placebo	257	0.842[a]								
Proportion of patients with 0 exacerbations in the 16-wk steroid-stable phase (%)	Omalizumab	268	85.4 (81.2; 89.7)	NR	NR	NR	NR	NR	NR	-	Busse 2001 table 3
	Placebo	257	76.7 (71.5; 81.8)								
Proportion of patients with SAEs during the 52-wk study (%)	Omalizumab	268	4.1 (1.7; 6.5)	NR	NR	NR	NR	NR	NR	-	Busse 2001 p188 and Lanier p157-158
	Placebo	257	4.7 (2.1; 7.2)								
Proportion of patients discontinued from the 52-wk study (%)	Omalizumab	268	11.6 (7.7; 15.4)	NR	NR	NR	NR	NR	NR	-	Busse 2001 p186 and Lanier p156
	Placebo	257	16.3 (11.8; 20.9)								

[a] No measures of variability reported; [b] Calculated difference omalizumab – placebo. In the EPAR (p20) the difference is shown as 0.373 (positive); [c] Rate ratio

FEV1, proportion of patients with ≥200 mL improvement in FEV1, asthma control, quality of life and sick leave were not reported in this study

-, not applicable; CI, confidence interval; EPAR, European Public Assessment Report; FEV1, forced expiratory volume in 1 s; IgE, immunoglobulin E; NR, not reported; RR, relative risk or rate ratio; SAE, serious adverse event

TABLE 60 RESULTS OF THE OMALIZUMAB SOLER 2001 STUDY

Trial name:	The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics										
NCT number:	Not found Study numbered 009C/E in the EPAR										
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**	**RR**	**95% CI**	**P value**		
Annualised rate of clinically significant exacerbations	Omalizumab	274	0.376[a]	-0.522[b]	NR	NR	0.419[c]	0.309; 0.568	<0.001	Poisson regression. Imputed values were used for discontinued patients	EPAR p20
	Placebo	272	0.898[a]								
Proportion of patients with 0 exacerbations in the 16-wk steroid-stable phase	Omalizumab	274	87.2 (83.3; 91.2)	NR	NR	NR	NR	NR	NR	-	Soler 2001 table 3
	Placebo	272	69.5 (64.0; 75.0)								
Change from baseline to wk 16 in quality of life (AQLQ)	Omalizumab	274	0.883 (0.781; 0.985)	NR	NR	<0.001	-	-	-	Analysis of covariance model, fitting centre, sex, treatment schedule and treatment as factors and baseline as a covariate	Buhl 2002b p1090 and figure 2a
	Placebo	272	0.592 (0.474; 0.710)								
Proportion of patients with SAEs during the 52-wk study (%)	Omalizumab	274	6.6 (3.6; 9.5)[d]	NR	NR	NR	NR	NR	NR	-	Soler 2001 p258 and Buhl 2002a p76
	Placebo	272	7.0 (4.0; 10.0)[d]								
Proportion of patients discontinued from the 52-wk study (%)	Omalizumab	274	10.6 (6.9; 14.2)[d]	NR	NR	NR	NR	NR	NR	-	Soler 2001 p256 and Buhl 2002a p75
	Placebo	272	24.3 (19.2; 29.4)[d]								

[a] No measures of variability reported; [b] Calculated difference omalizumab – placebo. In the EPAR (p20) the difference is shown as 0.522 (positive); [c] Rate ratio; [d] Events pooled for the main and extension period and N used for the main period (=ITT)

FEV1, proportion of patients with ≥200 mL improvement in FEV1, asthma control and sick leave were not reported in this study

-, not applicable; AQLQ, Asthma Quality of Life Questionnaire; CI, confidence interval; EPAR, European Public Assessment Report; FEV1; forced expiratory volume in 1 s IgE, immunoglobulin E; NR, not reported; RR, relative risk or rate ratio; SAE, serious adverse event

TABLE 61 RESULTS OF THE OMALIZUMAB HOLGATE 2004 STUDY

Trial name:	Efficacy and safety of a recombinant anti-immunoglobulin E antibody (omalizumab) in severe allergic asthma										
NCT number:	Not found Study numbered 011 in the EPAR										
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**	**RR**	**95% CI**	**P value**		
Annualised rate of clinically significant exacerbations	Omalizumab	176[a]	0.878[b]	-0.388[c]	NR	NR	0.694[d]	0.432; 1.114	0.130	Poisson regression	EPAR p20
	Placebo	165[a]	1.266[b]								
Proportion of patients with SAEs (%)	Omalizumab	126	0.8 (0.0; 2.3)	NR	NR	NR	NR	NR	NR	-	Holgate 2004 p635
	Placebo	120	4.2 (0.6; 7.7)								
Proportion of patients discontinued from the study (%)	Omalizumab	126	8.7 (3.8; 13.7)	NR	NR	NR	NR	NR	NR	-	Holgate 2004 p634
	Placebo	120	9.2 (4.0; 14.3)								

[a] Including additional 50 (omalizumab) and 45 (placebo) OCS-dependent patients. Numbers are reported for total N=339 and not for N=341; not clear in which group patients are missing, so ITT used; [b] No measures of variability reported; [c] Calculated difference omalizumab – placebo. In the EPAR (p20) the difference is shown as 0.388 (positive); [d] Rate ratio

Proportion of patients with 0 exacerbations, FEV1, proportion of patients with ≥200 mL improvement in FEV1, asthma control, quality of life and sick leave were not reported in this study

-, not applicable; CI, confidence interval; EPAR; European Public Assessment Report; FEV1; forced expiratory volume in 1 s; ITT, intention-to-treat; NR, not reported; OCS, oral corticosteroid; RR, relative risk or rate ratio; SAE, serious adverse event

TABLE 62 RESULTS OF THE OMALIZUMAB VIGNOLA 2004 STUDY

Trial name:	Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with concomitant allergic asthma and persistent allergic rhinitis: SOLAR										
NCT number:	Not found Study numbered 2304 in the EPAR										
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**	**RR**	**95% CI**	**P value**		
Annualised rate of clinically significant exacerbations	Omalizumab	209	0.454[a]	-0.216[b]	NR	NR	0.678[c]	0.432; 1.062	0.090	Poisson regression. Imputed values were used for discontinued patients	EPAR p20
	Placebo	196	0.67[a]								
Proportion of patients with 0 exacerbations over 28 weeks (%)	Omalizumab	209	81.8 (76.6; 87.0)	NR	NR	NR	NR	NR	NR	-	Vignola 2004 p711
	Placebo	196	74.5 (68.4; 80.6)								
Change from baseline to wk 28 in quality of life (AQLQ)	Omalizumab	209	1.321 (1.186; 1.456)	NR	NR	<0.05	-	-	-	Analysis of covariance model. with terms for treatment and centre and baseline as a covariate. LOCF used where necessary	Vignola 2004 figure 1A
	Placebo	196	1.072 (0.931; 1.213)								
Proportion of patients with SAEs (%)	Omalizumab	209	1.4 (0.0; 3.0)	NR	NR	NR	NR	NR	NR	-	Vignola 2004 p713
	Placebo	196	1.5 (0.0; 3.2)								
Proportion of patients discontinued from the study (%)	Omalizumab	209	2.4 (0.3; 4.5)	NR	NR	NR	NR	NR	NR	-	Vignola 2004 p711
	Placebo	196	7.7 (3.9; 11.4)								

[a] No measures of variability reported; [b] Calculated difference omalizumab – placebo. In the EPAR (p20) the difference is shown as 0.216 (positive); [c] Rate ratio

FEV1, proportion of patients with ≥200 mL improvement in FEV1, asthma control and sick leave were not reported in this study

-, not applicable; AQLQ, Asthma Quality of Life Questionnaire; CI, confidence interval; EPAR; European Public Assessment Report; FEV1; forced expiratory volume in 1 s; LOCF, last observation carried forward; NR, not reported; RR, relative risk or rate ratio; SAE, serious adverse event

TABLE 63 RESULTS OF THE OMALIZUMAB AYRES 2004 STUDY

Trial name:	Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with poorly controlled (moderate-to-severe) allergic asthma.										
NCT number:	Not found Study numbered 2304 in the EPAR										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome (population/subgroup)	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**	**RR**	**95% CI**	**P value**		
Annualised rate of clinically significant exacerbations (severe)	Omalizumab	115	1.26[a]	NR	NR	NR	0.41	0.288; 0.583	<0.001	Poisson regression. Imputation was used for patients who were withdrawn prematurely from the study	Niven 2008 p1373
	BSC	49	3.06[a]								
Proportion of patients with 0 exacerbations over 12 months (%) (ITT)	Omalizumab	206	49.5 (42.7; 56.3)	NR	NR	NR	NR	NR	NR	-	Ayres 2004 p703
	BSC	106	26.4 (18.0; 34.8)								
Proportion of patients with 0 exacerbations over 12 months (%) (severe)	Omalizumab	115	40.0 (31.0; 49.0)	NR	NR	NR	NR	NR	NR	-	Niven 2008 table 2
	BSC	49	34,7 (21.4; 48.0)								
Change from baseline to 1 year in FEV1 (L) (severe)	Omalizumab	115	0.16[b]	NR	NR	NR	NR	NR	NR	-	Niven 2008 p1373-1374
	BSC	49	-0.15[b]								
Proportion of patients with SAEs (%) (ITT)	Omalizumab	206	16.5 (11.4; 21.6)	NR	NR	NR	NR	NR	NR	-	Ayres 2004 p706
	BSC	106	13.2 (6.8; 19.7)								
Proportion of patients discontinued from the study[c] (%) (ITT)	Omalizumab	206	7.3 (3.7; 10.8)	NR	NR	NR	NR	NR	NR	-	Ayres 2004 p706
	BSC	106	0.0 (0.0; 2.8)[d]								
Sick leave; number of days absent due to asthma[e] (ITT)	Omalizumab	191	14 (1-365)[f]	NR	NR	NR	NR	NR	NR	-	Ayres 2004 table 3
	BSC	89	28 (1-259)[f]								
Sick leave; number of days absent due to asthma[e] (severe)	Omalizumab	115	15.5 (1-365)[f]	NR	NR	NR	NR	NR	NR	-	Niven 2008 table 2
	BSC	49	46 (3-186)[f]								

[a] No measures of variability reported; [b] Calculated from baseline and year 1 values. CI not estimable; [c] a discontinued due to AE/SAE; [d] Discontinuations were not reported in the BSC arm, so assumed to be zero; [e] For patients experiencing this outcome; [f] Median (range)

Proportion of patients with ≥200 mL improvement in FEV1, asthma control and quality of life were not reported in this study

-, not applicable; AE, adverse event; BSC, best standard care; CI, confidence interval; EPAR; European Public Assessment Report; FEV1; forced expiratory volume in 1 s; ITT, intention-to-treat; L, litre; NR, not reported; RR, relative risk or rate ratio; SAE, serious adverse event

TABLE 64 RESULTS OF THE OMALIZUMAB HUMBERT 2005 STUDY

Trial name:	Ph III, 28-wk, multicenter, randomised, double-blind, placebo-controlled, parallel-group study to assess efficacy, safety, tolerability of sc omalizumab in adults and adolescents w/ severe persist. allergic asthma & are inadequately controlled despite GINA (2002) step 4 Tx. INNOVATE										
NCT number:	00046748										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome (population/subgroup)	Study arm	N	Result (CI)	Difference	95% CI	P value	RR	95% CI	P value		
Clinically significant exacerbation rate in 28 weeks (amendment ITT)[a]	Omalizumab	209	0.68 (0.53; 0.87)	NR	NR	NR	0.738	0.552; 0.998	NR	Poisson regression via generalised estimating equations, with treatment, dosing schedule, country grouping and asthma medication strata included as parameters in the model and history of exacerbations as covariate. Imputation was performed for patients discontinued prematurely	Humbert 2005 p311 and figure 1
	Placebo	210	0.91 (0.73; 1.14)								
Proportion of patients with 0 exacerbations over 28 weeks (%) (amendment ITT)[a]	Omalizumab	209	56.9 (50.2; 63.7)	NR	NR	NR	NR	NR	NR	-	EPAR p25
	Placebo	210	51.4 (44.7; 58.2)								
Change from baseline to wk 28 in FEV1 (L) (amendment ITT)[a]	Omalizumab	209	0.190[b]	NR	NR	NR	NR	NR	NR	-	Humbert 2005 p312
	Placebo	210	0.096[b]								
Change from baseline to wk 28 in quality of life (AQLQ) (amendment ITT)[a]	Omalizumab	204	0.91[c]	0.45	NR	<0.001	NR	NR	NR	ANCOVA with LOCF (as applicable), with asthma medication strata, country grouping, dosing schedule and baseline as covariates	Humbert 2005 table 4
	Placebo	205	0.46[c]								
Proportion of patients with SAEs (%) (ITT)	Omalizumab	245	11.8 (7.8; 15.9)	NR	NR	NR	NR	NR	NR	-	Humbert 2005 table 5
	Placebo	237	15.6 (11.0; 20.2)								
Proportion of patients discontinued from the study (%) (ITT)	Omalizumab	245	12.2 (8.1; 16.3)	NR	NR	NR	NR	NR	NR	-	Humbert 2005 p311 and table 5
	Placebo	237	9.3 (5.6; 13.0)								

[a] Efficacy analyses were performed on the patient population randomised after implementation of a protocol amendment; [b] Mean values, LSmeans not reported; [c] No measures of variability reported
Proportion of patients with ≥200 mL improvement in FEV1, asthma control and sick leave were not reported in this study
-, not applicable; ANCOVA, analysis of covariance; AQLQ, Asthma Quality of Life Questionnaire; CI, confidence interval; EPAR, European Public Assessment Report; FEV1, forced expiratory volume in 1 s; GINA, Global Initiative for Asthma; ITT, intention-to-treat; L, litre; LOCF, last observation carried forward; NR, not reported; RR, relative risk or rate ratio; SAE, serious adverse event

TABLE 65 RESULTS OF THE OMALIZUMAB OHTA 2009 STUDY

Trial name:	Study of omalizumab in moderate to severe bronchial asthma										
NCT number:	00232050										
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**	**RR**	**95% CI**	**P value**		
Proportion of patients with 0 exacerbations over 16 weeks (%)	Omalizumab	151	96.0 (92.9; 99.1)	NR	NR	NR	NR	NR	NR	-	Ohta 2009 figure 6
	Placebo	164	89.0 (84.2; 93.8)								
Proportion of patients with SAEs (%)	Omalizumab	151	4.0 (0.9; 7.1)	NR	NR	NR	NR	NR	NR	-	Ohta 2009 table 2
	Placebo	164	6.7 (2.9; 10.5)								
Proportion of patients discontinued from the study (%)	Omalizumab	151	8.6 (4.1; 13.1)	NR	NR	NR	NR	NR	NR	-	Ohta p1158 and figure 1
	Placebo	164	17.1 (11.3; 22.8)								

Exacerbation rate, FEV1, proportion of patients with ≥200 mL improvement in FEV1, asthma control, quality of life and sick leave were not reported in this study

-, not applicable; CI, confidence interval; FEV1, forced expiratory volume in 1 s; NR, not reported; RR, relative risk; SAE, serious adverse event

TABLE 66 RESULTS OF THE OMALIZUMAB CHANEZ 2010 STUDY

Trial name:	Double blind placebo controlled study to assess the expression of IgE on basophils and dendritic cells during omalizumab treatment										
NCT number:	00454051										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**	**RR**	**95% CI**	**P value**		
Proportion of patients with 0 exacerbations over 16 weeks (%)	Omalizumab	20	45.0 (23.2; 66.8)	NR	NR	NR	NR	NR	NR	-	Chanez 2010 p1615
	Placebo	11	63.6 (35.2; 92.1)								
Proportion of patients with SAEs (%)	Omalizumab	20	0 (0.0; 15.0)	NR	NR	NR	NR	NR	NR	-	Chanez 2010 p1616
	Placebo	11	9.1 (0.0; 26.1)								
Proportion of patients discontinued from the study (%)	Omalizumab	20	15.0 (0.0; 30.6)	NR	NR	NR	NR	NR	NR	-	Chanez 2010 figure 1
	Placebo	11	27.3 (1.0; 53.6)								

Exacerbation rate, FEV1, proportion of patients with ≥200 mL improvement in FEV1, asthma control, quality of life and sick leave were not reported in this study

-, not applicable; CI, confidence interval; FEV1, forced expiratory volume in 1 s; IgE, immunoglobulin E; NR, not reported; RR, relative risk; SAE, serious adverse event

TABLE 67 RESULTS OF THE OMALIZUMAB BOUSQUET 2011 STUDY

Trial name:	A randomised, open label, parallel-group, international, multicenter study evaluating persistency of response to omalizumab during 32 weeks treatment given as add on to optimized asthma therapy in adult and adolescent patients with severe persistent allergic asthma, who remain inadequately controlled despite GINA (2004) step 4 therapy										
NCT number:	00264849										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome (population/subgroup)	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**	**RR**	**95% CI**	**P value**		
Clinically significant exacerbation rate over 32 weeks (mITT)	Omalizumab	272	0.55[a]	NR	NR	NR	0.57[b]	0.417; 0.778	<0.001	Analysed using a Poisson regression model	Bousquet 2011 table 4
	OAT	128	0.98[a]								
Median % reduction in daily OCS maintenance dose (severe subgroup)	Omalizumab	59	45 (32.2; 57.8)[c]	NR	NR	NR	NR	NR	NR	-	Siergiejko 2011 table 2
	OAT	23	-18.3 (-53.1; 16.5)[c]								
Proportion of patients with no OCS use (%) (severe subgroup)	Omalizumab	59	32.2 (20.3; 44.1)	NR	NR	NR	NR	NR	NR	-	Siergiejko 2011 p2225
	OAT	23	13.0 (0.0; 26.8)								
Change from baseline to wk 32 in FEV1 (L) (severe subgroup)	Omalizumab	NR	NR	0.13	0.03; 0.23	0.011	-	-	-	LS means changes from baseline compared using analysis of covariance	Bousquet 2011 p675
	OAT	NR	NR								
Change from baseline to wk 32 in asthma control (ACQ) (mITT)	Omalizumab	238	-0.91 (-1.07; -0.75)	-0.87	-1.09; -0.65	<0.001	-	-	-		Bousquet 2011 table 4
	OAT	104	-0.04 (-0.26; 0.18)								
Proportion of patients with SAEs (%) (safety population)	Omalizumab	274	12.0 (8.2; 15.9)	NR	NR	NR	NR	NR	NR	-	Bousquet 2011 table 5
	OAT	128	16.4 (10.0; 22.8)								
Proportion of patients discontinued from the study (%) (as-treated population)	Omalizumab	275	8.0 (4.8; 11.2)	NR	NR	NR	NR	NR	NR	-	Bousquet 2011 figure 1
	OAT	131	19.1 (12.4; 25.8)								

[a] No measures of variability reported; [b] Rate ratio; [c] Mean values, LSmeans not reported

Proportion of patients with 0 exacerbations, proportion of patients with ≥200 mL improvement in FEV1, quality of life and sick leave were not reported in this study. Proportion of patients with 50% reduction in OCS dose was not reported for the severe subgroup.

-, not applicable; ACQ, Asthma Control Questionnaire; CI, confidence interval; FEV1, forced expiratory volume in 1 s; GINA, Global Initiative for Asthma; mITT, modified intention-to-treat; L, litre; LS, least square; NR, not reported; OCS, oral corticosteroids; OAT, optimised asthma therapy; RR, relative risk or rate ratio; SAE, serious adverse event

TABLE 68 RESULTS OF THE OMALIZUMAB HANANIA 2011 STUDY

Trial name:	A phase IIIb multicenter, randomised, double-blind, placebo-controlled study of Xolair in subjects with moderate to severe persistent asthma who are inadequately controlled with high-dose inhaled corticosteroids and long-acting beta-agonists										
NCT number:	00314574[a]										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**	**RR**	**95% CI**	**P value**		
Exacerbation rate over 48 weeks	Omalizumab	427	0.66[b]	NR	NR	NR	0.75[c]	0.61; 0.92	0.006	Poisson regression with an overdispersion parameter and using the covariates dosing schedule, number of asthma exacerbations requiring systemic corticosteroids during the past year before screening and run-in period and concomitant asthma medications at baseline	Hanania 2011 table 2
	Placebo	421	0.88[b]								
Proportion of patients with 0 exacerbations over 48 weeks (%)	Omalizumab	427	64.4 (59.9; 68.9)	NR	NR	NR	NR	NR	NR	-	Hanania 2011 table 2
	Placebo	421	57.5 (52.8; 62.2)								
Change from baseline to wk 48 in asthma control (TASS)	Omalizumab	336	-1.9[d]	-0.26	-0.42; -0.10	NR	-	-	-	Mixed-effects models considered observed data across all visits and included treatment and time	Hanania 2011 figure 4
	Placebo	321	-1.6[d]								
Proportion of patients with SAEs (%)	Omalizumab	428	9.3 (6.6; 12.1)	NR	NR	NR	NR	NR	NR	-	Hanania 2011 table 3
	Placebo	420	10.5 (7.5; 13.4)								
Proportion of patients discontinued from the study (%)	Omalizumab	427	19.4 (15.7; 23.2)	NR	NR	NR	NR	NR	NR	-	Hanania 2011 figure 1
	Placebo	421	22.3 (18.3; 26.3)								

[a] In the publication, the NCT number is stated as NCT00314575, however, this number does not exist. The NCT number appears to be NCT00314574; [b] No measures of variability reported; [c] Rate ratio; [d] Calculated from baseline and week 48 values. CI not estimable

FEV1, proportion of patients with ≥200 mL improvement in FEV1 and sick leave were not reported in this study

-, not applicable; CI, confidence interval; FEV1, forced expiratory volume in 1 s; NR, not reported; RR, relative risk or rate ratio; SAE, serious adverse event; TASS, total asthma symptom severity

TABLE 69 RESULTS OF THE OMALIZUMAB BARDELAS 2012 STUDY

Trial name:	A 26-week, randomized, double-blind, parallel-group, placebo-controlled, multi-center study to evaluate the effect of omalizumab on improving the tolerability of specific immunotherapy in patients with at least moderate persistent allergic asthma inadequately controlled with inhaled corticosteroids										
NCT number:	00267202										
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**	**RR**	**95% CI**	**P value**		
Proportion of patients with 0 exacerbations over 24 weeks (%)	Omalizumab	136	89.7 (84.6; 94.8)	NR	NR	NR	NR	NR	NR	-	Bardelas 2012 p149
	Placebo	135	82.2 (75.8; 88.7)								
Change from baseline to wk 24 in FEV1	Omalizumab	136	0.08 (NR)	NR	-0.19; 0.02	0.123	NR	NR	NR	ANCOVA model with treatment, dosing regimen, baseline ACT total score, baseline IgE category (<150 or ≥150 IU/mL), baseline cockroach sensitivity and screening BMI category (<30 or ≥30 kg/m^2) as explanatory variables. Missing data were imputed using LOCF.	Bardelas 2012 table 4
	Placebo	135	0.16 (NR)								
Change from baseline to wk 24 in asthma control (ACT)	Omalizumab	136	5.01[a]	0.64	-0.30; 1.59	0.178	NR	NR	NR	ANCOVA model with treatment, dosing regimen, baseline ACT total score, baseline IgE category (<150 or ≥150 IU/mL), baseline cockroach sensitivity and screening BMI category (<30 or ≥30 kg/m^2) as explanatory variables. Missing data were imputed using LOCF.	Bardelas 2012 p148
	Placebo	135	4.36[a]								
Proportion of patients discontinued from the study (%)	Omalizumab	136	11.8 (6.3; 17.2)	NR	NR	NR	NR	NR	NR	-	Bardelas 2012 figure 2
	Placebo	135	9.6 (4.7; 14.6)								

[a] No measures of variability reported

Exacerbation rate, FEV1, proportion of patients with ≥200 mL improvement in FEV1, quality of life, SAEs and sick leave were not reported in this study

-, not applicable; ACT, Asthma Control Test; ANCOVA, analysis of covariance; BMI, body mass index; CI, confidence interval; FEV1, forced expiratory volume in 1 s; IgE, immunoglobulin E; LOCF, last observation carried forward; NR, not reported; RR, relative risk

TABLE 70 RESULTS OF THE OMALIZUMAB HOSHINO 2012 STUDY

Trial name:	Effects of adding omalizumab, an anti-immunoglobulin E antibody, on airway wall thickening in asthma										
NCT number:	Not found										
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**	**RR**	**95% CI**	**P value**		
Change from baseline to wk 16 in FEV1 (L)	Omalizumab	14	0.21[a]	NR	NR	NR	NR	NR	NR	-	Hoshino 2012 table 2
	Conventional therapy	16	0.02[a]								

[a] Calculated from baseline and week 16 values. CI not estimable

Exacerbation rate, proportion of patients with 0 exacerbations; proportion of patients with ≥200 mL improvement in FEV1, asthma control; quality of life, SAEs and sick leave were not reported in this study

-, not applicable; CI, confidence interval; FEV1, forced expiratory volume in 1 s; L, litre; NR, not reported; RR, relative risk

TABLE 71 RESULTS OF THE OMALIZUMAB RUBIN 2012 (QUALITX) STUDY

Trial name:	A randomized, open-label, multicenter study to evaluate the effect of Xolair (omalizumab) as add-on therapy to inhaled corticosteroid + long-acting beta agonist in fixed or flexible dosing compared to isolated inhaled corticosteroid + long-acting beta agonist in fixed or flexible dosing in the asthma-related quality of life in patients with severe persistent allergic asthma										
NCT number:	00567476										
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**	**RR**	**95% CI**	**P value**		
Proportion of patients with 0 exacerbations over 20 weeks (%)	Omalizumab	78	56.4 (45.4; 67.4)	NR	NR	NR	NR	NR	NR	-	Rubin 2012 p292
	ICS+LABA	38	47.4 (31.5; 63.2)								
Change from baseline to wk 20 in FEV1 (L)	Omalizumab	76	0.13 (0.052; 0.208)[a]	NR	NR	NR	NR	NR	NR	-	Rubin 2012 p291 and table 5
	ICS+LABA	37	-0.003 (-0.121; 0.115)[a]								
Change from baseline to wk 20 in quality of life (AQLQ)	Omalizumab	72	1.3 (1.104; 1.496)[a]	NR	NR	NR	NR	NR	NR	-	Rubin 2012 p290 and figure 1
	ICS+LABA	36	-0.1 (-0.296; 0.096)[a]								
Proportion of patients with SAEs (%)	Omalizumab	78	3.8 (0.0; 8.1)	NR	NR	NR	NR	NR	NR	-	Rubin 2012 p292
	ICS+LABA	38	0 (0.0; 7.9)								
Proportion of patients discontinued from the study (%)	Omalizumab	78	10.3 (3.5; 17.0)	NR	NR	NR	NR	NR	NR	-	Rubin 2012 table 1
	ICS+LABA	38	10.5 (0.8; 20.3)								

[a] Mean values, LSmeans not reported

Exacerbation rate, proportion of patients with ≥200 mL improvement in FEV1, asthma control and sick leave were not reported in this study

-, not applicable; AQLQ, Asthma Quality of Life Questionnaire; CI, confidence interval; FEV1, forced expiratory volume in 1 s; L, litre; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; NR, not reported; RR, relative risk; SAE, serious adverse event

TABLE 72 RESULTS OF THE OMALIZUMAB BUSSE 2013 STUDY

Trial name:	High eosinophil count: a potential biomarker for assessing successful omalizumab treatment effects										
NCT number:	Not found										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**	**RR**	**95% CI**	**P value**		
Exacerbation rate over 24 weeks	Omalizumab	157	0.21[a]	NR	NR	NR	0.73	0.44; 1.24	0.25	Poisson regression model adjusted for overdispersion. A non-parametric comparison between treatment groups was performed by using the rank-based van Elteren test with standardised mid-rank (modified ridit) weights. The analysis was adjusted for 2 covariates: dosing schedule and prior exacerbation status	Busse 2013 table 1
	Placebo	171	0.26[a]								
Proportion of patients with 0 exacerbations over 24 weeks (%)	Omalizumab	157	84.7 (79.1; 90.3)	NR	NR	NR	NR	NR	NR	-	Busse 2013 table 1
	Placebo	171	80.7 (74.8; 86.6)								
Change from baseline to wk 24 in FEV1 (L)	Omalizumab	157	0.055 (0.005; 0.105)[b]	NR	NR	NR	NR	NR	NR	-	Busse 2013 p486e2
	Placebo	171	-0.026 (-0.077; 0.025)[b]								
Proportion of patients with SAEs (%)	Omalizumab	157	2.5 (0.1; 5.0)	NR	NR	NR	NR	NR	NR	-	Busse 2013 table E4
	Placebo	171	3.5 (0.8; 6.3)								
Proportion of patients discontinued from the study (%)	Omalizumab	157	15.3 (9.7; 20.9)	NR	NR	NR	NR	NR	NR	-	Busse 2013 figure E1
	Placebo	171	11.7 (6.9; 16.5)								

[a] No measures of variability reported; [b] Mean values, LSmeans not reported

Proportion of patients with ≥200 mL improvement in FEV1, asthma control, quality of life and sick leave were not reported in this study.

-, not applicable; CI, confidence interval; FEV1, forced expiratory volume in 1 s; L, litre; NR, not reported; RR, relative risk; SAE, serious adverse event

TABLE 73 RESULTS OF THE OMALIZUMAB LI 2016 STUDY

Trial name:	A 24-week, phase III Randomised, double-blind, placebo controlled, parallel-group, multicenter study of Xolair® (omalizumab) in patients with moderate to severe persistent allergic asthma who remain not adequately controlled despite GINA (2009) step 4 therapy										
NCT number:	01202903										
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**	**RR**	**95% CI**	**P value**		
Change from baseline to wk 24 in asthma control (ACQ)	Omalizumab	210	-0.511 (-0.691; -0.331)	NR	NR	NR	NR	NR	NR	-	Li 2016 figure 3
	Placebo	211	-0.342 (-0.516; -0.168)								
Change from baseline to wk 24 in quality of life (AQLQ)	Omalizumab	182	0.51 (0.210; 0.810)	NR	NR	NR	NR	NR	NR	-	Li 2016 figure 5
	Placebo	178	0.10 (-0.208; 0.408)								
Proportion of patients with SAEs (%)	Omalizumab	310	1.9 (0.4; 3.5)	NR	NR	NR	NR	NR	NR	-	Li 2016 table 2
	Placebo	299	3.0 (1.1; 4.9)								
Proportion of patients discontinued from the study (%)	Omalizumab	308	3.6 (1.5; 5.6)	NR	NR	NR	NR	NR	NR	-	Li 2016 figure 1
	Placebo	308	5.2 (2.7; 7.7)								

Exacerbation rate, proportion of patients with 0 exacerbations, FEV, proportion of patients with ≥200 mL improvement in FEV1 and sick leave were not reported in this study. A rate ratio for exacerbations was reported as 0.61, p=0.097, but since no details were available on the exacerbation rate, the result was not comparable with the results from other studies and therefore not extracted

-, not applicable; ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; CI, confidence interval; FEV1, forced expiratory volume in 1 s; GINA, Global Initiative for Asthma; NR, not reported; RR, relative risk; SAE, serious adverse event

TABLE 74 RESULTS OF THE OMALIZUMAB MUKHERJEE 2019 STUDY

Trial name:	Randomised double blind placebo controlled trial of the steroid sparing effect of Xolair (omalizumab) in patients with persistent eosinophilic bronchitis										
NCT number:	02049294										
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**	**RR**	**95% CI**	**P value**		
Proportion of patients with 0 exacerbations over 32 weeks (%)	Omalizumab	4	75.0 (32.6;117.4)	NR	NR	NR	NR	NR	NR	-	Mukherjee 2019 p3
	Placebo	5	20.0 (0.0; 55.1)								
Proportion of patients discontinued from the study (%)	Omalizumab	5	20.0 (0.0; 55.1)	NR	NR	NR	NR	NR	NR	-	Mukherjee 2019 figure 1
	Placebo	6	16.7 (0.0; 46.5)								

Proportion of patients with 0 exacerbations, FEV, proportion of patients with ≥200 mL improvement in FEV1, asthma control, quality of life, SAEs and sick leave were not reported in this study

-, not applicable; CI, confidence interval; FEV1, forced expiratory volume in 1 s; NR, not reported; RR, relative risk, SAE, serious adverse event

8.6 Results per PICO (clinical question)

8.6.1 Dupilumab compared with mepolizumab

TABLE 75 RESULTS REFERRING TO THE ADDED CLINICAL VALUE OF DUPILUMAB *VS* MEPOLIZUMAB IN PATIENTS WITH UNCONTROLLED, PERSISTENT EOSINOPHILIC ASTHMA

Results per outcome	Studies included in the analysis	Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
		Difference	95% CI	P value	RR	95% CI	P value	
Annualised rate of exacerbations	DRI12544 (24-wk study) MUSCA (24-wk study)	-0.175	-0.352; 0.202	NC	0.657	0.309; 1.396	NC	See appendix 8.4
Annualised rate of exacerbations	QUEST (52-wk study) DREAM (52-wk study)	-0.186	-0.530; 0.324	NC	0.850	0.573; 1.261	NC	See appendix 8.4
Proportion of patients with 0 exacerbations/year	QUEST (52-wk study) DREAM (52-wk study)	-10.639	-21.897; 4.544	NC	0.804	0.596;1.084	NC	See appendix 8.4
Change from baseline in FEV1 (L)	QUEST (week 24) MENSA (week 32) MUSCA (week 24)	0.100	0.013; 0.188	NC	-	-	-	See appendix 8.4
Change from baseline in FEV1 (L)	QUEST (week 52) DREAM (week 52)	0.189	0.062; 0.316	NC	-	-	-	See appendix 8.4
Change from baseline in asthma control (ACQ-5)	DRI12544 (week 24) QUEST (week 24) MENSA (week 32) MUSCA (week 24)	-0.017	-0.218; 0.184	NC	-	-	-	See appendix 8.4
Change from baseline in quality of life (AQLQ)	DRI12544 (week 24) QUEST (week 24) MENSA (week 32) MUSCA (week 24)	-0.129	-0.319; 0.061	NC	-	-	-	See appendix 8.4
Proportion of patients with SAE (total)	DRI12544 (24-wk study) MENSA (32-wk study) MUSCA (24-wk study)	6.478	-1.596; 27.451	NC	1.974	0.760; 5.128	NC	See appendix 8.4
Proportion of patients with SAE (total)	QUEST (52-wk study) DREAM (52-wk study)	2.010	-5.669; 17.624	NC	1.153	0.567; 2.345	NC	See appendix 8.4
Proportion of patients discontinued from the study	DRI12544 (24-wk study) MENSA (32-wk study) MUSCA (24-wk study)	1.261	-2.085; 10.027	NC	1.304	0.498; 3.416	NC	See appendix 8.4
Proportion of patients discontinued from the study	QUEST (52-wk study) DREAM (52-wk study)	1.032	-6.704; 15.422	NC	1.066	0.573; 1.982	NC	See appendix 8.4

The proportion of patients with ≥200 mL improvement in FEV1 and sick leave could not be analysed since no data were available for mepolizumab

-, not applicable; ACQ-5, 5-item Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; CI, confidence interval; FEV1, forced expiratory volume in 1 s; ITT, intention-to-treat; L, litre; NC, not calculated; OCS, oral corticosteroids; RR, relative risk or risk ratio; SAE, serious adverse events

TABLE 76 RESULTS REFERRING TO THE ADDED CLINICAL VALUE OF DUPILUMAB *VS* MEPOLIZUMAB IN PATIENTS WITH OCS-DEPENDENT EOSINOPHILIC ASTHMA

Results per outcome	Studies included in the analysis	Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
		Difference	95% CI	P value	RR	95% CI	P value	
Annualised rate of exacerbations	VENTURE (24-wk study) SIRIUS (24-wk study	-0.555	-0.965; 0.210	NC	0.615	0.330; 1.146	NC	See appendix 8.4
Proportion of patients with no OCS use	VENTURE (24-wk study) SIRIUS (24-wk study	-0.501	-9.849; 27.632	NC	0.965	0.321; 2 .906	NC	See appendix 8.4
Proportion of patients with ≥50% reduction in OCS use	VENTURE (24-wk study) SIRIUS (24-wk study	-1.437	-21.028; 29.938	NC	0.973	0.608; 1.559	NC	See appendix 8.4
Change from baseline in FEV1 (L)	VENTURE (24-wk study) SIRIUS (24-wk study	0.106	-0.122; 0.334	NC	-	-	-	See appendix 8.4
Change from baseline in asthma control (ACQ-5)	VENTURE (24-wk study) SIRIUS (24-wk study	0.050	-0.413; 0.513	NC	-	-	-	See appendix 8.4
Change from baseline to wk 24 in quality of life (AQLQ)	VENTURE (24-wk study) SIRIUS (24-wk study	-0.006	-0.411; 0.398	NC	-	-	-	See appendix 8.4
Proportion of patients with SAE (total)	VENTURE (24-wk study) SIRIUS (24-wk study	25.969	1.498; 257.1	NC	19.549	2.070; 184.6	NC	See appendix 8.4
Proportion of patients discontinued from the study	VENTURE (24-wk study) SIRIUS (24-wk study	-1.809	-4.018;17.685	NC	0.579	0.066;5.113	NC	See appendix 8.4

Not possible to perform indirect comparisons of % reduction in daily OCS maintenance dose since data were reported differently in the 2 studies. The proportion of patients with 0 exacerbations/year and the proportion of patients with ≥200 mL improvement in FEV1 was not reported for mepolizumab. Sick leave was not reported for any of the studies in OCS-dependent eosinophilic asthma

-, not applicable; ACQ-5, 5-item Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; CI, confidence interval; FEV1, forced expiratory volume in 1 s; ITT, intention-to-treat; L, litre; NC, not calculated; OCS, oral corticosteroids; RR, relative risk or risk ratio; SAE, serious adverse events

8.6.2 Dupilumab compared with omalizumab

TABLE 77 RESULTS REFERRING TO THE ADDED CLINICAL VALUE OF DUPILUMAB *VS* OMALIZUMAB IN PATIENTS WITH UNCONTROLLED, PERSISTENT ALLERGIC ASTHMA WITH INCREASED EOS AND/OR INCREASED FENO

Results per outcome	Studies included in the analysis	Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
		Difference	95% CI	P value	RR	95% CI	P value	
Annualised rate of exacerbations	QUEST (52-wk study) Busse 2001 (52-wk study) Soler 2001 (52-wk study) Ayres 2004 (12-month study) Hanania 2011 (48-wk study)	-0.107	-0.268; 0.114	NC	0.845	0.612; 1.165	NC	See appendix 8.4
Proportion of patients with 0 exacerbations/year	QUEST (52-wk study) Ayres 2004 (12-month study) Hanania 2011 (48-wk study)	2.632	-5.591; 12.172	NC	1.046	0.902; 1.214	NC	See appendix 8.4
Change from baseline in FEV1 (L)	QUEST (week 24) Bousquet 2011 (week 32) Bardelas 2012 (week 24) Rubin 2012 (week 20) Busse 2013 (week 24)	0.096	0.011; 0.182	NC	-	-	-	See appendix 8.4
Change from baseline in asthma control (ACQ)	QUEST (week 24) Li 2016 (week 24)	-0.111	-0.417; 0.195	NC	-	-	-	See appendix 8.4
Change from baseline in quality of life (AQLQ)	QUEST (week 24) Vignola 2004 (week 28) Li 2016 (week 24)	-0.077	-0.304; 0.151	NC	-	-	-	See appendix 8.4
Proportion of patients with SAE (total) – 24 weeks	DRI12544 (24-wk study) Holgate 2004 (32-wk study) Vignola 2004 (28-wk study) Humbert 2005 (28-wk study) Bousquet 2011 (32-wk study) Rubin 2012 (20-wk study) Busse 2013 (24-wk study) Li 2016 (24-wk study)	2.981	-1.756; 14.890	NC	1.610	0.641; 4.048	NC	See appendix 8.4
Proportion of patients with SAE (total) – 52 weeks	QUEST (52-wk study) Busse 2001 (52-wk study) Soler 2001 (52-wk study) Hanania 2011 (48-wk study)	0.242	-2.693; 5.345	NC	1.036	0.596; 1.802	NC	See appendix 8.4

Results per outcome	Studies included in the analysis	Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
		Difference	95% CI	P value	RR	95% CI	P value	
Proportion of patients discontinued from the study – 24 weeks	DRI12544 (24-wk study) Holgate 2004 (32-wk study) Vignola 2004 (28-wk study) Humbert 2005 (28-wk study) Bardelas 2012 (24-wk study) Busse 2013 (24-wk study) Li 2016 (24-wk study) Mukherjee 2019 (32-wk study)	-0.547	-6.210; 12.471	NC	0.948	0.413; 2.180	NC	See appendix 8.4
Proportion of patients discontinued from the study – 52 weeks	QUEST (52-wk study) Busse 2001 (52-wk study) Soler 2001 (52-wk study) Hanania 2011 (48-wk study)	4.250	-1.961; 13.699	NC	1.306	0.859; 1.988	NC	See appendix 8.4

Proportion of patients with ≥200 mL improvement in FEV1 was only reported for dupilumab, thus no comparative analyses could be performed. Data for sick leave could not be compared statistically

No data were reported for OCS-dependent allergic asthma

-, not applicable; ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; CI, confidence interval; EOS, blood eosinophils; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 s; ITT, intention-to-treat; L, litre; NC, not calculated; OCS, oral corticosteroids; RR, relative risk or risk ratio; SAE, serious adverse events

8.6.3 Dupilumab compared with placebo

TABLE 78 RESULTS REFERRING TO THE ADDED CLINICAL VALUE OF DUPILUMAB *VS* PLACEBO IN PATIENTS WITH UNCONTROLLED, PERSISTENT ASTHMA AND INCREASED FENO

Results per outcome	Studies included in the analysis (population/subgroup)	Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
		Difference	95% CI	P value	RR	95% CI	P value	
Annualised rate of exacerbations	Castro 2018 (QUEST) (FeNO ≥25 ppb)	-0.65	-0.750; -0.500	NC	0.35[a]	0.25; 0.50	<0.0001	A negative binomial regression model, including the 4 intervention groups, age, geographic region, baseline EOS strata, baseline dose of ICS, and number of exacerbations in the previous year as covariates[b]
Proportion of patients with 0 exacerbations/year	Castro 2018 (QUEST) (FeNO ≥25 ppb)	20.75	11.74; 29.76	NC	1.37	1.179; 1.590	NC	See appendix 8.4
Change from baseline to week 52 in FEV1 (L)	Castro 2018 (QUEST) (FeNO ≥25 ppb)	0.3	0.22; 0.39	<0.0001	-	-	-	A mixed-effects model with repeated measures, including assigned intervention, age, sex, height, baseline EOS strata, baseline ICS dose, visit, intervention-by-visit interaction, the corresponding baseline value, and baseline-by-visit interaction as covariates
Proportion of patients with ≥200 mL improvement in FEV1 (%)	Castro 2018 (QUEST) (FeNO ≥25 ppb)	23.78	13.10; 34.45	NC	1.556	1.244; 1.947	NC	See appendix 8.4
Change from baseline to week 52 in asthma control (ACQ-5)	Castro 2018 (QUEST) (ITT)	-0.39	-0.53; -0.25	NC	-	-	-	A mixed-effects model with repeated measures, including assigned intervention, age, baseline EOS strata, baseline ICS dose, visit, intervention-by-visit interaction, the corresponding baseline value, and baseline-by-visit interaction as covariates
Change from baseline to wk 52 in quality of life (AQLQ)	Castro 2018 (QUEST) (ITT)	0.29	0.15; 0.44	NC	-	-	-	
Proportion of patients with SAE (total) (%)	Castro 2018 (QUEST) (ITT)	-0.54	-4.24; 3.16	NC	0.935	0.593; 1.475	NC	See appendix 8.4
Proportion of patients discontinued from the study (%)	Castro 2018 (QUEST) (ITT)	-0,89	-5.23; 3.44	NC	0.925	0.638; 1.341	NC	See appendix 8.4

[a] Rate ratio; [b] All severe exacerbations that occurred during the 52-week treatment period were included regardless of whether the patient remained on treatment

-, not applicable; ACQ-5, 5-item Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; CI, confidence interval; EOS, blood eosinophils; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 s; ICS, inhaled corticosteroids; ITT, intention-to-treat; L, litre; NC, not calculated; SAE, serious adverse event

TABLE 79 RESULTS REFERRING TO THE ADDED CLINICAL VALUE OF DUPILUMAB *VS* PLACEBO IN PATIENTS WITH OCS-DEPENDENT ASTHMA AND INCREASED FENO

Results per outcome	Studies included in the analysis (population/subgroup)	Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
		Difference	95% CI	P value	RR	95% CI	P value	
Annualised rate of exacerbations	Rabe 2018 (VENTURE) (FeNO ≥25 ppb)[a]	-0.948	-1.242; -0.133	NC	0.326	0.117; 0.905	NC	A negative binomial regression model was used
Proportion of patients with 0 exacerbations/year	Rabe 2018 (VENTURE) (FeNO ≥25 ppb)	36.84	20.38; 53.30	NC	1.84	1.336; 2.534	NC	See appendix 8.4
% reduction in daily OCS maintenance dose	Rabe 2018 (VENTURE) (FeNO ≥25 ppb)[a]	34.75	18.66; 54.05	NC	-	-	-	An analysis of covariance model including % reduction in OCS dose at wk 24 as the response variable, with treatment group, optimised OCS dose at baseline, geographic region, and baseline EOS subgroup as covariates[b]
Proportion of patients with no OCS use	Rabe 2018 (VENTURE) (ITT)	23.46	10.54; 36.37	NC	1.810	1.276; 2.566	NC	See appendix 8.4
Proportion of patients with ≥50% reduction in OCS use	Rabe 2018 (VENTURE) (ITT)	26.34	14.10; 38.58	NC	1.494	1.220; 1.830	NC	See appendix 8.4
Change from baseline to week 24 in FEV1 (L)	Rabe 2018 (VENTURE) (FeNO ≥25 ppb)[a]	0.25	0.04; 0.45	NC	-	-	-	See appendix 8.4
Proportion of patients with ≥200 mL improvement in FEV1 (%)	Rabe 2018 (VENTURE) (FeNO ≥25 ppb)	19.19	0.83; 37.56	NC	1.528	1.001; 2.333	NC	See appendix 8.4
Change from baseline to week 24 in asthma control (ACQ-5)	Rabe 2018 (VENTURE) (ITT)	-0.47	-0.76; -0.18	NC	-	-	-	A mixed effects model with a repeated-measures approach was used
Change from baseline to week 24 in quality of life (AQLQ)	Rabe 2018 (VENTURE) (ITT)	0.35	0.073; 0.627	NC	-	-	-	See appendix 8.4
Proportion of patients with SAE (total) (%)	Rabe 2018 (VENTURE) (ITT)	3.13	-3.85; 10.11	NC	1.558	0.575; 4.223	NC	See appendix 8.4
Proportion of patients discontinued from the study (%)	Rabe 2018 (VENTURE) (ITT)	-2.73	-7.54; 2.07	NC	0.416	0.082; 2.094	NC	See appendix 8.4

[a] Results were pooled for the 2 subgroups reported: FeNO≥25 to 50 ppb and FeNO≥50ppb; [b] For patients who discontinued the study or had missing data regarding the OCS dose at week 24 in the primary analysis, the missing data were handled with the use of a pattern-mixture model by multiple imputations

-, not applicable; ACQ-5, 5-item Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; CI, confidence interval; EOS, blood eosinophils; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 s; ITT, intention-to-treat; L, litre; NC, not calculated; OCS, oral corticosteroids ; SAE, serious adverse event

Medicinrådet

Medicinrådets protokol for vurdering af dupilumab til behandling af svær astma

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 protokollen

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

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

Dokumentoplysninger	
Godkendelsesdato	27. juni 2019
Ikrafttrædelsesdato	27. juni 2019
Dokumentnummer	52074
Versionsnummer	1.0

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

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

Indhold

1 Lægemiddelinformationer

Lægemidlets oplysninger	
Handelsnavn	Dupixent
Generisk navn	Dupilumab
Firma	Sanofi Genzyme
ATC-kode	D11AH05
Virkningsmekanisme	Dupilumab er et monoklonalt antistof rettet mod interleukin 4 receptor underenhed alfa (IL-4Rα). Denne underenhed deles af IL-4 og IL-13 receptorkomplekser, og derfor hæmmer dupilumab signaleringen fra både IL-4 og IL-13. IL-4 er den centrale mediator af naïve T-cellers differentiering til Type 2 cytokin-producerende effektorceller, eosinofil trafficking, B-celle-aktivering og underliggende øgning af IgE-produktion. IL-13 medierer ydermere remoduleringen af luftvejene ved bægercellehyperplasi, transformation af bronkiale fibroblaster til myofibroblaster, kollagen deposition og proliferation af glatte muskelceller i luftvejene. IL-13 medierer også glat muskelkontraktion samt bronkoepitelial production af FeNO.
Administration/dosis	Initial dosis på 400 mg (fordelt på to 200 mg subkutane injektioner), herefter 200 mg subkutan injektion hver anden uge i tillæg til standardbehandling. Patienter som er i vedligeholdelsesbehandling med orale kortikosteroider eller til patienter, som samtidig lider af moderat til svær atopisk eksem: initial dosis på 600 mg (fordelt på to 300 mg subkutane injektioner), herefter 300 mg subkutan injektion hver anden uge i tillæg til standardbehandling. *An initial dose of 400 mg (two 200 mg injections), followed by 200 mg given every other week administered as subcutaneous injection.* *For patients with severe asthma and who are on oral corticosteroids or for patients with severe asthma and co-morbid moderate-to-severe atopic dermatitis, an initial dose of 600 mg (two 300 mg injections), followed by 300 mg every other week administered as subcutaneous injection.*
Forventet EMA-indikation	Voksne, unge og børn > 12 år som tillægsbehandling til svær astma med type 2-inflammation karakteriseret ved forhøjet blod eosinofile celler og/eller forhøjet FeNO, som er utilstrækkeligt kontrolleret med højdosis ICS og en anden medicinsk vedligeholdelsesbehandling. *Adults and adolescents 12 years and older as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised FeNO, who are inadequately controlled with high dose ICS plus another medicinal product for maintenance treatment.*

2 Forkortelser

ACQ:	*Asthma Control Questionnaire* (astmakontrolspørgeskema)
ACT:	Asthma Control Test
AQLQ:	*Asthma Quality of Life Questionnaire* (astmalivskvalitetspørgeskema)
ATS:	American Thoracic Society
CI:	Konfidensinterval
DLS:	Dansk Lungemedicinsk Selskab
EMA:	*European Medicines Agency*
ERC:	*European Respiratory Society*
FeNO:	Fractional exhaled nitric oxide (fraction af udåndet nitrogenoxid)
FEV1:	*Forced Expiratory Volume* (forceret ekspirationsvolumen) på 1 sekund
GINA:	*Global Initiative of Asthma*
GRADE:	System til vurdering af evidens (Grading of Recommendations Assessment, Development and Evaluation)
ICS:	Inhaleret kortikosteroid
IL4:	Interleukin 4
IL5:	Interleukin 5
IL13:	Interleukin 13
LABA:	Long-acting beta2-agonist
LTRA:	Leukotrinreceptor antagonist
MD:	*Mean Difference* (gennemsnitlig forskel)
NO:	Nitrogenoxid
OCS:	Oral kortikosteroid
PICO:	Population, Intervention, *Comparator* (sammenligning) og *Outcome* (effektmål)
RR:	Relativ risiko
SABA:	Short-acting beta2-agonist
SAE's:	*Serious adverse events* (alvorlige uønskede hændelser)
SD:	Standardafvigelse
SMD:	*Standardized Mean Difference* (standardiseret gennemsnitlig forskel)

3 Formål

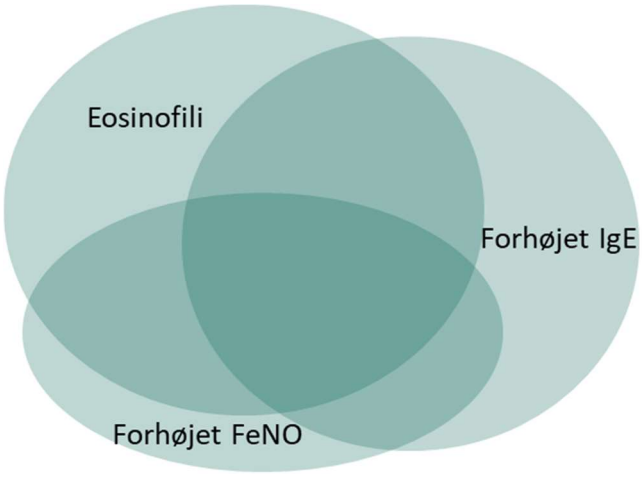
Protokollen har til formål at definere de kliniske spørgsmål, der ønskes belyst i vurderingen af dupilumab som mulig standardbehandling af patienter med svær astma. I protokollen angives en definition af population(er), komparator(er) og effektmål, der skal præsenteres i den endelige ansøgning, samt de metoder der ønskes anvendt til den komparative analyse. Arbejdet med protokollen er igangsat på baggrund af den foreløbige ansøgning vedrørende dupilumab modtaget den 28. marts 2019.

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

4 Baggrund

Astma er en heterogen sygdom, som oftest skyldes kronisk inflammation i luftvejene, der medfører hyperreaktive luftveje med tendens til sammentrækning. De typiske symptomer på astma er hoste, åndenød og pibende vejrtrækning samt tendens til lungeinfektioner. Symptomerne kan optræde spontant eller være forårsaget af udløsende faktorer som fysisk anstrengelse, luftvejsirritanter (f.eks. tobak) eller luftbårne allergener (f.eks. pollen, dyrehår eller husstøvmider). **Sværhedsgraden** af astma bestemmes retrospektivt på baggrund af den behandlingsintensitet, som kræves for at opnå tilfredsstillende sygdomskontrol. **Graden af sygdomskontrol** vurderes ud fra hyppigheden af dagsymptomer, natsymptomer, begrænsning i aktivitet, og behov for anfaldsmedicin, mens den fremtidige risiko for kontroltab og eksacerbationer vurderes ud fra bl.a. lungefunktion og evt. tidligere eksacerbationer [1]. Behandlingen justeres ud fra sygdomskontrol. ”Manglende kontrol af astma”, ”ukontrolleret astma” eller ”dårligt kontrolleret astma” er synonymer og beskriver alene symptomgennembrud på den aktuelle behandling og siger i sig selv intet om den underliggende astmasværhedsgrad. I dag vurderes det, at 7-11 % af den danske population har astma [2]. Prævalensen af **svær astma** er estimeret til at udgøre 5-15 % af alle patienter med astma [3].

Ca. 50 % af patienter med svær astma har **type 2-inflammation**, der er karakteriseret ved cytokinerne IL-4, IL-5 og IL-13, der udløst af allergener produceres af det adaptive immunsystem. Type 2-inflammation kan også initieres af virus, bakterier og irritanter, der stimulerer det innate immunsystem via produktion af IL-25, IL-33, og thymic stromal lymfopoitin (TSLP), hvoraf der er biologiske lægemidler på vej til blokade af de to sidstnævnte (anti-IL-33 og anti-TSLP). Type 2-inflammation er ofte karakteriseret ved forhøjet blodeosinofile celler (**eosinofil astma**) og/eller forhøjet nitrogenoxid i udåndingsluften (FeNO) (**astma med forhøjet FeNO**) og/eller allergi (**allergisk astma**) med IgE-sensibilisering for allergener påvist ved direkte måling af forhøjet specifikt IgE i blodet eller ved hudpriktest med standardiserede allergenekstrakter [4]. Nogle patienter med svær astma med type 2 inflammation er alene karakteriseret ved forhøjede blodeosinofile celler, forhøjet FeNO eller allergi, men nogle patienter har flere eller alle tre karakteristika (se nedenstående figur 1), der kan gøre valg af biologisk lægemiddel vanskeligt; dvs. anti-IL5, anti-IgE eller anti-IL4R. Ydermere kan op til 50 % af børn, unge og yngre voksne (der har haft astmadebut i barndommen) med svær allergisk astma også have samtidig svær atopisk dermatitis.



Figur 1: Figur over udvalgte fænotyper indenfor svær astma.
Figuren illustrerer, at der er overlap mellem patientpopulationerne indenfor svær astma i forhold til de tre udvalgte fænotyper: eosinofili ≥ 150 celler pr. mikroliter, FeNO ≥ 25 bpp, og specifik IgE ≥ 0,35 KU/L.

4.1 Nuværende behandling

Dansk Lungemedicinsk Selskab (DLS) definerer svær astma i overensstemmelse med ERS (European Respiratory Society)/ATS' (American Thoracic Society) guidelines [3,5]: astma som gennem minimum det sidste år har krævet behandling med høj dosis inhalationssteroid samt en eller flere tillægsbehandlinger (2nd controller (typisk langtidsvirkende beta2-agonist, LABA), og/eller som har krævet peroralt steroid i ≥ 50 % af tiden) for at forebygge, at astmaen bliver ukontrolleret eller trods denne behandling forbliver ukontrolleret. Systematisk udredning af mulig svær astma er afgørende for at sikre diagnosen, og at den manglende sygdomskontrol ikke skyldes forkert diagnose, manglende adhærens med den ordinerede behandling, behandlelige komorbiditeter eller undgåelige triggers [3].

Der vil dog være en mindre andel af patienter, som ikke opnår tilstrækkelig sygdomskontrol trods ovenstående tiltag. Til patienter med svær eosinofil astma er en yderligere behandlingsmulighed tillægsterapi med mepolizumab, reslizumab eller benralizumab, som er antistoffer rettet mod interleukin 5 (IL-5) eller IL-5-receptoren (IL-5R). Mepolizumab er af EMA godkendt til voksne og børn over 6 år [6]. Reslizumab og benralizumab er godkendt til voksne [7,8]. IL-5 er et cytokin, som spiller en central rolle i produktion, modning og overlevelse af eosinofile granulocytter, og binding af antistofferne til IL-5 eller IL-5R medfører dermed en reduktion i antallet af eosinofile granulocytter, resulterende i bedre sygdomskontrol.

Til voksne patienter og børn over 6 år med svær allergisk astma, som har en positiv hudpriktest eller in vitro-reaktivitet for et helårs luftbåret allergen, er en behandlingsmulighed desuden tillægsterapi med anti-IgE-behandling i form af omalizumab. Omalizumab er et antistof rettet mod IgE, som hindrer binding af IgE til immunsystemets celler, hvorved allergiske reaktioner reduceres [9].

4.2 Dupilumab

Dupilumab er et monoklonalt antistof rettet mod interleukin 4-receptor underenhed alfa (IL-4Rα). Denne underenhed deles af IL-4- og IL-13-receptorkomplekser, og derfor hæmmer dupilumab signaleringen fra både IL-4 og IL-13. IL-4 er den centrale mediator af naïve T-cellers differentiering til Type 2-cytokin-producerende effektorceller, eosinofil trafficking, B-celle-aktivering og underliggende øgning af IgE-produktion. IL-13 medierer ydermere remoduleringen af luftvejene ved bægercellehyperplasi, transformation af bronkiale fibroblaster til myofibroblaster, kollagendeposition og proliferation af glatte muskelceller i luftvejene. IL-13 medierer også glat muskelkontraktion samt epithelial produktion af FeNO. Dupilumabs

virkningsmekanisme er således upstream i signaleringskaskaden for omalizumabs og anti-IL5-lægemidlernes virkningsmekanismer. Dupilumab hæmmer således type 2-inflammation mere bredt.
Dupilumab er indiceret som tillæg til vedligeholdelsesbehandling til voksne og unge fra 12 år og derover med svær astma med type 2-inflammation, karakteriseret ved forhøjet eosinofiltal i blodet og/eller forhøjet FeNO, der ikke er tilstrækkeligt kontrolleret med høj dosis inhalationskortikosteroid plus et andet lægemiddel til vedligeholdelsesbehandling.

På baggrund af dupilumabs indikation og virkningsmekanisme kan dupilumabs anvendelse spænde over flere patientpopulationer, hvor der på nuværende tidspunkt er forskellige medicinske alternativer. Fagudvalget vurderer, at der er tale om 3 nedenstående populationer:

1) Patienter med svær eosinofil astma hvor dupilumab er et medicinsk alternativ til anti-IL5-lægemidler (mepolizumab, reslizumab, benralizumab).

2) Patienter med svær allergisk astma som samtidig har eosinofili og/eller forhøjet FeNO, hvor dupilumab er et medicinsk alternativ til omalizumab.

3) Patienter med svær astma, og som er karakteriseret ved forhøjet FeNO uden samtidig eosinofili eller allergi, hvor dupilumab vil være det eneste biologiske lægemiddel.

4.2.1 Administration og dosering

Dupilumab administreres med forfyldt injektionssprøjte og kan administreres som hjemmebehandling. Dupilumab anvendes som langtidsbehandling til svær astma.

1. Dupilumab administreres med en initial dosis på 400 mg (fordelt på to 200 mg subkutane injektioner), herefter gives 200 mg subkutan injektion hver anden uge.

Til patienter med svær astma som er i vedligeholdelsesbehandling med orale kortikosteroider eller til patienter med svær astma, som samtidig lider af moderat til svær atopisk eksem:

2. Dupilumab administreres med en initial dosis på 600 mg (fordelt på to 300 mg subkutane injektioner), herefter gives 300 mg subkutan injektion hver anden uge.

4.3 Prævalens

Fagudvalget estimerer følgende prævalens og incidens:

Der estimeres at være 500-600 patienter med svær astma, som er kandidater til biologisk behandling i Danmark, ca. 50 af disse patienter er børn eller unge under 18 år. Biologisk behandling tilbydes til ca. 60 nye patienter pr. år.

De fleste patienter under 18 år behandles med omalizumab (ca. 90 %), resten med mepolizumab. Hvis disse patienter skulle behandles med dupilumab, ville ca. 50 % skulle have 200 mg og 50 % have 300 mg pga. samtidig atopisk dermatitis, mens daglig OCS vedligeholdelsesbehandling meget sjældent anvendes.

I den voksne patientpopulation behandles ca. 80 % med anti-IL5-lægemidler (heraf 80 % mepolizumab) og 15 % med omalizumab. De resterende 5 % opfylder ikke indikationen for hverken anti-IL-5-lægemidler eller omalizumab, men kunne opfylde indikationen for dupilumab. Hvis de voksne patienter skulle behandles med dupilumab, ville ca. 10-20 % opfylde kriterierne for dosering med 300 mg grundet daglig OCS vedligeholdelsesbehandling.

5 Kliniske spørgsmål

Nedenfor beskrives de kliniske spørgsmål, som danner grundlag for Medicinrådets vurdering af den kliniske merværdi af dupilumab til behandling af svær astma karakteriseret ved type 2-inflammation. Der er valgt flere komparatorer, da dupilumabs indikation og virkningsmekanisme omfatter flere alternativer. Mepolizumab er valgt som eneste komparator fra gruppen af ligestillede anti-IL5-lægemidler, da dette lægemiddel er 1. valg i lægemiddelrekommandationen, samt at evidensen for dette lægemiddel er baseret på studier, hvor populationen bedst relaterer sig til danske forhold.

Da dupilumab er en tillægsbehandling til svær astma, vil der være en underliggende behandling, som kaldes "standardbehandling". Ved betegnelsen "standardbehandling" menes i relation til svær astma: høj dosis inhalationssteroid samt en anden forebyggende behandling (langtidsvirkende beta2-agonist, leukotrien antagonist, langtidsvirkende antikolinergikum eller theofyllin eller fast behandling med peroralt steroid). Standardbehandlingen ønskes ikke undersøgt som intervention eller som komparator af Medicinrådet. Delkomponenter af en standardbehandling kan dog i visse tilfælde være et effektmål, f.eks. hvis formålet er at reducere forbruget af øvrige typer medicin som f.eks. OCS.

5.1 *Hvilken klinisk merværdi tilbyder dupilumab sammenlignet med mepolizumab ved behandling af patienter > 12 år med svær astma med type 2-inflammation karakteriseret ved eosinofili?*

Population
Patienter > 12 år med svær astma med type 2-inflammation karakteriseret ved eosinofili. Eosinofili defineres som i Medicinrådets behandlingsvejledning for biologiske lægemidler til svær astma og er: blodeosinofile ≥ 150 celler pr. mikroliter observeret indenfor den seneste måned eller blodeosinofile ≥ 300 celler pr. mikroliter observeret indenfor det seneste år, eller ved sputumeosinofili ≥ 3 % målt indenfor seneste år.

Intervention
Dupilumab i initial dosis på 400 mg (fordelt på to 200 mg subkutane injektioner), herefter 200 mg subkutan injektion hver anden uge i tillæg til standardbehandling.

Patienter som er i vedligeholdelsesbehandling med orale kortikosteroider eller til patienter, som samtidig lider af moderat til svær atopisk eksem:

Dupilumab i en initial dosis på 600 mg (fordelt på to 300 mg subkutane injektioner), herefter 300 mg subkutan injektion hver anden uge i tillæg til standardbehandling.

Komparator
Mepolizumab (100 mg) subkutan injektion hver 4. uge i tillæg til standardbehandling. Data fra studier som anvender mepolizumab i 75 mg intravenøs dosis kan anvendes som komparator, da denne dosis anses som ækvivalent til 100 mg subkutan dosering.

5.2 *Hvilken klinisk merværdi tilbyder dupilumab sammenlignet med omalizumab ved behandling af patienter > 12 år med svær astma med type 2-inflammation karakteriseret ved allergi og samtidig eosinofili eller karakteriseret ved allergi og samtidig forhøjet FeNO?*

Population

Patienter > 12 år med svær astma med type 2-inflammation karakteriseret ved allergi og samtidig eosinofili eller karakteriseret ved allergi og samtidig forhøjet FeNO.

- Eosinofili defineres som i Medicinrådets behandlingsvejledning for biologiske lægemidler til svær astma og er: blod eosinofile ≥ 150 celler pr. mikroliter observeret indenfor den seneste måned eller blod eosinofile ≥ 300 celler pr. mikroliter observeret indenfor det seneste år eller ved sputum eosinofili ≥ 3 % målt indenfor seneste år.
- Allergi defineres som i Medicinrådets behandlingsvejledning for biologiske lægemidler til svær astma og er: påvist sensibilisering overfor et helårsallergen ved priktest og/eller måling af forhøjede specifikke IgE-antistoffer (> 0,35 kU/L) samt symptomer ved relevant eksponering for allergenet.
- Forhøjet FeNO defineres som FeNO ≥ 25 ppb observeret inden for seneste måned.

Intervention
Dupilumab i initial dosis på 400 mg (fordelt på to 200 mg subkutane injektioner), herefter 200 mg subkutan injektion hver anden uge i tillæg til standardbehandling.

Patienter som er i vedligeholdelsesbehandling med orale kortikosteroider eller til patienter, som samtidig lider af moderat til svær atopisk eksem:

Dupilumab i en initial dosis på 600 mg (fordelt på to 300 mg subkutane injektioner), herefter 300 mg subkutan injektion hver anden uge i tillæg til standardbehandling.

Komparator
Omalizumab (dosis og doseringshyppighed afhænger af indholdet af IgE i blodet og af legemsvægten) subkutan injektion hver 2. eller 4. uge i tillæg til standardbehandling.

5.3 *Hvilken klinisk merværdi tilbyder dupilumab sammenlignet med placebo ved behandling af patienter > 12 år med svær astma med type 2-inflammation karakteriseret ved forhøjet FeNO uden samtidig eosinofili og uden samtidig allergi?*

Population
Patienter > 12 år med svær astma med type 2-inflammation karakteriseret ved forhøjet FeNO, uden samtidig eosinofili og uden samtidig allergi.

- Eosinofili defineres som i Medicinrådets behandlingsvejledning for biologiske lægemidler til svær astma og er: blodeosinofile ≥ 150 celler pr. mikroliter observeret indenfor den seneste måned eller blodeosinofile ≥ 300 celler pr. mikroliterobserveret indenfor det seneste år eller ved sputum eosinofili ≥ 3 % målt indenfor seneste år.
- Allergi defineres som i Medicinrådets behandlingsvejledning for biologiske lægemidler til svær astma og er: påvist sensibilisering overfor et helårsallergen ved priktest og/eller måling af forhøjede specifikke IgE-antistoffer (> 0,35 kU/L) samt symptomer ved relevant eksponering for allergenet.
- Forhøjet FeNO defineres som FeNO ≥ 25 bpp observeret inden for seneste måned.

Intervention
Dupilumab i initial dosis på 400 mg (fordelt på to 200 mg subkutane injektioner), herefter 200 mg subkutan injektion hver anden uge i tillæg til standardbehandling.

Patienter som er i vedligeholdelsesbehandling med orale kortikosteroider eller til patienter, som samtidig lider af moderat til svær atopisk eksem:

Dupilumab i en initial dosis på 600 mg (fordelt på to 300 mg subkutane injektioner), herefter 300 mg subkutan injektion hver anden uge i tillæg til standardbehandling.

Komparator
Placebo i tillæg til standardbehandling.

5.4 Valg af effektmål

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

For alle effektmål ønskes både absolutte og relative værdier, jf. ansøgningsskemaet. Der ønskes både punktestimater og konfidensintervaller (for de absolutte værdier ønskes dog ikke konfidensintervaller, hvor metoderne til beregning af disse ikke er veldefinerede). For de absolutte værdier, hvor der kan beregnes konfidensintervaller efter veldefinerede metoder, vurderes den kliniske relevans (værdi), jf. tabel 3 i Medicinrådets håndbog for vurdering af nye lægemidler. For de relative værdier vurderes den kliniske relevans (værdi), jf. væsentlighedskriterierne beskrevet i Medicinrådets håndbog. De relative effektestimater skal angives i relativ risiko (RR) eller hazard ratio (HR). Hvis studierne resulterer i en odds ratio (OR), skal denne transformeres til relativ risiko, jf. appendiks 2 i Medicinrådets håndbog. Det skal begrundes i ansøgningen, hvis der afviges fra de ønskede effektmål.

Effektmålene og deres mindste klinisk relevante forskel er uændret i forhold til tidligere behandlinger af biologiske lægemidler til svær astma. Fagudvalget finder det vigtigt, at lægemidlerne vurderes på lige vilkår, medmindre særlige ting gør sig gældende. I dette tilfælde er der ikke fundet anledning til at lave ændringer i forhold til tidligere.

Tabel 1. Oversigt over valgte effektmål. For hvert effektmål er angivet deres vigtighed. For kritiske og vigtige effektmål er desuden angivet den mindste klinisk relevante forskel (retningsgivende og evt. justeret) samt indplacering i de tre kategorier (”dødelighed” ”livskvalitet, alvorlige symptomer og bivirkninger” og ”ikkealvorlige symptomer og bivirkninger”).

Effektmål*	Vigtighed	Kategori	Måleenhed	Mindste klinisk relevante Forskel (MKFR)	Justeret MKRF
Eksacerbationsrate	Kritisk	Alvorlige symptomer	Gennemsnitlig reduktion i årlige antal eksacerbationer	Minimum reduceret med 1 årlig eksacerbation	Minimum reduceret med 0,5 årlig eksacerbation
			Andel af patienter som opnår 0 årlige eksacerbationer	10 procentpoint	5 procentpoint
Peroral vedligeholdelses-behandling med kortikosteroid	Kritisk	Alvorlige symptomer	Gennemsnitlig %-reduktion i daglig dosis (vedligeholdelsesbehandling)	20 % (dog minimum 2,5 mg prednisolon ækvivalent)	10 % (dog minimum 1,25 mg prednisolon ækvivalent)
			Andel af patienter som bliver helt fri for vedligeholdelsesbehandling med peroral kortikosteroid	5 procentpoint	2,5 procentpoint
			Andel af patienter som opnår ≥ 50 % reduktion af peroral kortikosteroid	10 procentpoint	5 procentpoint
Lungefunktion FEV_1	Vigtig	Alvorlige symptomer	Gennemsnitlig ændring i lungefunktion	200 ml for voksne	100 ml for voksne
			Andelen af patienter der opnår en forbedring på 200 ml (voksne)	15 procentpoint	7,5 procentpoint
Astmakontrol	Vigtig	Alvorlige symptomer	Gennemsnitlig ændring i astmakontrol. I prioriteret rækkefølge ønskes data fra: • ACQ (Asthma Control Questionnaire) • Andre lignende spørgeskemaer	ACQ: 0,5	ACQ: 2,5
Livskvalitet	Vigtig	Livskvalitet	Gennemsnitlig ændring i livskvalitet. I prioriteret rækkefølge ønskes data fra: • Astma Quality of Life Questionnaire (AQLQ) • Øvrige skemaer	AQLQ: 0,5	AQLQ: 2,5
Serious adverse events (SAE’s)	Vigtig	Alvorlige bivirkninger	Den samlede forekomst (antal) af SAE’s	5 procentpoint for den samlede forekomst af SAE’s	2,5 procentpoint for den samlede forekomst af SAEs
			Specifikke undertyper af SAE’s, herunder anafylaksi, vurderes, ift. om det præsenterer sig ensartet mellem grupperne	Der angives ikke en klinisk relevant forskel for forekomsten af specifikke SAE’s	-

Frafald af patienter i studier	Vigtigt	Ikke-alvorlige symptomer og bivirkninger	Andel af patienter som er frafaldet ved studiets afslutning (forskel mellem "intention to treat"-populationen og afsluttede patienter)	10 procentpoint	5 procentpoint
Sygefravær	Vigtigt	Ikke-alvorlige symptomer og bivirkninger	Gennemsnitligt antal sygedage pr. år – dage hvor pt. ikke kan gå i skole eller på arbejde	5 dage pr. år	2,5 dage pr. år

For alle effektmål ønskes data med længst mulig opfølgningstid. Opfølgningstiden for eksacerbationsraten skal være på minimum et år.

5.4.1 Kritiske effektmål

Eksacerbationsrate: Eksacerbationer er akutte astmaforværringer, der medfører stort ubehag for patienten og er en potentielt livstruende tilstand. En eksacerbation defineres som en ikkeplanlagt astmarelateret kontakt med læge, som fører til indlæggelse eller minimum 3 dages oral kortikosteroidbehandling. For børn defineres det som enhver form for akut astmarelateret kontakt med læge, som medfører en intervention. En reduktion i antallet af eksacerbationer betragtes derfor som et kritisk effektmål for vurderingen af et præparat til behandling af svær astma. Der findes ikke et anerkendt mål for den mindste klinisk relevante forskel i eksacerbationsrate [10]. Den mindste klinisk relevante forskel i absolutte tal skal dog være en forskel på minimum 1 årlig eksacerbation i gennemsnit mellem grupperne.

Herudover har fagudvalget vurderet, at det udover en gennemsnitlig betragtning vil være relevant at se på andelen af patienter, der bliver helt fri for eksacerbationer (0 årlige eksacerbationer). Da dette som oftest er meget syge mennesker, som således kan blive helt fri for eksacerbationer, blev det vurderet af fagudvalget, at en forskel mellem grupperne på 10 procentpoint er klinisk relevant.

Af fagudvalget vurderes det, at den gennemsnitlige patient, der indstilles til behandling med biologiske lægemidler, har minimum 2 årlige eksacerbationer.

Peroral vedligeholdelsesbehandling med systemisk kortikosteroid er forbundet med en lang række bivirkninger. En andel af patienter med svær astma modtager periodevis kontinuerlig vedligeholdelsesbehandling med oral kortikosteroid for at bedre sygdomskontrol eller reducere eksacerbationsraten. Det er derfor relevant at undersøge, om anvendelsen af biologiske lægemidler til svær astma muliggør en reduktion i behandling med oral kortikosteroid uden øgning af eksacerbationsraten. Måleenheden for effektmålet er den procentvise reduktion i den gennemsnitlige daglige dosis. En forskel mellem grupperne på 20 % i reduktion af den gennemsnitlige daglige steroiddosis anses for at være klinisk relevant. Den mindste klinisk relevante forskel i absolutte tal skal dog minimum være 2,5 mg prednisolon ækvivalent pr. dag i gennemsnit mellem grupperne.

Der ønskes herudover viden om, hvor stor en andel af patienter der helt kan undvære den perorale vedligeholdelsesbehandling med kortikosteroider. En forskel mellem interventionen og komparator på 5 procentpoint anses her for at være klinisk relevant.

Fagudvalget vurderede desuden, at andelen af patienter som opnår $\geq$ 50 % reduktion af peroral vedligeholdelsesbehandling med systemisk kortikosteroid er et relevant effektmål, idet en sådan reduktion ville betyde færre bivirkninger. En forskel mellem interventionen og komparator på 10 procentpoint anses her for at være klinisk relevant.

Af fagudvalget vurderes det, at den gennemsnitlige patient, der behandles med peroralt steroid i vedligeholdelsesbehandling, har en daglig dosis på < 10 mg prednisolon ækvivalent.

5.4.2 Vigtige effektmål

En nedsat **lungefunktion** målt ved FEV_1 er associeret med øget risiko for eksacerbationer og nedsat livskvalitet. At bevare en normal lungefunktion er et af målene for astmabehandling. Lungefunktion er et af flere mål for astmakontrol og betragtes i denne protokol som et vigtigt effektmål for vurderingen af et præparat til behandling af svær astma. Den mindste klinisk relevante forskel i lungefunktionstest er ikke klarlagt inden for astma. For FEV_1 er det i litteraturen beskrevet at ligge mellem 100-230 ml for voksne [11,12]. Samtidig definerer man en ændring på 200 ml i FEV_1 som en positiv bronchodilator reversibility-test for voksne. Data ønskes opgjort på to måder: 1) Den gennemsnitlige forskel i ændringen af lungefunktion mellem intervention og komparator med mindste klinisk relevante forskel på 200 ml for voksne. 2) Andelen af patienter der opnår en ændring på den mindste klinisk relevante forskel på 200 ml for voksne. Her anses 15 procentpoints forskel mellem grupperne for at være klinisk relevant.

Astmakontrol er målet for behandlingen, og behandlingen optrappes, hvis astmakontrollen ikke er tilstrækkelig på det pågældende behandlingstrin. Daglige symptomer er en del af astmakontrolspørgeskemaer og kan give et indtryk af, hvor generet den enkelte patient er i sin dagligdag. Flere forskellige spørgeskemaer bruges til vurdering af astmakontrol. Astma Control Questionnaire (ACQ) er det mest brugte i den internationale litteratur, og der ønskes derfor primært data fra dette. Astma Control Test (ACT) er også et anvendt redskab, og data herfra vil blive anvendt, i tilfælde hvor ACQ-data ikke er til rådighed. Data fra øvrige astmakontrolspørgeskemaer medtages, hvis ACQ eller ACT ikke er anvendt. Mindste klinisk relevante forskelle er defineret i de enkelte måleredskaber og er 0,5 for ACQ [1]. Der ønskes data på den gennemsnitlige forskel i ændringen af astmakontrol mellem intervention og komparator.

Livskvalitet måles inden for astma med det såkaldte Astma Quality of Life Questionnaire (AQLQ). I praksis er dette det mest brugte mål for livskvalitet i relation til astma, og derfor foretrækkes data herfra frem for data fra generiske spørgeskemaer om livskvalitet (f.eks. EQ5D). Data fra øvrige livskvalitetsspørgeskemaer medtages, hvis AQLQ ikke er anvendt. Den mindste kliniske forskel er defineret i redskabet og er 0,5 [13]. Der ønskes data på den gennemsnitlige forskel i ændringen af livskvalitet mellem intervention og komparator.

Serious adverse events (SAE's) er i sagens natur alvorlige. Fagudvalget har vurderet, at SAE's er et vigtigt effektmål for behandling af svær astma med biologiske lægemidler. SAE's defineres som enhver hændelse eller en bivirkning, som uanset dosis resulterer i død, er livstruende, medfører hospitalsindlæggelse eller forlængelse af hospitalsophold, resulterer i betydelig eller vedvarende invaliditet eller uarbejdsdygtighed eller fører til en medfødt anomali eller misdannelse. Forekomsten af SAE's vurderes ikke som værende kritisk i dette projekt, idet øvrige vigtige effektmål vurderes at have større betydning for denne patientgruppe. For den samlede forekomst af SAE's anses en forskel mellem grupperne på 5 procentpoint for at være klinisk relevant. Fagudvalget vil desuden vurdere forekomsten af specifikke undertyper af SAE's, herunder forekomsten af anafylaktisk shock. Grundet graden af alvorlighed af f.eks. anafylaktisk shock og den sjældne forekomst af specifikke undertyper af bivirkninger kan der ikke sættes en retvisende grænse for, hvornår en forskel er klinisk relevant. Den kliniske relevans af en evt. forskel mellem lægemidler vil blive vurderet efterfølgende af fagudvalget.

Frafald af patienter i studier betragtes som et samlet udtryk for tyngden af bivirkninger og effekten af behandlingen og giver samtidig et indtryk af, hvor mange patienter der vil kunne gennemføre behandlingen med lægemidlerne i den kliniske hverdag. En forskel mellem grupperne på 10 procentpoint anses for klinisk relevant.

Sygefravær er et vigtigt og patientrelevant mål. Fagudvalget vurderer, at det at kunne passe sin skole/sit arbejde er af stor psykologisk og økonomisk betydning for den enkelte patient. Sygefraværet berøres delvist i spørgeskemaer for livskvalitet og astmakontrol, men da dette specifikke element anses for at være af specielt

stor vigtighed, vurderes det som et separat effektmål. En forskel mellem grupperne på 5 dage anses for at være klinisk relevant, og det ønskes opgjort i antal sygefraværsdage per år.

6 Litteratursøgning

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

Sekretariatet har på baggrund af den foreløbige ansøgning undersøgt, om der findes et eller flere peer-reviewede publicerede fuldtekstartikler, hvor dupilumab er sammenlignet direkte med komparatorerne.

Sekretariatet har ikke fundet artikler, som kan anvendes til direkte sammenligning af dupilumab med alle komparatorer.

Virksomheden skal derfor søge efter studier, der kan anvendes til sammenligninger af dupilumab med mepolizumab og omalizumab og placebo i de nævnte patientpopulationer. Det betyder, at der både skal søges efter primærstudier af dupilumabs effekt og efter primærstudier af effekten af mepolizumab og omalizumab. Til det formål har sekretariatet udarbejdet søgestrenge, som skal anvendes i MEDLINE (via PubMed) og CENTRAL (via Cochrane Library). Søgestrengene kan findes i bilag 1. Derudover skal EMAs European public assessment reports (EPAR) konsulteres for både det aktuelle lægemiddel og dets komparator(er).

Kriterier for udvælgelse af litteratur
Virksomheden skal først ekskludere artikler på titel- og abstractniveau, dernæst ved gennemlæsning af fuldtekstartikler. Artikler, der ekskluderes ved fuldtekstlæsning, skal fremgå med forfatter, årstal og titel i en eksklusionsliste, hvor eksklusionen begrundes kort. Den samlede udvælgelsesproces skal afrapporteres ved brug af et PRISMA-flowdiagram *(*http://prisma-statement.org/PRISMAStatement/FlowDiagram.aspx*)*.

Ved usikkerheder om, hvorvidt en artikel på titel- og abstractniveau lever op til inklusions- og eksklusionskriterierne, skal der anvendes et forsigtighedsprincip til fordel for artiklen, hvorved fuldtekstartiklen vurderes.

Inklusions- og eksklusionskriterier
Kun randomiserede studier ønskes medtaget. Studier, som ikke rapporterer på svær astma, ekskluderes. Studier, som ikke rapporterer mindst et af de kritiske eller vigtige effektmål, ekskluderes. For studier på mepolizumab godtages data på subkutan 100 mg og intravenøs 75 mg, da disse anses for ækvivalente doser. For dupilumab ønskes data for indikationen. For effektmålet 'Peroral vedligeholdelsesbehandling med kortikosteroid' ønskes data for dosis på 300 mg. For øvrige effektmål ønskes data for dosis på 200 mg. For omalizumab ønskes kun data for den indicerede dosis.

7 Databehandling og analyse

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

Baseline- og studiekarakteristika ønskes i samme format som medicinrådets behandlingsvejledning for biologiske lægemidler til svær astma bilag 13 og 14 [14].

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. Oplysning om, hvor data på de enkelte effektmål stammer fra, samt beskrivelse af, hvilke analysemetoder der er blevet anvendt til hvilke effektmål, skal fremgå.

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

For effektmål (ORR, SAE, behandlingsstop pga. bivirkninger og ikkealvorlige bivirkninger), hvor det er naturligt at beregne både absolut og relativ forskel, vil den relative forskel være basis for statistiske analyser. Den absolutte forskel vil derefter blive beregnet, baseret på den estimerede relative forskel for et antaget niveau på hændelsesraten i komparatorgruppen. Det antagne niveau vil afspejle det forventede niveau i Danmark ved behandling med komparator (hvis relativ risiko (RR) = 0,5 og antaget andel med hændelse i komparatorgruppen er 30 %, da er den absolutte risikoreduktion (ARR) = 30 – 30 x 0,5 = 15 %-point).

Hvis der er mere end ét sammenlignende studie, foretages en metaanalyse for de effektmål, hvor det er metodemæssigt forsvarligt. Hvis der ikke foreligger sammenlignende studier, kan data eventuelt syntetiseres indirekte (evt. i form af formelle netværksmetaanalyser eller ved brug af Buchers metode), hvis intervention og komparator er sammenlignet med samme alternative komparator i separate studier. Medicinrådet forbeholder sig retten til at foretage sensitivitets- og subgruppeanalyser på baggrund af studiernes validitet og relevans. Såfremt metaanalyser og/ eller sammenlignende indirekte analyser vil være relevante, ønskes en vurdering af, om studierne er homogene nok til at sammenlignes.

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) eller sammenlignende analyser, 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 (statistisk analyse eller narrativ beskrivelse) begrundes, og specifikke analysevalg truffet i forhold til metoden skal fremgå tydeligt.

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9 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende svær astma

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To patienter/patientrepræsentanter	Danske Patienter

Medicinrådets sekretariat

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10 Versionslog

Version	Dato	Ændring
1.0	xx.xx.2019	Godkendt af Medicinrådet.

11 Bilag 1: Søgestrenge

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

#	Søgetermer	Kommentar
1	Asthma[mh] OR asthma*[tiab]	Søgeord for indikation. De søges som MeSH term, og som fritekst i titel og abstract
2	SAR231893[nm] OR dupilumab[tiab] OR REGN668[tiab] OR REGN-668[tiab] OR SAR-231893[tiab] OR SAR23189[tiab] OR dupixent*[tiab]	Søgeord for ansøgers lægemiddel og komparator. De søges som Supplementary Concept/Substance, MeSH termer, og som fritekst i titel og abstract
3	mepolizumab[nm] OR SB-240563[tiab] OR SB240563[tiab] OR nucala*[tiab]	
4	Omalizumab[mh] OR omalizumab[tiab] OR xolair*[tiab]	
5	#2 OR #3 OR #4	
6	**#1 AND #5**	**Indikation og lægemidler kombineres**
7	Animals[mh] NOT Humans [mh]	Eksklusion af (indekserede) dyreforsøg
8	#6 NOT #7	
9	randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti]	Afgrænsning til randomiserede, kontrollerede forsøg. **Linje 10 = endeligt resultat, hvis I ikke ønsker afgrænsning på publikationstyper.**
10	#8 AND #9	
11	Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR News[pt] OR Review[pt] OR Systematic Review[pt]	Afgrænsning: eksklusion af (indekserede) bestemte publikationstyper (valgfrit) **Linje 12 = endeligt resultat**
12	**#10 NOT #11**	

Feltkoder:

mh = MeSH Term

nm = Supplementary Concept/Substance

tiab = title/abstract, inkl. forfatterkeywords

pt = publication type

Søgestrategi, Central https://www.cochranelibrary.com/

#	Søgetermer	
#1	asthma:kw OR asthma*:ti,ab	Søgeord for indikationen. Der søges på fritekst i titel og abstract, samt på indekserede termer fra både Medline og Embase.
#2	(SAR231893 OR dupilumab or REGN668 OR "REGN 668" OR dupixent*):ti,ab,kw	Søgeord for ansøgers lægemiddel samt komparator. Der søges på fritekst i titel og abstract, samt på indekserede termer fra Medline og Embase
#3	(mepolizumab OR "SB 240563" OR SB240563 OR nucala*):ti,ab,kw	
#4	(omalizumab OR olizumab OR xolair* OR "hu 901" OR HU901):ti,ab,kw	
#5	#2 OR #3 OR #4	
#6	**#1 and #5**	**Indikation og lægemidler kombineres**
#7	conference abstract:pt	Afgrænsning (eksklusion) på publikationstype samt (en del) af de resultater, der kommer fra clinicaltrials.gov.
#8	review:pt	
#9	NCT*:au	
#10	("clinicaltrials gov" OR trialsearch):so	
#11	#7 OR #8 OR #9 OR #10	
#12	#6 NOT #11	
#13	pubmed:an	Ekskludering af poster, der kommer fra Pubmed. **Endeligt resultat = linje #14**
#14	**#12 NOT #13 in Trials**	

Feltkoder:

ti: title

ab: abstract

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

pt = publication type