Baggrund for Medicinrådets anbefaling af benralizumab som mulig standardbehandling til svær, eosinofil astma

Handelsnavn	Fasenra
Generisk navn	Benralizumab
Firma	AstraZeneca AB
ATC-kode	R03DX10
Virkningsmekanisme	Benralizumab er et monoklonalt antistof rettet mod interleukin 5 (IL-5)-receptorer. IL-5 er et cytokin, som spiller en central rolle i produktion, modning og overlevelse af eosinofile granulocytter. Binding af antistofferne til IL-5-receptorer medfører dermed en reduktion i antallet af eosinofile granulocytter, hvilket resulterer i bedre sygdomskontrol.
Administration/dosis	Benralizumab administreres ved en forfyldt injektionssprøjte. Den anbefalede dosis er 30 mg ved subkutan injektion hver 4. uge for de første 3 doser, dernæst hver 8. uge.
EMA-indikation	Benralizumab er indiceret som en tillægsvedligeholdelsesbehandling til voksne patienter (> 18 år) med svær, eosinofil astma, der ikke kontrolleres tilstrækkeligt på trods af høj dosis af inhalationskortikosteroider plus langtidsvirkende β-agonister.
Godkendelsesdato Offentliggørelsesdato Dokumentnummer Versionsnummer	30. maj 2018 30. maj 2018 18468 1.0
Fagudvalgets sammensætning og sekretariatets arbejdsgruppe	Se afsnit 7

Om Medicinrådet:

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

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

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

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

Indhold

1 Medicinrådets anbefaling

Medicinrådet **anbefaler** benralizumab som mulig standardbehandling til svær, eosinofil astma.

Det kliniske spørgsmål, som ligger til grund for anbefalingen, er som følger: "Hvilken klinisk merværdi tilbyder benralizumab sammenlignet med mepolizumab ved behandling af patienter med svær, eosinofil astma?"

2 Introduktion

2.1 Om indikationen

Benralizumab er indiceret som tillægsbehandling til voksne med svær, eosinofil astma, som er ukontrolleret trods øvrig behandling.

Svær astma har gennem minimum det sidste år krævet behandling med høj dosis inhalationssteroid samt en eller flere tillægsbehandlinger (2nd controller (typisk langtidsvirkende beta2-agonist, LABA), og/eller krævet peroralt steroid i ≥ 50 % af tiden) for at opretholde sygdomskontrol eller trods denne behandling er forblevet ukontrolleret.

2.2 Sagsbehandlingstid og proces for Medicinrådets vurdering

Medicinrådet modtog den foreløbige ansøgning på benralizumab den 15. november 2017. Ansøgers endelige ansøgning blev modtaget den 19. februar 2018. Vurderingsrapporten blev godkendt af Medicinrådet den 24. april 2018. Medicinrådet har gennemført vurderingen af benralizumab på 14 uger og 2 dage.

3 Medicinrådets vurdering af samlet klinisk merværdi

Medicinrådet vurderer, at benralizumab til patienter med svær, eosinofil astma giver **ingen klinisk merværdi** sammenlignet med mepolizumab. Evidensens kvalitet vurderes at være **lav**.

4 Høring

Vurderingsrapporten blev den 17. april 2018 sendt i høring hos ansøger. Høringssvaret blev modtaget den 25. april 2018. Høringssvaret gav ikke anledning til ændringer i kategoriseringen.

5 Resumé af økonomisk beslutningsgrundlag

Analysen estimerer de gennemsnitlige omkostninger pr. patient og de samlede budgetkonsekvenser for regionerne ved ibrugtagning af benralizumab som mulig standardbehandling til patienter med svær, eosinofil astma. I analyserne sammenlignes behandling med benralizumab med behandling med mepolizumab.

Resultatet af omkostningsanalysen viser, at de samlede gennemsnitlige omkostninger pr. patient i behandling med benralizumab over fem år er 15.069 kr. (ved AIP) højere end de samlede gennemsnitlige

omkostninger pr. patient i behandling med mepolizumab. Analysens resultater påvirkes i altovervejende grad af omkostningerne forbundet med anskaffelse af lægemidlerne. Resultaterne er derfor meget følsomme over for nuværende og fremtidige rabatter på AIP. Eftersom omkostningerne forbundet med de sammenlignede behandlinger er meget ens vil en anbefaling af benralizumab være forbundet med meget små budgetkonsekvenser.

Det konkluderes, at behandling med benralizumab og behandling med mepolizumab er forbundet med sammenlignelige behandlingsomkostninger, uanset om der ses på de samlede behandlingsomkostninger, eller om man vurderer behandlingerne i et mere snævert perspektiv og kun ser på lægemiddelomkostningerne.

Amgros vurderer, at der er et rimeligt forhold mellem den kliniske merværdi og de omkostninger, der er forbundet med behandling med benralizumab (Fasenra).

6 Overvejelser omkring alvorlighed/forsigtighed

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

7 Sammensætning af fagudvalg

Formand t.o.m. 31. marts 2018	*Indstillet af*
Uffe Christian Heitmann Bødtger *Forskningslektor*	Lægevidenskabelige Selskaber
Formand fra 1. april 2018	*Indstillet af*
Bo Chawes *Afdelingslæge, seniorforsker, dr.med., ph.d.*	Dansk Pædiatrisk Selskab
Medlemmer	*Udpeget af*
Kirsten Sidenius *Praktiserende speciallæge, ph.d.*	Inviteret af formanden
Kan ikke udpege	Region Nordjylland
Pernille Hauschildt *Ledende overlæge, ph.d.*	Region Midtjylland
Hanne Madsen *Ledende overlæge, ph.d.*	Region Syddanmark
Niels Maltbæk *Overlæge*	Region Sjælland
Lars Pedersen *Overlæge, klinisk lektor, ph.d.*	Region Hovedstaden
Pernille Printzlau *Farmaceut, cand.pharm.*	Dansk Selskab for Sygehusapoteksledelse
Daniel Pilsgaard Henriksen *Læge, ph.d.*	Dansk Selskab for Klinisk Farmakologi
To patienter/patientrepræsentanter	Danske Patienter

Medicinrådets sekretariat

Medicinrådet Dampfærgevej 27-29, 3. 2100 København Ø + 45 70 10 36 00 medicinraadet@medicinraadet.dk
Sekretariatets arbejdsgruppe: Louise Klokker Madsen (projekt- og metodeansvarlig) Pernille Skaarup Arrevad (projektdeltager) Anette Pultera Nielsen (koordinator) Annemette Anker Nielsen (teamleder)

8 Bilag

Bilagsliste:

1) Amgros' beslutningsgrundlag
2) Amgros' sundhedsøkonomiske analyse
3) Høringssvar fra ansøger
4) Vurdering af den kliniske merværdi af benralizumab
5) Ansøgers endelige ansøgning
6) Protokol for vurdering af den kliniske merværdi af benralizumab

Amgros I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

medicin@amgros.dk
www.amgros.dk

Beslutningsgrundlag til Medicinrådet

Dette dokument er Amgros' anbefaling til Medicinrådet om vurdering af benralizumab (Fasenra) til mulig standardbehandling af svær, eosinofil astma. Indstillingen er baseret på en vurdering af lægemidlets inkrementelle omkostninger (baseret på Amgros' aftalepriser) sammenholdt med Medicinrådets vurdering af den kliniske merværdi.

Dato for Medicinrådsbeslutning	30-05-2018
Firma	AstraZeneca
Lægemiddel	Benralizumab (Fasenra)
Indikation	Svær, eosinofil astma

Amgros' anbefaling af lægemidlet

- Amgros anbefaler, at Medicinrådet anbefaler benralizumab (Fasenra) til mulig standardbehandling for patienter med svær, eosinofil astma.

Overordnet konklusion

Medicinrådet har vurderet, at benralizumab (Fasenra) ingen klinisk merværdi har sammenlignet med mepolizumab (Nucala).

Amgros vurderer, at der er et rimeligt forhold mellem den kliniske merværdi og de omkostninger, der er forbundet med behandling med benralizumab (Fasenra).

Amgros har indgået en aftale med AstraZeneca om indkøb af benralizumab (Fasenra) til en aftalepris, som er lavere end AIP. Konklusionen er baseret på aftaleprisen for benralizumab (Fasenra).

Konklusion per population

Tabel 1: Merværdi, meromkostninger og Amgros' anbefaling

Population	Komparator	Merværdi	Usikkerhed for klinisk merværdi	Amgros' konklusion om forhold mellem omkostninger og klinisk merværdi	Anbefaling som mulig standardbehandling
Svær, eosinofil astma	Mepolizumab (Nucala)	Ingen klinisk merværdi	Lav evidenskvalitet	Acceptabelt	Ja

Supplerende informationer (resumé af resultaterne i afrapporteringen)

Konklusion på omkostnings- og budgetkonsekvensanalyserne

Aftalepriserne på benralizumab (Fasenra) og mepolizumab (Nucala) påvirker nedenstående resultater. Foretages analyserne på baggrund af aftalepriser og ikke på AIP, er benralizumab (Fasenra) forbundet med lavere behandlingsomkostninger end behandling med mepolizumab (Nucala).

For uddybende gennemgang af analyse og resultater henvises til afrapporteringen.

Inkrementelle omkostninger per patient

Resultatet af omkostningsanalysen viser, at de samlede gennemsnitlige meromkostninger ved behandling med benralizumab (Fasenra) over fem år er på 15.069 kr. (ved AIP) pr. patient.

Analysens resultater påvirkes i altovervejende grad af omkostningerne forbundet med anskaffelse af lægemidlerne. Resultaterne er derfor meget følsomme over for nuværende og fremtidige rabatter på AIP.

Tabel 1: Estimerede omkostninger pr. patient, AIP, (diskonterede)

Behandling		År 1	År 2	År 3	År 4	År 5	Total
Benralizumab (Fasenra)	Antal doser	8	6	7	6	7	*34*
	I alt	152.764	110.274	123.830	102.165	114.734	*603.767*
Mepolizumab (Nucala)	Antal doser	13	13	13	13	13	*65*
	I alt	126.668	122.029	117.568	113.279	109.155	*588.698*
Inkrementel omkostning		*26.096*	*-11.755*	*6.262*	*-11.114*	*5.579*	*15.069*

Budgetkonsekvenser

Eftersom omkostningerne forbundet med de sammenlignede behandlinger er meget ens vil en anbefaling af benralizumab (Fasenra) være forbundet med meget små budgetkonsekvenser.

Kontraktforhold

Amgros har indgået en aftale med AstraZeneca. Aftalen indeholder en rabat. Aftalen vil løbe indtil det næste udbud, som bliver annonceret efter Medicinrådet har godkendt det endelige sammenligningsgrundlag, der udarbejdes ifbm. terapiområdevurderingen af svær astma.

BENRALIZUMAB (FASENRA)

SVÆR EOSINOFIL ASTMA

AMGROS 5. marts 2018

AMGROS

Resumé

Baggrund

Benralizumab (Fasenra) er et lægemiddel, som er godkendt til behandling af voksne patienter med svær, eosinofil astma. AstraZeneca er markedsføringstilladelsesindehaver. Ifølge Medicinrådets behandlingsvejledning for svær, eosinofil astma skønnes antal prævalente patienter med svær, eosinofil astma, som er i behandling med anti-IL5 præparaterne mepolizumab (Nucala) eller reslizumab (Cinqaero) i Danmark at være 140 patienter. Endvidere skønnes det, at yderligere 140 patienter i 2018 vil påbegynde behandling. Eftersom lægemidlerne er forholdsvis nye, forventes der at være flest nye patienter i den første årrække og herefter muligvis lidt færre

Analyse

Analysen estimerer de gennemsnitlige omkostninger pr. patient og de samlede budgetkonsekvenser for regionerne ved ibrugtagning af benralizumab (Fasenra) som mulig standardbehandling til patienter med svær, eosinofil astma. I analyserne sammenlignes behandling med benralizumab (Fasenra) med behandling med mepolizumab (Nucala).

I analyserne i denne afrapportering anvendes AIP på benralizumab (Fasenra) og mepolizumab (Nucala).

Inkrementelle omkostninger og budgetkonsekvenser

Resultatet af omkostningsanalysen viser, at de samlede gennemsnitlige omkostninger pr. patient i behandling med benralizumab (Fasenra) over fem år er 15.069 kr. (ved AIP) højere end de samlede gennemsnitlige omkostninger pr. patient i behandling med mepolizumab (Nucala).

Analysens resultater påvirkes i altovervejende grad af omkostningerne forbundet med anskaffelse af lægemidlerne. Resultaterne er derfor meget følsomme over for nuværende og fremtidige rabatter på AIP.

Eftersom omkostningerne forbundet med de sammenlignede behandlinger er meget ens vil en anbefaling af benralizumab (Fasenra) være forbundet med meget små budgetkonsekvenser.

Konklusion

Overordnet kan det konkluderes, at behandling med benralizumab (Fasenra) og behandling med mepolizumab (Nucala) er forbundet med sammenlignelige behandlingsomkostninger uanset om der ses på de samlede behandlingsomkostninger eller om man vurderer behandlingerne i et mere snævert perspektiv og kun ser på lægemiddelomkostningerne.

INDHOLD

Ansøgning	
Lægemiddelfirma:	AstraZeneca
Handelsnavn:	Fasenra
Generisk navn:	Benralizumab
Indikation:	Svær eosinofil astma
ATC-kode:	R03DX10

Proces	
Ansøgning modtaget hos Amgros:	19-02-2018
Endelig rapport færdig:	05-03-2018
Sagsbehandlingstid fra endelig ansøgning:	14 dage
Arbejdsgruppe:	**Asbjørn Lydert Hansen** Asger Lindvig Andreas Pagh Rasmussen

Priser

Alle lægemiddelpriser i denne afrapportering er på AIP-niveau. Amgros har ofte aftaler om rabatter på de analyserede lægemidler. Derfor vil analyser på AIP-niveau ikke altid afspejle regionernes faktiske omkostninger til anskaffelse af lægemidlerne. Da rabatterne varierer betragteligt på tværs af lægemidler, vil prisforskellene i afrapporteringen, ikke altid afspejle de faktiske prisforskelle.

Anbefalingerne i Amgros' beslutningsgrundlag, som sendes sammen med denne afrapportering, bygger på regionernes faktiske anskaffelsespriser (SAIP).

1. BAGGRUND

Benralizumab (Fasenra) er godkendt af Europakommissionen til behandling af voksne patienter med svær, eosinofil astma, der ikke kontrolleres tilstrækkeligt på trods af høj dosis af inhalationskortikosteroider samt langtidsvirkende β agonister (1). AstraZeneca er markedsføringstilladelsesindehaver af benralizumab (Fasenra) og har indsendt en ansøgning til Medicinrådet om ibrugtagning af benralizumab (Fasenra) som mulig standardbehandling af svær, eosinofil astma på danske hospitaler. Medicinrådet har endeligt modtaget ansøgningen den 19. februar 2018. Som et led i denne ansøgning vurderer Amgros på vegne af Medicinrådet de økonomiske analyser, AstraZeneca har sendt som en del af den samlede ansøgning til Medicinrådet. Denne rapport er Amgros' vurdering af de indsendte økonomiske analyser (herefter omtalt som analysen).

1.1 Problemstilling

Formålet med analysen er at estimere omkostningerne forbundet med behandling af svær, eosinofil astma i form af de gennemsnitlige omkostninger pr. patient og de samlede budgetkonsekvenser for regionerne ved ibrugtagning af benralizumab (Fasenra) som mulig standardbehandling. I analyserne sammenlignes behandling med benralizumab (Fasenra) med behandling med mepolizumab (Nucala).

1.2 Patientpopulation

Astma er en hyppigt forekommende kronisk sygdom i Danmark hos både børn og voksne. Det vurderes, 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 (2) og omkring 50 % af svær astma patienter har øget eosinofiltal (3). Der indlægges ca. 1.500 patienter med akut astma om året i Danmark. Mildere tilfælde af akut astma, som håndteres af vagtlæge eller akutmodtagelse, er langt hyppigere (2).

I henhold til Medicinrådets behandlingsvejledning for svær, eosinofil astma anbefales behandling med mepolizumab (Nucala) og reslizumab (Cinqaero) for patienter som opfylder følgende kriterier:

- Der er foretaget systematisk udredning af mulig svær astma, jf. DLS' retningslinjer (4)
- Behandlingstrin svarende til svær astma, jf. ERS/ATS' retningslinjer (4), dvs. kombinationsbehandling med højdosis ICS samt en eller flere tillægsbehandlinger og/eller fast behandling med OCS
- Eosinofili:
    - blodeosinofile er ≥ 150 celler per mikroliter observeret indenfor den seneste måned inden opstart af behandling med anti-IL5 eller
    - blodeosinofile ≥ 300 celler per mikroliter er observeret indenfor det seneste år eller
    - 3 % sputum eosinofili er observeret indenfor det seneste år
    - FeNO-niveau kan ikke anvendes som proxymål for blod- eller sputum eosinofili
- ≥ 2 årlige eksacerbationer eller daglig vedligeholdelsesbehandling med OCS i en dosis på ≥ 5 mg prednisolon ækvivalent i mere end 50 % af tiden i det foregående år

Ifølge Medicinrådets behandlingsvejledning for svær, eosinofil astma skønnes antal prævalente patienter med svær, eosinofil astma, som er i behandling med anti-IL5 præparaterne mepolizumab (Nucala) eller reslizumab (Cinqaero) i Danmark at være 140 patienter. Endvidere skønnes det, at yderligere 140 patienter i 2018 vil påbegynde behandling. Eftersom lægemidlerne er forholdsvis nye, forventes der at være flest nye patienter i den første årrække og herefter muligvis lidt færre (4). Ansøger har analyseret salgstallene for disse produkter og estimerer, at 220-230 patienter er i behandling med enten mepolizumab (Nucala) eller reslizumab (Cinqaero) (estimeret december 2017), og at omkring 140 patienter forventes at begynde behandling i 2018.

1.3 Behandling af svær, eosinofil astma

Behandling med benralizumab (Fasenra)

Indikation

Benralizumab (Fasenra) er indiceret som en tillægsvedligeholdelsesbehandling til voksne patienter med svær, eosinofil astma, der ikke kontrolleres tilstrækkeligt på trods af høj dosis af inhalationskortikosteroider plus langtidsvirkende β agonister (1).

Virkningsmekanisme

Benralizumab (Fasenra) er et monoclonalt antistof rettet mod IL-5 receptorer. IL-5 er et cytokin, som spiller en central rolle i produktion, modning og overlevelse af eosinofile granulocytter. Binding af antistofferne til IL-5 receptorer medfører dermed en reduktion i antallet af eosinofile granulocytter, resulterende i bedre sygdomskontrol (1).

Dosering

Benralizumab (Fasenra) administreres ved en forfyldt injektionssprøjte. Den anbefalede dosis er 30 mg ved subkutan injektion hver 4. uge for de første 3 doser, dernæst hver 8. uge (1).

Komparator

Medicinrådet har defineret mepolizumab (Nucala) som relevant komparator for benralizumab (Fasenra).

Da både benralizumab (Fasenra) og mepolizumab (Nucala) er tillægsbehandling ved svær, eosinofil astma, vil der være en underliggende behandling, som benævnes standardbehandling (SoC). SoC ved svær, eosinofil astma: Høj dosis inhalationssteroid samt en anden forebyggende behandling (langtidsvirkende beta2-agonist, leukotrien antagonist, langtidsvirkende antikolinergikum eller theofyllin eller fast behandling med peroralt steroid) (2). I ansøgningen behandles SoC ikke, da den forventes at være ens mellem benralizumab (Fasenra) og mepolizumab (Nucala).

1.5 Tidshorisont

I Medicinrådets protokol angives ikke en specifik tidshorisont (2).

De tre store fase III studier, som er grundlaget for den indirekte sammenligning med mepolizumab (Nucala), eksacerbationsstudierne CALIMA og SIROCCO samt OCS-reduktionsstudiet ZONDA, forløb i henholdsvis 56, 48 og 28 uger. Amgros vurderede på formødet med ansøger, at en tidshorisont på 2 år i basecasen vil være repræsentativt for den økonomiske sammenligning med mepolizumab (Nucala), eftersom de inkluderede omkostninger i denne analyse, ikke er relateret til effekten af lægemidlerne og derfor ikke forbundet med samme usikkerhed.

2. VURDERING AF INDSENDT ØKONOMISK ANALYSE

2.1 Model, metode og forudsætninger

I analysen estimeres de gennemsnitlige omkostninger pr. patient ved behandling med benralizumab (Fasenra) og mepolizumab (Nucala). Eftersom der ikke foreligger et head-to-head studie af benralizumab (Fasenra) vs. mepolizumab (Nucala), har ansøger fået udført en indirekte sammenligning, Matching Adjusted Indirect Comparison (MAIC). Denne viser generelt numeriske men ikke statistisk signifikante forskelle på de sammenlignede effektmål. På grund af dette anvendes i denne analyse udelukkende omkostninger, som ikke er relateret til effekten af lægemidlerne.

Modelbeskrivelse

Analysen estimerer de gennemsnitlige omkostninger pr. patient, som behandles med benralizumab (Fasenra) og mepolizumab (Nucala) over en 2-årig periode. Der anvendes et begrænset samfundsperspektiv i analysen, herunder direkte omkostninger afholdt på hospitalerne for behandling af svær, eosinofil astma i form af anskaffelse og administration af lægemiddel samt indirekte omkostninger relateret til patienttransport og patienttid.

Idet der kun anvendes ikke-effekt relaterede omkostninger i analysen og eftersom administrationsformen samt behandlingsforløbet er ens mellem benralizumab (Fasenra) og mepolizumab (Nucala), vil dette være en simpel opgørelse af forskelle i omkostninger forbundet med administrationsfrekvens samt lægemiddelpriser.

Ressourceforbruget ved behandling af svær, eosinofil astma er estimeret på baggrund af produktresuméet for benralizumab (Fasenra) og mepolizumab (Nucala) (1,5), Medicinrådets behandlingsvejledning for svær, eosinofil astma (4) samt 4 kvalitative interviews med navngivne læger, der behandler patienter med svær, eosinofil astma. Behandling med antistoffer (mepolizumab (Nucala) og reslizumab (Cinqaero)) ved svær, eosinofil astma finder sted på følgende 8 hospitaler i Danmark: Bispebjerg, Gentofte, Hvidovre, Roskilde, Aalborg, Aarhus, Odense og Vejle. Ansøger har modtaget feedback fra en læge i fire af de fem regioner.

Enhedsomkostningerne, der anvendes i analysen, er baseret på officielle markedspriser eller takster:

- Administrationsomkostninger, DAGS-takst fra www.sundhedsdatastyrelsen.dk
- Omkostninger relateret til patienttransport, Amgros' værdisætning af enhedsomkostninger (6)
- Omkostninger relateret til patienttid, Amgros' værdisætning af enhedsomkostninger (6)

Analysens tidshorisont strækker sig over to år, og derfor er omkostningerne i år 2 diskonterede i henhold til Amgros' metodevejledning for omkostningsanalyser. Der er en anvendt en diskonteringsrente på 4 %, hvilket er baseret på den nutidige samfundsøkonomiske diskonteringsrente fra Finansministeriet (7).

Amgros' vurdering

Amgros vurderer, at analyseperspektiv, tidshorisont, diskonteringsrente og den overordnede modeltilgang er acceptabel.

Omkostninger

Det følgende afsnit om omkostninger redegør for hvordan og hvilke omkostninger ansøger har inkluderet i analysen. I gennemgangen fokuseres både på opgørelse af det anvendte ressourceforbrug og værdisætningen af dette.

Lægemidler

Alle analyser i denne ansøgning anvender AIP for benralizumab (Fasenra) og mepolizumab (Nucala).

Da benralizumab (Fasenra) og mepolizumab (Nucala) er tillægsbehandling ved svær, eosinofil astma, vil der som tidligere nævnt være en underliggende SoC ved begge behandlinger. I denne ansøgning medregnes udgifter til SoC ikke, da den forventes at være ens for benralizumab (Fasenra) og mepolizumab (Nucala).

De anvendte enhedspriser er angivet i tabellen nedenfor.

Tabel 1: Lægemiddelpriser, AIP, 16/4-2018

Behandlingsregime	Pakning	Pris pr. pakning, kr.
Benralizumab (Fasenra)	1 stk. 30 mg inj. væske	17.953,40
Mepolizumab (Nucala)	1 stk. 100 mg pulv.t.inj.væske	8.601,54

Mepolizumab (Nucala) administreres hver 4. uge, hvilket betyder 13 administrationer pr. år. Benralizumab (Fasenra) administreres ved injektion hver 4. uge for de første 3 doser, dernæst hver 8. uge, hvilket betyder 7,5 administration i år 1 og 6,5 administration pr. år i alle efterfølgende år så længe patienten er i behandling.

Tabel 2: Gennemsnitlige antal doser pr. patient pr. år

Behandlingsregime	År 1	År 2	Total
Benralizumab (Fasenra)	7,5	6,5	14
Mepolizumab (Nucala)	13	13	26

Amgros' vurdering

Doseringen af lægemidlerne er i tråd med lægemidlernes SmPC'er. Reelt betyder doseringen af benralizumab (Fasenra), at der skal gives 8 doseringer (selvom den gennemsnitligt kan beregnes til 7,5, da 9. dosis først gives 4 uger inde i år 2) i første kalenderår og 6 doseringer i næste kalenderår. Doseringen vil i år 3 være på 7 doser og derefter 6 doser i år 4. Set over tidshorisonten på de to år er den samlede dosering angivet af ansøger derfor korrekt, men ser man i stedet på året med loading dosis vil doseringen være 8 og den gennemsnitlige årlige vedligeholdelsesdosis vil være på 6,5.

Amgros har derfor valgt at ændre præsentationen af resultaterne så de følger logikken i tabellen nedenfor:

Tabel 3: Antal doser pr. patient i hhv. første behandlingsår og gennemsnitlige doser i efterfølgende behandlingsår

Behandlingsregime	Opstart *år 1*	Vedligeholdelse *år 2, 3, 4, 5, n,*
Benralizumab (Fasenra)	8	6,5
Mepolizumab (Nucala)	13	13

Administration

Ved påbegyndelse af behandling med antistoffer ved svær, eosinofil astma vil patienter som regel gennemgå en udredning hvor bl.a. en klinisk vurdering af astma-kontrol, blodprøver, spirometri osv. foretages. Patienterne vil desuden løbende monitoreres gennem ambulante besøg (4).

For at sikre at alle relevante omkostninger for benralizumab (Fasenra) og mepolizumab (Nucala) relateret til opstart af behandling, administration og monitorering inkluderes i analysen, har ansøger foretaget interviews med fire forskellige læger i forskellige regioner i Danmark. Alle fire læger forventer at behandlingsforløbet og derved ressourceforbruget (foruden administrationsfrekvensen) for behandling med benralizumab (Fasenra) og mepolizumab (Nucala) er ens.

Både benralizumab (Fasenra) og mepolizumab (Nucala) administreres subkutant på hospitalet ved et ambulant besøg, og ansøger forventer derfor ikke at være en betydelig forskel på personaletid, lokaleanvendelse, utensilier m.v. relateret hertil.

Da der ikke forventes betydelige forskelle i ressourceforbruget har ansøger valgt at estimere ressourceforbruget forbundet med administration af lægemidlerne gennem en makroomkostningstilgang, hvilket vil sige brug af takster. Baseret på feedback fra klinikerne angående diagnosekode og procedurekode, har ansøger takseret et ambulant besøg for administration med antistoffer (mepolizumab (Nucala) eller reslizumab (Cinqaero)) med DAGS-taksten PG12B på 13.948 kr. Ansøger beskriver at denne DAGS-takst formentlig også dækker udgifterne til antistofferne. Eftersom lægemiddelpriserne inkluderes separat i beregningerne, er lægemiddelprisen for mepolizumab (Nucala) fratrukket. Dette betyder at ansøger har estimeret en omkostning pr. ambulant besøg til 5.126 kr.

Amgros' vurdering

Den anvendte DAGS-takst PG12B indeholder omkostninger til medicin. Der er tale om en takst, der bygger på de gennemsnitlige omkostninger for en lang række lægemidler med meget forskellige omkostninger tilknyttet. Amgros mener derfor ikke, at det er hensigtsmæssigt at trække prisen på mepolizumab (Nucala) fra taksten for at opnå en proxy for administrationsomkostningerne.

Med ændringerne i DRG-systemet pr. 1. januar 2018 skelnes ikke længere mellem ambulante (DAGS) og stationære (DRG) takster. Det betyder at taksterne for medicingivning ved subkutan injektion med diagnosekoden DJ451 (ikke-allergisk astma) er gået fra 672 kr. i 2017 til 5.277 kr. i 2018.

Det er muligt, at et besøg takseres med den nuværende takst på 5.277 kr., men denne takst dækker over et gennemsnit af meget varierende underliggende ydelser, herunder både ambulante og stationære aktiviteter. I Amgros' vejledning til værdisætning af enhedsomkostninger nævnes det, at anvendte takster skal afspejle det underliggende ressourceforbrug. Amgros mener hverken det er tilfældet ved at bruge ansøgers tilgang med at fratrække medicinomkostningerne fra en takst, der beregnes ud fra gennemsnitlige medicinomkostninger på tværs af en række meget forskellige lægemidler, eller ved at bruge taksten fra DRG 2018 på 5.277 kr.

Amgros har derfor valgt at værdisætte et ambulant besøg til DAGS-taksten BG50A (Ambulant besøg, pat. mindst 7 år) fra 2017, som i 2017 var på 672 kr. Taksten er PL-reguleret til 676,7 kr.

De af Amgros estimerede administrationsomkostninger er forbundet med hhv. benralizumab (Fasenra) og mepolizumab (Nucala) i år 1 og gennemsnitlige efterfølgende år er illustreret i tabellen nedenfor.

Tabel 4: Antal gennemsnitlige administrationer og estimerede administrationsomkostninger (udiskonterede), kr.

Behandlingsregime		Opstart, *år 1*	Vedligeholdelse, *år 2, 3, 4, 5, n,*
Benralizumab (Fasenra)	Antal administrationer	8	6,5
	Omkostning (BG50A)	5.413,60 kr.	4.398,55 kr.
Mepolizumab (Nucala)	Antal administrationer	13	13
	Omkostning (BG50A)	8.797,10 kr,	8.797,10 kr,

Patienttid og transport

Ansøger har estimeret omkostningerne relateret til patienten på baggrund af førnævnte interview med forskellige læger. Ansøger spurgte bl.a. lægerne om patienternes gennemsnitlige antal kilometer til og fra hospital, samt den gennemsnitlige tid patienterne bruger pr. behandling.

Ansøger har værdisat transport til og fra behandling på hospitalerne til det dobbelte af taksten som er angivet i Amgros' værdisætning af enhedsomkostninger, dvs. 200 kr. per besøg. Dette er baseret på besvarelserne fra lægerne og det faktum at der i alt kun findes 8 hospitaler i Danmark, hvor behandling med antistoffer ved svær, eosinofil astma udføres. En times patienttid værdisættes til 183 kr./timen jf. Amgros' værdisætning af enhedsomkostninger.

Antal transporter til og fra behandling pr. år er lig antallet af ambulante besøg pr. år. Tidsforbruget fra patienten forlader hjemmet/arbejdet til patienten er tilbage, er estimeret til 4 timer pr. gang. Ud fra antallet af transporter pr. år er det samlede antal patienttimer pr. år beregnet.

Amgros' vurdering

Amgros vurderer ikke at ansøgers metode - at spørge de behandlende læger, til afdækning af patienternes transportafstand giver et validt estimat af patienternes faktiske transportafstand. I Amgros' arbejde med udarbejdelse af et udvidet sammenligningsgrundlag til brug i arbejdet med terapiområdevurderingen, der sker sideløbende med vurderingen af benralizumab (Fasenra), tilkendegav klinikerne at en gennemsnitlig administration med mepolizumab (Nucala) medførte én times patienttid på klinikken. Amgros vurderer samtidig, at dokumentationen, der ligger til grund for de øgede transportomkostninger ift. Amgros' standard på 100 kr., ikke er tilstrækkelig til at Amgros vil acceptere 200 kr. i transportomkostninger pr. administration. Amgros vælger derfor at regne med én times transporttid pr. administration, én times patienttid på selve administrationen af lægemidlet og 100 kr. som enhedsomkostning pr. transport.

2.2 Resultater

Amgros vurderer, at analysen er fornuftigt opbygget og estimater af ressourceforbrug og værdisætning af dette er sket i tråd med Amgros' retningslinjer. Resultaterne, der præsenteres i det følgende, bygger derfor på indsendte model, med de justeringer foretaget af Amgros, som er præsenteret i ovenstående afsnit.

Opsummeret er justeringerne følgende:

- År 1 og år 2 er erstattet af År 1 – opstart og År n – vedligeholdelsesbehandling
- Administrationsomkostningerne estimeres gennem en PL-reguleret DAGS-takst, da Amgros vurderer, at de af ansøger anvendte takster, ikke afspejler de faktiske omkostninger som administration af benralizumab (Fasenra) og mepolizumab (Nucala) medfører

Resultatet af omkostningsanalysen viser, at de gennemsnitlige meromkostninger pr. patient i behandling med benralizumab (Fasenra) sammenlignet med behandling med mepolizumab (Nucala) er på 26.096 kr. i et opstartsår. I et gennemsnitligt vedligeholdelsesår er der ved behandling med benralizumab (Fasenra) reducerede behandlingsomkostninger på 2.547 kr. sammenlignet med behandling med mepolizumab (Nucala).

Tabellen nedenfor giver et overblik over størrelsen på de forskellige omkostningselementer for de forskellige behandlingsalternativer.

Tabel 5: Gennemsnitlige behandlingsomkostninger (udiskonterede), kr.

Behandling	Omkostningselement	Opstart *år 1*	Vedligeholdelse *år 2, 3, 4, 5, n,*
Benralizumab (Fasenra)	Antal doser	8	6,5
	Lægemiddel (AIP)	143.627	116.697
	Ydelser på hospital	5.414	4.399
	Patientomkostninger	3.724	3.025
	I alt	**152.764**	**124.121**
Mepolizumab (Nucala)	Antal doser	13	13
	Lægemiddel (AIP)	111.820	111.820
	Ydelser på hospital	8.797	8.797
	Patientomkostninger	6.051	6.051
	I alt	**126.668**	**126.668**
Inkrementel omkostning		***26.096***	***-2.547***

Tabellen nedenfor giver et overblik over størrelsen på de forskellige omkostningselementer over tid for begge behandlingsalternativer. Resulaterne er diskonteret med 4 % pr. år.

Overordnet kan det konkluderes, at behandling med mepolizumab (Nucala) over tid er forbundet med sammenlignelige behandlingsomkostninger ift. behandling med benralizumab (Fasenra). Billedet er det samme, uanset om der ses på de samlede behandlingsomkostninger, eller om man vurderer behandlingerne i et mere snævert perspektiv, og kun ser på lægemiddelomkostningerne.

Tabel 6: Årlige antal doser og gennemsnitlige behandlingsomkostninger over tid, (diskonteret), kr.

Behandling	Omkostningselement	År 1	År 2	År 3	År 4	År 5	Total
Benralizumab (Fasenra)	Antal doser	8	6	7	6	7	***34***
	Lægemiddel	143.627	103.577	116.192	95.763	107.426	***566.587***
	Ydelser på hospital	5.414	3.904	4.380	3.610	4.049	***21.356***
	Patientomkostninger	3.724	2.793	3.258	2.793	3.258	***15.825***
	I alt	**152.764**	**110.274**	**123.830**	**102.165**	**114.734**	***603.767***
Mepolizumab (Nucala)	Antal doser	13	13	13	13	13	***65***
	Lægemiddel	111.820	107.519	103.384	99.408	95.584	***517.715***
	Ydelser på hospital	8.797	8.459	8.133	7.821	7.520	***40.730***
	Patientomkostninger	6.051	6.051	6.051	6.051	6.051	***30.254***
	I alt	**126.668**	**122.029**	**117.568**	**113.279**	**109.155**	***588.698***
Inkrementel omkostning		***26.096***	***-11.755***	***6.262***	***-11.114***	***5.579***	***15.069***

Sensitivitetsanalyser

Analysen er en simpel opgørelse af forskelle i omkostninger forbundet med administrationsfrekvens, patientressourcer samt lægemiddelpriser, og det er derfor et begrænset antal parametre som kan testes i sensitivitetsanalysen. Ansøger har indsendt en sensitivitetsanalyse, der tester de forskellige parametres indflydelse på resultatet. Resultatet af omkostningsanalysen (inkrementelle omkostning per patient) er mest sensitiv ved variation af administrationsomkostningerne og prisen på benralizumab (Fasenra) og mepolizumab (Nucala).

Et vigtigt parameter er administrationsomkostningerne. I basecaseanalysen fra Amgros anvendes en ældre DAGS-takst, som proxy for subkutan administration. Foretages analysen i stedet med den nyere DRG-takst 04MA24, som dækker over subkutan injektion med diagnosekoden DJ451 (ikke-allergisk astma), ser de samlede resultater en anderledes ud. Anvendes denne højere administrationsomkostning vil benralizumab (Fasenra) stadig være forbundet med de højeste omkostninger i første behandlingsår. I de efterfølgende behandlingsår, vil omkostningerne forbundet med behandling med benralizumab (Fasenra) være lavere end behandling med mepolizumab (Nucala). Amgros mener dog, som tidligere nævnt, at DRG-taksten 04MA24 dækker over så heterogene aktiviteter. at den er et dårligt mål for de reelle omkostninger forbundet med en ambulant subkutan injektion. Resultaterne af sensitivitetsanalysen er illustreret i tabellen nedenfor.

Tabel 7: Gennemsnitlige behandlingsomkostninger ved højere administrationsomkostning (udiskonterede), kr.

Behandling	Omkostningselement	Opstart, *år 1*	Vedligeholdelse, *år 2, 3, 4, 5, n,*
Benralizumab (Fasenra)	Lægemiddel	143.627	116.697
	Ydelser på hospital	42.216	34.301
	Patientomk.	3.724	3.025
	I alt	**189.567**	**154.023**
Mepolizumab (Nucala)	Lægemiddel	111.820	111.820
	Ydelser på hospital	68.601	68.601
	Patientomk.	6.051	6.051
	I alt	**186.472**	**186.472**
Inkrementel omkostning		*3.095*	*-32.449*

3. VURDERING AF INDSENDT BUDGETKONSEKVENSANALYSE

Patientpopulation og markedsandel

Ifølge Medicinrådets behandlingsvejledning for svær, eosinofil astma skønnes antal prævalente patienter med svær, eosinofil astma, som er i behandling med anti-IL5 præparaterne mepolizumab (Nucala) eller reslizumab (Cinqaero) i Danmark at være 140 patienter. Det skønnes, at yderligere 140 patienter vil påbegynde behandling i 2018. Eftersom lægemidlerne er forholdsvis nye, forventes der at være flest nye patienter i den første årrække og herefter muligvis lidt færre (4). Som tidligere beskrevet estimerer ansøger, baseret på salgstallene for disse lægemidler, at 220-230 patienter er i behandling med enten mepolizumab (Nucala) eller reslizumab (Cinqaero) (estimeret december 2017) og at omkring 140 patienter forventes at begynde behandling i 2018.

Budgetkonsekvensanalysen tager udgangspunkt i to scenarier:

- Benralizumab (Fasenra) anbefales som mulig standardbehandling af Medicinrådet til patienter med svær, eosinofil astma
- Benralizumab (Fasenra) anbefales ikke som mulig standardbehandling af Medicinrådet til patienter med svær, eosinofil astma

Patientpopulationens størrelse er baseret på antal solgte pakninger og dosering i forhold til indikationen (reslizumab (Cinqaero) doseres ift. legemsvægt og her er patientpopulations gennemsnitlige legemsvægt 80 kg. (4)), hvilket er omregnet på baggrund af salgsdata fra DLI.

I begge scenarier estimeres et total antal på henholdsvis 415 og 595 patienter for år 2018 og 2019. Eftersom benralizumab (Fasenra) forventes at komme på markedet i løbet af 2018 er estimaterne af antal patienter opgjort for perioden maj 2018 - maj 2019 (år 1) og maj 2019 - maj 2020 (år 2).

Hvis benralizumab (Fasenra) anbefales som mulig standardbehandling antager ansøger, at benralizumab (Fasenra) får en markedsandel på 24 % og 32 % i henholdsvis år 1 og 2. Det estimeres desuden, at benralizumab (Fasenra) vil blive tilbudt størstedelen af de nye patienter (hovedsageligt dem som ellers ville blive behandlet med mepolizumab (Nucala)), hvis det anbefales som mulig standardbehandling. Anbefales benralizumab (Fasenra) ikke som mulig standardbehandling estimerer ansøger at benralizumab (Fasenra) opnår en lille markedsandel på 4 % og 6 % i første og andet år.

Markedsandelen blandt de forskellige lægemidler forventes at være størst for mepolizumab (Nucala) med henholdsvis 60 % og 46 % samt 75 % 64 % i år 1 og 2 ved anbefaling/ikke anbefaling af benralizumab (Fasenra) som mulig standardbehandling

Reslizumab (Cinqaero) og dupilumab (Dupixent) angives ikke i protokollen fra Medicinrådet som relevante komparatorer til benralizumab (Fasenra). Reslizumab (Cinqaero) anvendes kun af en lille del af patientpopulationen i dag, og det antages, at markedsandelen ikke vil vokse betragteligt i år 2. Ud fra samtaler med klinikere har ansøger indtrykket af, at reslizumab (Cinqaero) i flere tilfælde anvendes som skiftebehandling fra mepolizumab (Nucala), hvis der er manglende effekt af mepolizumab (Nucala) eller andre forhold gør sig gældende. Dupilumab (Dupixent) kommer sandsynligvis til at udgøre en del af behandlingen for samme patientpopulation, men det afhænger også af om dette produkt bliver anbefalet af Medicinrådet. Derfor antages det, at disse behandlinger vil udgøre en mindre del af markedsandelen i år 1, og tage lidt af markedsandelen fra mepolizumab (Nucala) i år 2.

Tabel 8: Ansøgers estimering af patienter i behandling med lægemidler til svær, eosinofil astma, antal patienter

	Benralizumab (Fasenra) anbefales ikke		Benralizumab (Fasenra) anbefales	
Behandling	År 1	År 2	År 1	År 2
Benralizumab (Fasenra)	18	33	100	188
Mepolizumab (Nucala)	310	382	249	276
Reslizumab (Cinqaero)	54	74	46	58
Dupilumab (Dupixent)	33	106	20	73
Total	**415**	**595**	**415**	**595**

Foruden det estimerede antal patienter og markedsandel for de forskellige lægemidler, danner omkostningsanalysens basecase resultat grundlag for budgetkonsekvensanalysen. Med andre ord er budgetkonsekvenserne baseret på model, metode og forudsætninger, som er beskrevet tidligere i denne ansøgning. Budgetkonsekvenserne opgøres som differencen mellem budgetkonsekvenserne i de to scenarier.

Reslizumab (Cinqaero) udgør og dupilumab (Dupixent) kommer sandsynligvis til at udgøre en del af behandlingen for samme patientpopulation som benralizumab (Fasenra). De totale omkostninger for behandling med reslizumab (Cinqaero) og dupilumab (Dupixent) er derfor konservativt estimeret til at medføre de samme totale omkostninger pr. patient som mepolizumab (Nucala).

Amgros' vurdering af estimeret patientpopulation og markedsandel

Amgros vurderer at estimeringen af populationsstørrelserne er behæftet med relativt stor usikkerhed, men det er Amgros' vurdering, at tilgangen er acceptabel.

Amgros vurderer dog ikke, at det er realistisk at benralizumab (Fasenra) opnår selv små markedsandele såfremt lægemidlet ikke anbefales som mulig standardbehandling, hvorfor det antal patienter (hhv. 18 i år 1 og 33 i år 2) fordeles forholdsmæssigt på de øvrige behandlingsalternativer.

Amgros vurderer, at antagelsen vedr. omkostninger forbundet med behandling med reslizumab (Cinqaero) og dupilumab (Dupixent) er acceptable ift. at give et konservativt overslag over budgetkonsekvenserne.

Resultater

Under de nævnte antagelser om populationernes størrelse og markedsandele er budgetkonsekvenserne ved anbefaling af benralizumab (Fasenra) som mulig standardbehandling til patienter med svær, eosinofil astma illustreret i nedenstående tabel.

Tabel 9: Estimerede budgetkonsekvenser år 1 og 2 (udiskonterede omkostninger), kr.

	Benralizumab (Fasenra) anbefales ikke		Benralizumab (Fasenra) anbefales	
Behandling	År 1	År 2	År 1	År 2
Benralizumab (Fasenra)	0	0	15.276.424	21.539.758
Mepolizumab (Nucala)	41.047.357	51.228.298	31.540.260	34.960.288
Reslizumab (Cinqaero)	7.150.185	9.923.806	5.826.715	7.346.727
Dupilumab (Dupixent)	4.369.557	14.215.182	2.533.354	9.246.743
Total	52.567.099	75.367.287	55.176.752	73.093.515
Budgetkonsekvenser år 1				**2.609.653**
Budgetkonsekvenser år 2				**--2.273.772**

I første behandlingsår vil en anbefaling af benralizumab (Fasenra) som mulig standardbehandling betyde samlede meromkostninger på ca. 2,6 mio. kr. I andet år vil en anbefaling af benralizumab (Fasenra) som mulig standardbehandling betyde reducerede meromkostninger på ca. 2,3 mio. kr.

4. DISKUSSION

De præsenterede analyser er ikke foretaget på baggrund af aftalepriser, men på baggrund af AIP. Analysens resultater afspejler derfor ikke de reelle omkostninger, der er forbundet med anskaffelse af de analyserede lægemidler.

Analysens samlede resultater påvirkes i altovervejende grad af omkostningerne forbundet med anskaffelse af lægemidlerne. Nuværende og fremtidige rabatter på benralizumab (Fasenra) og mepolizumab (Nucala), har derfor stor betydning for hvilken behandling, der er forbundet med de laveste omkostninger.

Amgros vurderer, at estimeringen af behandlingsomkostninger er forbundet med en relativt lav grad af usikkerhed, da de samlede behandlingsomkostninger i altovervejende grad udgøres af lægemiddelomkostningerne.

Overordnet set vurderer Amgros, at AstraZeneca har indsendt en tilfredsstillende analyse, der gør det muligt at vurdere de gennemsnitlige inkrementelle omkostninger pr. patient i behandling med benralizumab (Fasenra) sammenlignet med de gennemsnitlige omkostninger pr. patient i behandling med mepolizumab (Nucala). Analysen gør det muligt at estimere de potentielle budgetkonsekvenser ved anbefaling af benralizumab (Fasenra) som mulig standardbehandling.

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AMGROS

REGIONERNES
LÆGEMIDDELORGANISATION

AMGROS I/S
DAMPFÆRGEVEJ 27-29
2100 KØBENHAVN Ø

TLF: 8871 3000
WWW.AMGROS.DK

Medicinrådet
Dampfærgevej 27–29
2100 København Ø

Sendt som e-mail til medicinraadet@medicinraadet.dk

AstraZeneca A/S
Arne Jacobsens Allé 13
DK-2300 Copenhagen S
T: +45 4366 6462
astrazeneca.com
astrazeneca.dk

25. april 2018

Vedr.: Vurderingsrapport Fasenra (benralizumab), AstraZeneca.

Tak for den fremsendte evaluering af de kliniske spørgsmål og vores ansøgning.

Vi er enige i den overordnede konklusion, at data på benralizumab ikke kan udløse en klinisk merværdi i forhold til den valgte komparator Nucala (mepolizumab).

Af de prædefinerede kliniske spørgsmål er det kun peroral kortikosteroid (100% reduktion), som møder den absolutte værdi defineret i protokollen (dog med et bredt konfidensinterval). Selvom dette er et kritisk klinisk spørgsmål og af betydning i klinikken supporterer vi, at det ikke kan ændre på den generelle konklusion omkring merværdien vs. mepolizumab.

Da det på forhånd var bekendt, at mepolizumab ikke havde data på FEV1 200 ml og sygefravær var det måske unødigt at vi brugte tid og resurser på dette, da det ikke rigtig blev en del af den endelige evaluering.

Det er glædeligt, at rapporten anerkender, at den subkutane injektion og administrationshyppigheden hver 8. uge er en fordel for patienter og behandlere.

Kort og godt så har AstraZeneca ikke input til høringsfasen, som kan ændre ved den overordnede kliniske merværdi konklusion.

Med venlig hilsen

Søren Clausen
Market Access Director

AstraZeneca A/S
AstraZeneca Nordic Marketing Company | Market Access Department
Arne Jacobsens Allé 13, DK-2300 Copenhagen S, Denmark
Visitors: Edvard Thomsens Vej 14
T: +45 4366 6462 M: +45 23615584
soren.clausen@astrazeneca.com

Medicinrådets vurdering af klinisk merværdi af benralizumab til svær, eosinofil astma

Handelsnavn	Fasenra
Generisk navn	Benralizumab
Firma	AstraZeneca AB
ATC-kode	R03DX10
Virkningsmekanisme	Benralizumab er et monoklonalt antistof rettet mod interleukin 5 (IL-5)-receptorer. IL-5 er et cytokin, som spiller en central rolle i produktion, modning og overlevelse af eosinofile granulocytter. Binding af antistofferne til IL-5-receptorer medfører dermed en reduktion i antallet af eosinofile granulocytter, hvilket resulterer i bedre sygdomskontrol.
Administration/dosis	Benralizumab administreres ved en forfyldt injektionssprøjte. Den anbefalede dosis er 30 mg ved subkutan injektion hver 4. uge for de første 3 doser, dernæst hver 8. uge.
EMA-indikation	Fasenra er indiceret som en tillægsvedligeholdelsesbehandling til voksne patienter (> 18 år) med svær, eosinofil astma, der ikke kontrolleres tilstrækkeligt på trods af høj dosis af inhalationskortikosteroider plus langtidsvirkende β-agonister.
Godkendelsesdato Offentliggørelsesdato Dokumentnummer Versionsnummer (Fagudvalgets sammensætning og sekretariatets arbejdsgruppe, se bilag 1)	24.04.18 24.04.18 11302 1.0

Medicinrådets konklusion

Medicinrådet vurderer, at benralizumab til patienter med svær, eosinofil astma skal kategoriseres til **ingen klinisk merværdi** sammenlignet med mepolizumab. Evidensens kvalitet vurderes at være **lav**.

Definition af klinisk merværdi:

Medicinrådet kategoriserer lægemidlets kliniske merværdi i en af følgende kategorier:

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

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

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

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

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

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

Om Medicinrådet:

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

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

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

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

Forkortelser

ACQ 5:	*Asthma Control Questionnaire* (astmakontrolspørgeskema)
AQLQ:	*Asthma Quality of Life Questionnaire* (astmalivskvalitetspørgeskema)
ATS:	*American Thoracic Society*
CI:	Konfidensinterval
DLS:	Dansk Lungemedicinsk Selskab
EMA:	Det Europæiske Lægemiddelagentur *(European Medicines Agency)*
EPAR:	*European public assessment reports*
ERS:	*European Respiratory Society*
FEV1:	*Forced Expiratory Volume* (forceret ekspirationsvolumen) på 1 sekund
FP	Fluticasone propionate
GINA:	*Global Initiative of Asthma*
GRADE:	System til vurdering af evidens (*Grading of Recommendations Assessment, Development and Education System*)
i.v.:	Intravenøs
ICS:	Inhaleret kortikosteroid
IL-5:	Interleukin 5
LABA:	Langtidsvirkende beta2-agonist
MD:	Gennemsnitlig forskel *(Mean Difference)*
NICE:	*National Institute of Clinical Excellence*
NO:	Nitrogenoxid
OCS:	Oral kortikosteroid
RR:	Relativ risiko (*Risk Ratio)*
s.c.:	Subkutan
SAE:	Alvorlige uønskede hændelser *(Serious Adverse Events)*
SGRQ:	*St. George Respiratory Questionnaire*
SMD:	Standardiseret gennemsnitlig forskel *(Standardized Mean Difference)*

Indhold

1 Formål

Formålet med Medicinrådets vurdering af klinisk merværdi af benralizumab (Fasenra) til svær, eosinofil astma er at vurdere den kliniske merværdi i forhold til et eller flere lægemidler til samme patientgruppe (komparatorer).

Der er to mulige komparatorer til benralizumab; mepolizumab (Nucala) eller reslizumab (Cinqaero), som i Medicinrådets behandlingsvejledning for biologiske lægemidler til svær astma (LINK) er vurderet som værende ligestillede, hvad angår effekt og bivirkninger. Der er valgt én komparator, mepolizumab, da evidensen for dette lægemiddel er baseret på studier, hvor populationen bedst relaterer sig til danske forhold.

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

2 Baggrund

Svær, eosinofil 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). Symptomer kan optræde hele døgnet, og de kan svinde spontant eller efter specifik behandling. Fysiologisk er astma kendetegnet ved en reversibel, obstruktiv lungefunktionsnedsættelse, hvor lungefunktionen meget ofte vil være normal, når patienten ikke har symptomer. Stor astmasymptombyrde medfører generelle symptomer som påvirket søvn, træthed, uoplagthed, koncentrationsbesvær og nedsat selvværd og livskvalitet [1]. Astma kan debutere i alle aldre, men oftest i barndom eller ungdom. Debut før puberteten er associeret med en større sandsynlighed for, at astmaen har en allergisk komponent. Både arvelige og miljømæssige faktorer er af betydning for udvikling af astma [1]. Astma er hyppigst en selvstændig sygdom, men kan optræde som element i systemsygdomme.

Astma er en hyppigt forekommende kronisk sygdom i Danmark hos både børn og voksne. I dag vurderes det, at 7-11 % af den danske population har astma [1]. Prævalensen af **svær astma** er estimeret til at udgøre 5-15 % af alle patienter med astma [2]. Der indlægges ca. 1.500 patienter med akut astma om året i Danmark. Mildere tilfælde af akut astma, som håndteres af vagtlæge eller skadestue, er langt hyppigere [3].

Astmadiagnosen stilles på baggrund af karakteristiske symptomer og påvisning af variabel luftvejsobstruktion. Der findes ikke en guldstandard, som i alle sammenhænge kan stille diagnosen astma. Almindeligvis anvendes spirometri med reversibilitet, dvs. stigning i lungefunktionen efter enten hurtigvirkende, inhaleret betaagonist eller behandlingsforsøg med inhaleret eller systemisk kortikosteroid eller induktion af luftvejsobstruktion ved bronkiale provokationstest med anstrengelse, hyperventilation eller inhalation af metacholin eller mannitol. Der er mange differentialdiagnoser, hvor hyppigheden varierer med patientens alder og symptombillede [1,4]. Når astmadiagnosen stilles, skal omfanget og betydningen af eventuelle komorbiditeter og triggers (f.eks. allergi, røg, irritanter) beskrives. Sammenfattet bør alle astmapatienter udover farmakologisk behandling tilbydes astmauddannelse, behandles for og rådgives om komorbiditeter og modificérbare risikofaktorer samt udredes og behandles for allergi.

To adskilte begreber er centrale i håndteringen af astma. **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, behov for anfaldsmedicin, mens den fremtidige risiko vurderes ud fra bl.a. lungefunktion og evt. tidligere eksacerbationer [5]. 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. En patient kan således godt have mild, ukontrolleret astma.

Eosinofil astma er en undertype af astma, som er forbundet med øget antal eosinofile celler i luftvejsslimhinder. Der findes ingen tilgængelige metoder til direkte påvisning heraf i daglig klinisk praksis. I forskningssammenhæng kan eosinofil luftvejsinflammation påvises ved kikkertundersøgelse (bronkoskopi) med vævsprøver eller ved induceret sputum, hvor luftvejssekret analyseres for eosinofilkoncentration. Eosinofil luftvejsinflammation er positivt associeret til antallet af eosinofile celler i perifert blod og til koncentration af nitrogenoxid (NO) i udåndingsluft, som dermed kan bruges som proxyvariable [4].

Nuværende behandling

Dansk Lungemedicinsk Selskab (DLS) definerer **svær astma** i overensstemmelse med ERS (European Respiratory Society)/ATS' (American Thoracic Society) guidelines [2,4]: 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 opretholde sygdomskontrol, eller trods denne behandling forbliver ukontrolleret. Systematisk udredning af mulig svær astma anbefales for at sikre diagnosen, og at den manglende sygdomskontrol ikke skyldes forkert diagnose, manglende adhærens med den ordinerede behandling, behandlelige komorbiditeter eller undgåelige triggers [2].

Der vil dog være en mindre andel af patienter, som ikke opnår tilstrækkelig sygdomskontrol trods ovenstående tiltag, og som derfor har svær astma. For patienter med svær, eosinofil astma er der mulighed for tillægsterapi i form af de biologiske lægemidler mepolizumab eller reslizumab, som begge er antistoffer rettet mod interleukin 5 (IL-5) [5]. 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 medfører dermed en reduktion i antallet af eosinofile granulocytter, resulterende i bedre sygdomskontrol.

Anvendelse af det nye lægemiddel

Benralizumab er et monoklonalt antistof rettet mod IL-5-receptoren [5] og adskiller sig dermed fra mepolizumab og reslizumab, der begge er direkte hæmmere af IL-5. Bindingsaffiniteten til receptoren er høj, og virkningen vurderes ensartet sammenlignet med de direkte IL-5-hæmmere, idet binding af antistofferne til IL-5-receptorer ligeledes medfører en markant reduktion i antallet af eosinofile granulocytter (typisk ≥ 95 % af alle eosinofile granulocytter i blodet depleteres indenfor 24 timer) (EPAR, Fasenra). Benralizumab er indiceret som tillægsbehandling til voksne patienter med svær, eosinofil astma, som er ukontrolleret trods behandling med højdosis inhalationssteroid samt langtidsvirkende β2-agonist.

Benralizumab administreres ved en forfyldt injektionssprøjte. Den anbefalede dosis er 30 mg ved subkutan injektion hver 4. uge for de første 3 doser, dernæst hver 8. uge. Benralizumab anvendes som langtidsbehandling og skal administreres af en sundhedsprofessionel. Fortsat behandling bør revurderes

mindst én gang årligt, baseret på astmasværhedsgrad og eksacerbationskontrol. Benralizumab skal opbevares ved 2-8°C.

3 Metode

Ansøgers endelige ansøgning blev modtaget den 19. februar 2018. Ansøgers anvendte metode er valideret af Medicinrådets sekretariat.

Ansøger har anvendt og fulgt den præspecificerede metode, jf. protokollen, som blev godkendt i Medicinrådet d. 13. december 2017 (LINK). Protokollen blev udarbejdet af fagudvalget vedr. svær astma og definerede det kliniske spørgsmål inklusive effektmål, der ønskes belyst i vurderingen af benralizumab.

4 Litteratursøgning

Ansøger har søgt litteratur som beskrevet i protokollen. Der blev identificeret syv randomiserede, placebokontrollerede kliniske studier, som havde undersøgt henholdsvis effekten af benralizumab og effekten af mepolizumab. Studiernes resultater blev publiceret i otte artikler, hvoraf en dog er en pooled analyse af CALIMA- og SIROCCO-studierne, der derfor ikke medtages i analyserne. De syv fremsøgte publikationer, som ligger til grund for Medicinrådets vurdering, fremgår af Tabel 1.

Tabel 1: Publikationer som ligger til grund for Medicinrådets vurdering af den kliniske merværdi af benralizumab sammenlignet med mepolizumab

Reference	Titel	Klinisk studie
Benralizumab		
Bleecker 2016 [6]	Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial	SIROCCO
Fitzgerald 2016 [7]	Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial	CALIMA
Nair 2017 [8]	Oral Glucocorticoid–Sparing Effect of Benralizumab in Severe Asthma	ZONDA
Mepolizumab		
Pavord 2012 [9]	Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial.	DREAM
Ortega 2014 [10]	Mepolizumab treatment in patients with severe eosinophilic asthma.	MENSA
Bel 2014 [11]	Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma.	SIRIUS
Chupp 2017 [12]	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	MUSCA

Derudover har ansøger refereret til; "Methods for population-adjusted indirect comparisons in submission to NICE" [13], GINA-guidelines [5] og Medicinrådets behandlingsvejledning for biologiske lægemidler til svær astma (LINK). Ansøger har desuden medsendt European public assessment report (EPAR) for benralizumab (LINK).

5 Databehandling

Der er ikke foretaget head-to-head-studier, som sammenligner effekten af benralizumab med komparator (mepolizumab). Ansøger har derfor udfærdiget en indirekte sammenligning af benralizumab vs. mepolizumab ved henholdsvis Buchers metode og Matching Adjusted Indirect Comparison (MAIC). MAIC er

accepteret af NICE [6] i tilfælde, hvor direkte evidens ikke er tilgængelig. Medicinrådets sekretariat har fået tilsendt og valideret ansøgers MAIC-rapport, som, ansøger ønsker, holdes fortrolig. Resultater fremkommet ved henholdsvis Buchers metode og MAIC-analyse er begge accepterede. For nærmere beskrivelse af MAIC-analysen og ansøgers anvendelse af denne, se bilag 2.

For enkelte effektmål har ansøger valgt at udføre flere analyser med data fra forskellige opfølgningstidspunkter. Jf. protokollen ønskes data fra længst mulige opfølgningstidspunkt, hvorfor kun disse analyser tages i betragtning i Medicinrådets vurdering.

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

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

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

6 Klinisk merværdi

6.1 Konklusion

Hvilken klinisk merværdi tilbyder benralizumab sammenlignet med mepolizumab ved behandling af patienter med svær, eosinofil astma?

Fagudvalget vurderer, at benralizumab til patienter med svær, eosinofil astma skal kategoriseres til **ingen klinisk merværdi** sammenlignet med mepolizumab. Evidensens kvalitet vurderes at være **lav**.

6.1.1 Gennemgang af studier

Studiekarakteristika

De syv studier, der ligger til grund for vurderingen, er alle randomiserede, placebokontrollerede og dobbeltblindede. I ingen af studierne er der beskrevet systematisk udredning af ukontrolleret, mulig svær astma, hvilket er guldstandard i Danmark i henhold til DLS' retningslinjer [2]. I alle studierne fortsætter patienterne med at tage deres vedligeholdelsesbehandling, undtagen i SIRIUS og ZONDA. Alle studier er firmasponsorerede. Studiekarakteristika for de inkluderede studier fremgår af bilag 3.

I alle tre benralizumabstudier blev patienterne randomiseret 1:1:1 til henholdsvis benralizumab 30 mg én gang hver 4. uge, benralizumab 30 mg hver 8. uge (første tre doser hver 4. uge) eller placebo hver 4. uge

som tillæg til deres standardbehandling. Patienter i behandling hver 8. uge modtog injektion med placebo hver 4. uge i de uger, hvor de ellers ikke skulle modtage behandling.

I mepolizumabstudierne blev patienterne randomiseret 1:1 til injektion med 100 mg henholdsvis mepolizumab eller placebo (SIRIUS og MUSCA), eller 1:1:1 til 75 mg intravenøs injektion med mepolizumab eller injektion med 100 mg henholdsvis mepolizumab eller placebo (MENSA), eller 1:1:1:1 til en af tre doser intravenøs mepolizumab (75 mg, 250 mg, eller 750 mg) eller placebo (100 ml 0,9 % NaCl) (DREAM).

Baselinekarakteristika

De inkluderede studier vurderes overordnet at have en ensartet patientpopulation. Dog varierer patienterne i studierne i forhold til antal eosinofile celler i blodet, andel af patienter med ≥ 2 eksacerbationer inden for det seneste år, vedligeholdelses-OCS-dosis ved baseline og definition af højdosis ICS. Relevante baselinekarakteristika for de inkluderede studier fremgår af bilag 4.

Population

Fagudvalget vurderer, at den underliggende standardbehandling og udredning i studierne ikke er direkte overførbar til danske forhold.

Ingen af studierne beskriver, at der er foretaget en systematisk udredning af de inkluderede patienter for at sikre, at de reelt har svær astma, hvilket er dansk guldstandard. Populationen i studierne er derfor en mindre selekteret gruppe, hvor en del sandsynligvis ikke har svær astma, men muligvis ukontrolleret astma af mere mild grad.

Desuden inkluderes i studierne patienter, som får såvel middel- som højdosis inhalationssteroid. Dog er analyserne tilsendt af ansøger alene foretaget på populationen, som har fået højdosis inhalationssteroid (≥ 880 µg FP dagligt eller ækvivalent, se bilag 2). Dette valg er taget fordi denne population i højere grad svarer til danske forhold, hvor man pr. definition kun har svær astma, hvis man er i behandling med højdosis inhalationssteroid (defineret som ≥ 1000 µg FP dagligt eller ækvivalent).

Med hensyn til alder, køn, rygeanamnese og BMI er der overensstemmelse mellem studiepopulationen og danske forhold. Med hensyn til etnicitet er studiepopulationen mere blandet end generelt i en dansk population. Dette vurderes imidlertid ikke at have nævneværdig betydning.

Samlet set vurderes det, at datagrundlaget kan anvendes til at kategorisere effekten og bivirkningerne af benralizumab, dog uden direkte overførbarhed til danske forhold.

6.1.2 Resultater og vurdering

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

I ansøgers databehandling inkluderes kun resultater fra behandling med det godkendte dosisregime og styrke, dvs. for benralizumab 30 mg hver 8. uge (første tre doser hver 4. uge) og for mepolizumab 75 mg eller 100 mg hver 4. uge (vurderet ligeværdige styrker).

Det kliniske spørgsmål, som ønskes besvaret, er: *"Hvilken klinisk merværdi tilbyder benralizumab sammenlignet med mepolizumab ved behandling af patienter med svær, eosinofil astma?"*

6.1.2.1 Eksacerbationsrate (kritisk)

Effektmålet er angivet med to delmål: *"Gennemsnitlig reduktion i årlige eksacerbationer"* og *"andel af patienter som opnår 0 årlige eksacerbationer"*.

Gennemsnitlig reduktion i årlige eksacerbationer

For *"Gennemsnitlig reduktion i årlige eksacerbationer"* har ansøger foretaget en MAIC-analyse til den indirekte sammenligning og inkluderet benralizumabstudierne SIROCCO og CALIMA og mepolizumabstudierne MENSA og DREAM. Resultaterne fra mepolizumabstudiet MUSCA beskrives narrativt og sammenlignes således ikke med benralizumabstudier.

Tabel 2: Vurdering af klinisk merværdi: Gennemsnitlig reduktion i årlige antal eksacerbationer

	Forhåndsdefineret grundlag for vurdering		**Resultater**
Absolutte forskelle	Minimum reduceret med 0,5 årlig eksacerbation		-0,03 årlig eksacerbation [-0,11; 0,07]
Relative forskelle*	Stor merværdi	Øvre konf.gr. < 0,75 og risiko > 5 %[a]	
	Vigtig merværdi	Øvre konf.gr. < 0,90	
	Lille merværdi	Øvre konf.gr. < 1,00	
	Ingen merværdi	**Øvre konf.gr. ≥ 1,00**	**RR: 0,94 [0,78; 1,13][b]**
	Negativ merværdi	Nedre konf.gr. > 1,00	
Evidensens kvalitet	Moderat		

RR: relativ risiko
* Øvre grænse for konfidensintervallet for den relative effekt (relativ risiko, odds ratio eller hazard ratio) må ikke overskride væsentlighedskriteriet for at kvalificere til den foreløbige kategori.
[a] Risikoen skal være > 5 % i mindst én af de sammenlignede grupper.
[b] Resultatet for den ujusterede analyse viser en relativ risiko på 1,06 [95 % CI: 0,88, 1,28].

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

Baseret på den absolutte og relative effektforskel vurderer fagudvalget, at benralizumab ingen klinisk merværdi har vedr. reduktion af antal årlige eksacerbationer, idet den absolutte forskel ikke opnår den mindste klinisk relevante forskel på minimum 0,5 årlig eksacerbation, og den øvre grænse for konfidensintervallet for den relative risiko er > 1 (moderat evidenskvalitet).

MUSCA viser en positiv signifikant effekt af mepolizumab, sammenlignet med placebo, med en relativ risiko på 0,42 [0,31;0,56]. Fagudvalget vurderer ikke, at inklusion af dette resultat ville ændre på vurderingen af effektmålet, idet de studier der er medtaget i analysen har sammenlignelig effekt, i forhold til placebo.

Andel af patienter, der opnår 0 årlige eksacerbationer

For *"andel af patienter, der opnår 0 årlige eksacerbationer"* har ansøger foretaget en indirekte sammenligning ved hjælp af Buchers metode for at vurdere, om der er klinisk relevant forskel mellem de to behandlinger. Der er inkluderet tre studier for benralizumab (SIROCCO, CALIMA og ZONDA) og to studier

for mepolizumab (DREAM og MENSA). Resultaterne er udtryk for, hvor stor andel der opnår 0 eksacerbationer i studieperioden og altså ikke nødvendigvis målt henover et år. Ansøgers sammenlignende analyse er opsat således, at sammenligningen sker for patienter, der oplever > 0 eksacerbationer, hvorfor væsentlighedskriterierne kan anvendes direkte.

Tabel 3: Vurdering af klinisk merværdi: Andel af patienter, der oplever > 0 eksacerbationer i studieperioden

	Forhåndsdefineret grundlag for vurdering		**Resultater**
Absolutte forskelle	10 %-point		-2,6 %-point (-12,7 %; 10,3 %)
Relative forskelle*	Stor merværdi	Øvre konf.gr. < 0,75 og risiko > 5 %[a]	
	Vigtig merværdi	Øvre konf.gr. < 0,90	
	Lille merværdi	Øvre konf.gr. < 1,00	
	Ingen merværdi	**Øvre konf.gr. ≥ 1,00**	**RR: 0,94 [0,73; 1,22]**
	Negativ merværdi	Nedre konf.gr. > 1,00	
Evidensens kvalitet	Moderat		

RR: relativ risiko
[a] Risikoen skal være > 5 % i mindst én af de sammenlignede grupper.
* Øvre grænse for konfidensintervallet for den relative effekt (relativ risiko, odds ratio eller hazard ratio) må ikke overskride væsentlighedskriteriet for at kvalificere til den foreløbige kategori.

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

Baseret på den absolutte og relative effektforskel vurderer fagudvalget, at benralizumab ingen klinisk merværdi har vedr. andel af patienter, som opnår 0 årlige eksacerbationer, idet forskellen ikke overstiger den mindste klinisk relevante forskel på 10 %-point, og den øvre grænse for konfidensintervallet for den relative risiko er > 1 (moderat evidenskvalitet).

Samlet vurdering af effektmålet "eksacerbationsrate (kritisk)"

Samlet vurderer fagudvalget, at benralizumab **ingen klinisk merværdi** har vedr. effektmålet *"eksacerbationsrate"*, idet ingen af de to opstillede mål for behandling med benralizumab opnår en klinisk relevant forskel i forhold til behandling med mepolizumab (moderat evidenskvalitet).

6.1.2.2 Peroral vedligeholdelsesbehandling med kortikosteroid (kritisk)

Effektmålet er angivet med tre mål: *"Gennemsnitlig %-reduktion i daglig dosis"*, *"andel af patienter der ophører med peroral kortikosteroid"* og *"andel af patienter der opnår 50 % reduktion af peroral kortikosteroid"*. For førstnævnte er foretaget en MAIC-analyse, for de øvrige en indirekte sammenligning ved Buchers metode. For alle målene er inkluderet ét randomiseret studie for henholdsvis benralizumab 30 mg s.c. (ZONDA) og mepolizumab 100 mg s.c. (SIRIUS). I begge studier var alle patienter i vedligeholdelsesbehandling med OCS. Data er fra længste opfølgningstidspunkt i studierne.

Gennemsnitlig %-reduktion i daglig dosis peroral kortikosteroid

Tabel 4: Vurdering af klinisk merværdi: Gennemsnitlig %-reduktion i daglig dosis peroral kortikosteroid (vedligeholdelsesbehandling)

	Forhåndsdefineret grundlag for vurdering	**Resultater**
Absolutte forskelle	20 %-point (dog minimum 2,5 mg prednisolon ækvivalent)	5,1 %-point [-22,4; 32,5] [b]
Evidensens kvalitet	Lav	

[b] Resultatet for den ujusterede analyse viser en absolut forskel på 21,07 %-point [95% CI: -5,95; 48,09].

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

Baseret på den absolutte effektforskel på 5 %-point vurderer fagudvalget, at benralizumab ingen klinisk merværdi har vedr. effektmålet *"gennemsnitlig %-reduktion i daglig dosis*" (vedligeholdelsesbehandling), idet forskellen ikke overstiger den mindste klinisk relevante forskel på 20 %-point (lav evidenskvalitet).

Andel af patienter der ophører med peroral kortikosteroid

Tabel 5: Vurdering af klinisk merværdi: Andel af patienter som ophører med peroral kortikosteroid (vedligeholdelsesbehandling)

	Forhåndsdefineret grundlag for vurdering		**Resultater**
Absolutte forskelle	5 %-point		6,9 %-point [-8,4-61,0]*
Relative forskelle	Stor merværdi	Nedre konf.gr. > 1,33	
	Vigtig merværdi	Nedre konf.gr. > 1,11	
	Lille merværdi	Nedre konf.gr. > 1,00	
	Ingen merværdi	**Nedre konf.gr. ≤ 1,00**	**RR: 1,48 [0,42; 5,2]**
	Negativ merværdi	Øvre konf.gr. < 1,00	
Evidensens kvalitet	Lav		

RR: relativ risiko
* Baseret på eventraten for mepolizumab (10/69 = 14,5 %).

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

Effektestimatet for den absolutte effektforskel er 6,9 %-point, hvilket overstiger den mindste klinisk relevante forskel på 5 %-point. Da konfidensintervallet er meget bredt, fra -8,4 til 61, og forskellen dermed

ikke er signifikant, vurderer fagudvalget, at der skal lægges mest vægt på den relative effektforskel og dermed, at behandling med benralizumab ingen klinisk merværdi har ift. *"andel af patienter, der ophører med vedligeholdelsesbehandling med peroral kortikosteroid"* (lav evidenskvalitet).

Andel af patienter der opnår 50 % reduktion af peroral kortikosteroid

Tabel 6: Vurdering af klinisk merværdi: Andel af patienter som opnår ≥ 50 % reduktion af peroral kortikosteroid

	Forhåndsdefineret grundlag for vurdering		**Resultater**
Absolutte forskelle	10 %-point		5,1 %-point [-19,0; 45,8]
Relative forskelle	Stor merværdi	Øvre konf.gr. < 0,85	
	Vigtig merværdi	Øvre konf.gr. < 0,95	
	Lille merværdi	Øvre konf.gr. < 1,00	
	Ingen merværdi	**Øvre konf.gr. ≥ 1,00**	**RR: 1,1 [0,65; 1,86]**
	Negativ merværdi	Nedre konf.gr. > 1,00	
Evidensens kvalitet	Lav		

RR: relativ risiko

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

Baseret på den absolutte og relative effektforskel vurderer fagudvalget, at benralizumab ingen klinisk merværdi har vedr. *"andel af patienter, som opnår ≥ 50 % reduktion af peroral kortikosteroid"*, idet forskellen ikke overstiger den mindste klinisk relevante forskel på 10 %-point, og den øvre grænse af konfidensintervallet er > 1 (lav evidenskvalitet).

Samlet vurdering af effektmålet "peroral vedligeholdelsesbehandling med kortikosteroid"

Samlet vurderer fagudvalget, at benralizumab **ingen klinisk merværdi** har vedr. effektmålet *"peroral vedligeholdelsesbehandling med kortikosteorid"*, idet de opstillede mål for behandling med benralizumab ikke opnår en statistisk signifikant samt klinisk relevant forskel i forhold til behandling med mepolizumab (lav evidenskvalitet).

6.1.2.3 Lungefunktion FEV1 (vigtig)

Effektmålet er angivet som henholdsvis *"gennemsnitlig ændring i FEV1"* og *"andel som opnår en forbedring på 200 ml i FEV1"*.

Gennemsnitlig ændring i FEV1

Den gennemsnitlige ændring i lungefunktion (FEV1) blev rapporteret i benralizumabstudierne SIROCCO og CALIMA og mepolizumabstudierne DREAM og MENSA, som alle var inkluderet i ansøgers MAIC-analyse. Resultater fra MUSCA beskrives narrativt.

Tabel 7: Vurdering af klinisk merværdi: Gennemsnitlig ændring i lungefunktion

	Forhåndsdefineret grundlag for vurdering	**Resultater**
Absolutte forskelle	200 ml for voksne	20 ml [-60; 100][b]
Evidensens kvalitet	Moderat	

[b] Resultatet for den ujusterede analyse er uændret (20 ml [-60; 100]).

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

MENSA adskiller sig med en studievarighed på 32 uger fra de tre øvrige studier, DREAM (52 uger), SIROCCO (48 uger) og CALIMA (56 uger). Derfor har ansøger foretaget en sensitivitetsanalyse uden MENSA, der viser lignende resultat (30 ml (-80;140)).

MUSCA viser en positiv signifikant effekt af mepolizumab sammenlignet med placebo med en absolut forskel på 102 ml [47;192], som dermed ikke opnår en klinisk relevant forskel. Fagudvalget vurderer ikke, at inklusion af dette resultat ville ændre på vurderingen af aktuelle effektmål.

Baseret på den absolutte effektforskel for pre-FEV1 på 20 ml vurderer fagudvalget, at benralizumab ingen klinisk merværdi har vedr. *"gennemsnitlig ændring i lungefunktion"*, idet forskellen ikke overstiger den mindste klinisk relevante forskel på 200 ml (moderat evidenskvalitet).

Andel som opnår en forbedring på 200 ml i FEV1

SIROCCO og CALIMA har rapporteret andel af patienter, som opnår en forbedring på 200 ml i FEV1, for henholdsvis benralizumab og placebo. Data fra de to studier blev sammenlagt og viste, at der for benralizumab var 56 % og for placebo 47 %, som opnåede dette, dvs. en forskel på 9 %-point. Der findes ingen data for mepolizumab, hvorfor det ikke er muligt at foretage en indirekte sammenligning af de to lægemidler og vurdere, om den klinisk relevante forskel på 15 %-point opnås.

Samlet vurdering af effektmålet "lungefunktion FEV1"

Samlet vurderer fagudvalget, at benralizumab **ingen klinisk merværdi** har vedr. effektmålet *"lungefunktion FEV_1"*, idet det ene af de to opstillede mål for behandling med benralizumab ikke opnår en klinisk relevant forskel sammenlignet med behandling med mepolizumab, mens der ikke findes data for det andet mål (moderat evidenskvalitet).

6.1.2.4 Astmakontrol (vigtig)

Astmakontrol er undersøgt i alle syv studier ved brug af Asthma Control Questionnaire (ACQ), dog i forskellige versioner. For benralizumab anvender alle tre studier ACQ6. For mepolizumab anvender tre studier ACQ5 (MENSA, MUSCA og SIRIUS) og ét anvender ACQ6 (DREAM). Den mindste klinisk relevante forskel er en gennemsnitlig forskel på 0,5 point for alle versioner af ACQ. Resultatet fra SIRIUS er ikke medtaget i dataanalysen, da designet i dette studie adskiller sig fra øvrige studier ved, at OCS nedtrappes under studiet. Resultatet fra SIRIUS beskrives derfor narrativt. Ansøger har inkluderet ZONDA med et design tilsvarende SIRIUS. Dette vurderes imidlertid ikke at påvirke resultatet og den samlede vurdering af dette effektmål, idet ZONDA er et lille studie. Ansøger har foretaget en metaanalyse og vha. Buchers metode er forskellen mellem de to behandlinger beregnet.

Tabel 8: Vurdering af klinisk merværdi: gennemsnitlig ændring i astmakontrol

	Forhåndsdefineret grundlag for vurdering	**Resultater**
Absolutte forskelle	ACQ: 0,5-point	MD: 0,01 [95 % CI; - 0,21; 0,23]
Evidensens kvalitet	Lav	

MD: mean difference, gennemsnitlig forskel.

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

I SIRIUS var der en forbedring af astmakontrol ved ACQ5 for mepolizumab vs. placebo (MD: - 0,52 [95 % CI: - 0,87; - 0,17]). Til sammenligning var der i ZONDA en forbedring af astmakontrol ved ACQ5 for benralizumab vs. placebo (MD: - 0,41 [95 % CI: - 0,78; - 0,04]). Fagudvalget vurderer, at resultatet fra SIRIUS ikke ændrer ved vurderingen af den kliniske merværdi.

Baseret på den absolutte effektforskel på 0,01 vurderer fagudvalget, at benralizumab **ingen klinisk merværdi** har for *"astmakontrol*", idet forskellen ikke er signifikant, og den kliniske relevante forskel på 0,5 ikke opnås i forhold til behandling med mepolizumab (lav evidenskvalitet).

6.1.2.5 Livskvalitet (vigtig)

Sygdomsspecifik livskvalitet er undersøgt i alle syv studier. For benralizumab anvender alle tre studier Asthma Quality of Life Questionnaire (AQLQ), i versionen AQLQ(S)+12 som er udviklet til personer > 12 år. For mepolizumab anvender ét studie AQLQ (DREAM), mens tre studier (MENSA, MUSCA og SIRIUS) anvender data på et andet sygdomsspecifikt spørgeskema, St. George Respiratory Questionnaire (SGRQ). Den mindste klinisk relevante forskel i AQLQ er 0,5-point, og den mindste klinisk relevante forskel i SGRQ er 4 point.

Ansøger har foretaget en metaanalyse, hvor data er omregnet til standardiseret gennemsnitlig forskel (SMD), idet forskellige spørgeskemaer er anvendt i studierne. I tabel 9 er SMD angivet, og desuden den omregnede gennemsnitlige forskel (MD) på baggrund af standardafvigelsen for de studier med data for AQLQ. Dette estimat kan sammenlignes med den på forhånd definerede mindste klinisk relevante forskel.

Data fra SIRIUS er ikke medtaget i analysen pga. studiedesign, hvorfor resultater fra dette studie er beskrevet narrativt. Ansøger har inkluderet ZONDA med tilsvarende design. Dette vurderes imidlertid ikke at påvirke resultatet og den samlede vurdering af dette effektmål, idet ZONDA er et lille studie. Indirekte sammenligning er foretaget ved hjælp af Buchers metode.

Tabel 9: Vurdering af klinisk merværdi: Gennemsnitlig ændring i livskvalitet

	Forhåndsdefineret grundlag for vurdering	**Resultater**
Absolutte forskelle	AQLQ: 0,5 point	SMD: -0,06 [-0,32; 0,20] MD: -0,07 [-0,36; 0,23]*
Evidensens kvalitet	Moderat	

SMD: standardised mean difference, standardiseret gennemsnitlig forskel.
* Under antagelse af standardafvigelse på 1,14 (gennemsnit af interventionsgruppen i de inkluderede studier med data for AQLQ).

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

I SIRIUS var der en forbedring af livskvalitet målt ved SGRQ for mepolizumabbehandling vs. placebo (MD: -5,8 [95 % CI: -10,6; -1,0]), hvor den kliniske relevante forskel er 4 point. Således er effektestimatet klinisk relevant, mens den nedre konfidensgrænse ligger under den mindste kliniske relevante forskel. Til sammenligning var der i ZONDA en forbedring af livskvalitet målt ved AQLQ for benralizumab vs. placebo (MD: 0,35 [95 % CI: 0,01; 0,69]). Fagudvalget vurderer, at resultatet fra SIRIUS ikke ændrer ved vurderingen af den kliniske merværd.

Baseret på den absolutte effektforskel på -0,07 vurderer fagudvalget, at benralizumab **ingen klinisk merværdi** har for *"gennemsnitlig ændring i livskvalitet*", idet forskellen ikke er signifikant og ikke opnår den klinisk relevante forskel på 0,5 (moderat evidenskvalitet).

6.1.2.6 *Alvorlige uønskede hændelser (serious adverse events, SAE) (vigtig)*

Alle syv randomiserede studier har rapporteret SAEs. I alle syv studier var der generelt en lav indrapportering af SAEs.

Ansøger har foretaget en indirekte sammenligning ved hjælp af Buchers metode. Analysen er udført med data fra "safety populationen", dvs. inkluderede patienter, der har modtaget behandling med enten lægemiddel eller placebo i studieperioden. Data fra SIRIUS er ikke medtaget i analysen pga. studiedesign. Ansøger har inkluderet ZONDA med tilsvarende design. Dette vurderes imidlertid ikke at påvirke resultatet og den samlede vurdering af dette effektmål, idet ZONDA er et lille studie.

Tabel 10: Vurdering af klinisk merværdi: Samlede forekomst (antal) af SAEs

	Forhåndsdefineret grundlag for vurdering		**Resultater**
Absolutte forskelle	5 %-point for den samlede forekomst af SAEs		1,5%-point [-2,0; 6,8]
Relative forskelle*	Stor merværdi	Øvre konf.gr. < 0,75[a]	
	Vigtig merværdi	Øvre konf.gr. < 0,90	
	Lille merværdi	Øvre konf.gr. < 1,00	
	Ingen merværdi	**Øvre konf.gr. ≥ 1,00**	**1,18 [0,75; 1,85]**
	Negativ merværdi	Nedre konf.gr. > 1,00	
Evidensens kvalitet	Lav		

[a] Risikoen skal være > 5 % i mindst én af de sammenlignede grupper.
* Øvre grænse for konfidensintervallet for den relative effekt (relativ risiko, odds ratio eller hazard ratio) må ikke overskride væsentlighedskriteriet for at kvalificere til den foreløbige kategori.

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

I SIRIUS var der færre, der oplevede en SAE med mepolizumabbehandling vs. placebo (RR: 0,08 [95 % CI: 0,01; 0,60]). Til sammenligning var der i ZONDA ingen forskel på andelen, der oplevede en SAE med benralizumabbehandling vs. placebo (RR: 0,51 [95 % CI: 0,22; 1,20]). Fagudvalget vurderer, at resultatet fra SIRIUS ikke ændrer ved vurderingen af den kliniske merværdi.

Jf. protokollen kan der ikke sættes en retvisende grænse for en klinisk relevant forskel i graden af alvorlighed af f.eks. anafylaktisk chok og sjældne forekomster af specifikke undertyper af bivirkninger. Ingen af de syv randomiserede studier rapporterer om tilfælde af anafylaksi på baggrund af behandlingen. Det er derfor ikke muligt at vurdere, om der er en klinisk relevant forskel i forhold til anafylaksi mellem de to behandlinger.

Baseret på den absolutte og relative effektforskel vurderer fagudvalget, at benralizumab ingen klinisk merværdi har for *"SAEs"*, idet der ikke opnås en klinisk relevant forskel på 5 %-point, og den øvre grænse for konfidensintervallet for den relative risiko > 1.

Samlet vurderer fagudvalget, at benralizumab **ingen klinisk merværdi** har vedr. effektmålet *"Alvorlige uønskede hændelser"* sammenlignet med mepolizumab (lav evidenskvalitet).

6.1.2.7 Frafald af patienter i studierne (vigtig)

Frafald af patienter er opgivet i alle syv randomiserede studier. Metaanalysen er foretaget med data fra henholdsvis benralizumab vs. placebo og mepolizumab vs. placebo. Den indirekte sammenligning er foretaget med Buchers metode. Data fra SIRIUS er ikke medtaget i analysen pga. studiedesign. Ansøger har inkluderet ZONDA med tilsvarende design. Dette vurderes imidlertid ikke at påvirke resultatet og den samlede vurdering af dette effektmål, idet ZONDA er et lille studie.

Tabel 11: Vurdering af klinisk merværdi: Andel af patienter som er frafaldet ved studiets afslutning (forskel mellem "intention to treat"- population og afsluttede patienter)

	Forhåndsdefineret grundlag for vurdering		**Resultater**
Absolutte forskelle	10 %-point		2,6 %-point [-1,3; 9,5]**
Relative forskelle*	Stor merværdi	Ikke muligt	
	Vigtig merværdi	Øvre konf.gr. < 0,80	
	Lille merværdi	Øvre konf.gr. < 0,90	
	Ingen merværdi		**RR: 1,40 [0,80; 2,43]**
	Negativ merværdi		
Evidensens kvalitet	Lav		

RR: relativ risiko
* Øvre grænse for konfidensintervallet for den relative effekt (relativ risiko, odds ratio eller hazard ratio) må ikke overskride væsentlighedskriteriet for at kvalificere til den foreløbige kategori.
** Omregnet af ansøger via medianen af mepolizumab eventrate (6,7 %).

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

I SIRIUS var der færre, der faldt fra med mepolizumabbehandling vs. placebo (RR: 0,72 [95 % CI: 0,17; 3,08]). Til sammenligning var der i ZONDA ingen forskel på andelen, der faldt fra med benralizumabbehandling vs. placebo (RR: 2,05 [95 % CI: 0,53; 7,91]). Fagudvalget vurderer, at resultatet fra SIRIUS ikke ændrer ved vurderingen af den kliniske merværdi.

Baseret på den absolutte effektforskel på 2,6 %-point og den relative effektforskel hvor konfidensintervallet indeholder 1, vurderer fagudvalget, at benralizumab **ingen klinisk merværdi** har for *"frafald af patienter"* idet den klinisk relevante forskel på 10 %-point ikke opnås, og der ikke opnås en signifikant forskel (lav evidenskvalitet).

6.1.2.8 Sygefravær (vigtig)

Fagudvalget ønskede at vurdere effekten af benralizumab på sygefravær, målt som gennemsnitligt antal sygedage fra arbejde eller skole på et år. De to benralizumabstudier SIROCCO og CALIMA rapporterede data for ugentligt fravær fra arbejdet (antal timer) på grund af sundhedsrelaterede problemer hos patienter, der blev behandlet med benralizumab sammenlignet med placebo. Data fra de to studier blev sammenlagt og viste gennemsnitligt 4,91 ugentlige tabte arbejdstimer ved patienter behandlet med benralizumab i forhold til 6,11 ugentlige tabte arbejdstimer ved patienter behandlet med placebo, dvs. en ikkesignifikant forskel på -1,20 timer [-2,92; 0,53].

Der foreligger ikke data på sygefravær for mepolizumab, hvorfor der ikke kan foretages en analyse på forskellen på benralizumab og mepolizumab for dette effektmål. Fagudvalget vurderer på baggrund heraf, at benralizumab har en **ikkedokumenterbar merværdi** sammenlignet med mepolizumab.

6.1.3 Evidensens kvalitet

Evidensens kvalitet for benralizumab sammenlignet med mepolizumab som tillægsbehandling til svær, eosinofil astma er samlet set vurderet som værende **lav**. Oversigt over evidensens kvalitet kan ses i bilag 5.

Overordnet er der lav risiko for bias i de inkluderede studier, hvorfor der ikke er nedgraderet for dette. Der er nedgraderet for indirekthed, idet de sammenlignende analyser er indirekte. Fagudvalget vurderer, at den manglende beskrivelse i studierne af en systematisk udredning ikke afspejler dansk guldstandard. Dette vurderes imidlertid ikke at have betydning for sammenligningen mellem benralizumab og mepolizumab, idet det samme gør sig gældende for alle studierne. Derfor nedgraderes der ikke endnu et niveau for indirekthed. For effektmålene omhandlende peroral kortikosteroidbehandling samt astmakontrol er der nedgraderet et niveau for unøjagtighed, da konfidensintervallet er bredt og overskrider den forhåndsdefinerede mindste klinisk relevante forskel i begge retninger. For effektmålet alvorlige uønskede hændelser er der ligeledes nedgraderet et niveau for unøjagtighed, da konfidensintervallet er bredt og overskrider den forhåndsdefinerede mindste klinisk relevante forskel i den ene retning.

6.1.4 Konklusion, samlet

For hvert effektmål, hvor det er muligt at sammenligne effekten, vurderer fagudvalget, at benralizumab ikke har nogen klinisk merværdi i forhold til mepolizumab. For effektmålene sygefravær og deleffektmålet ”andel som opnår en forbedring på 200 ml i FEV1” har det ikke været muligt at sammenligne effekten.

Samlet vurderer fagudvalget, at benralizumab til svær, eosinofil astma giver **ingen klinisk merværdi** for patienter med svær, eosinofil astma (**lav** evidenskvalitet).

7 Andre overvejelser

Patientværdier og -præferencer

Fagudvalget vurderer, at patienter vil foretrække behandling hver 8. uge frem for hver 4. uge, så tidsforbruget og injektionshyppigheden mindskes. Ligeledes er det fagudvalgets vurdering, at patienter foretrækker subkutan frem for intravenøs administration. Fagudvalget pointerer, at nedsættelse af sygefravær har stor betydning for den enkelte patient.

Særligt for børn

Indikationen for benralizumab gælder for voksne (18+). Datagrundlaget for alderen 12-17 år er sparsomt med ganske få inkluderede patienter og ingen subgruppeanalyser i denne aldersgruppe. Der afventes særskilte børnestudier for anti-IL5-behandling i aldersgruppen 12-17 år.

Farmakologi

Det vurderes ikke, at der er en væsentlig forskel på benralizumab og mepolizumabs farmakologiske egenskaber, til trods for forskellige virkningsmekanismer. Begge lægemidler har høj affinitet samt specificitet for deres mål, henholdsvis IL-5-receptoren og IL-5. Reduktionen af blodeosinofile er hurtigere og mere udtalt for benralizumab end for mepolizumab, men der er, for begge lægemidler, ikke set en direkte sammenhæng mellem blodeosinofile og klinisk effekt.

Benralizumab er et cytolytisk IgG1κ monoklonalt antistof målrettet mod IL-5-receptor alfa subunit (IL-5Rα). Lægemidlet binder til IL-5Rα-receptoren med høj affinitet (KD=16 pM) og høj specificitet (IC-50 0.3 nmol), hvilket fører til apoptose af blodeosinofile- og basofile celler, medieret af NK-celler. Det estimeres at $\geq$ 95 % af alle eosinofile granulocytter depleteres i blodet indenfor 24 timer. Effekten på eosinofile granulocytter i luftvejene er, som i blodet, også udtalt.

Mepolizumab er et IgG1κ-antistof, der binder direkte til IL-5 med høj affinitet (Kd 1,28 nM) og specificitet (IC-50 286 pM) førende til en reduktion af blodeosinofile på 84 % over en 4-ugers periode sammenlignet med placebo.

Biotilgængeligheden for subkutan administration af benralizumab estimeres til 58 % og for mepolizumab 64%-75 % afhængigt af administrationssted. Fordelingsvolumina for benralizumab og mepolizumab er henholdsvis 2,5-3,2L og 3,2L. Halveringstiden for benralizumab er estimeret til 15 dage, hvorimod mepolizumabs halveringstid er på 16-22 dage.

Fagudvalget vurderer, at benralizumab og mepolizumab er sammenlignelige på trods af forskellige virkningsmekanismer.

8 Fagudvalgets vurdering af samlet klinisk merværdi og samlet evidensniveau

Samlet vurderer fagudvalget, at benralizumab til svær, eosinofil astma giver **ingen klinisk merværdi** for patienter med svær, eosinofil astma sammenlignet med mepolizumab. Evidenskvaliteten vurderes at være **lav**.

Fagudvalget lægger vægt på relationen til eksisterende behandling (se afsnit 10).

9 Rådets vurdering af samlet klinisk merværdi og samlet evidensniveau

Medicinrådet vurderer, at benralizumab til svær, eosinofil astma giver **ingen klinisk merværdi** for patienter med svær, eosinofil astma sammenlignet med mepolizumab. Evidenskvaliteten vurderes at være **lav**.

10 Relation til eksisterende behandlingsvejledning

Nærværende vurderingsrapport for benralizumab til svær, eosinofil astma relaterer sig til Medicinrådets behandlingsvejledning for biologiske lægemidler til svær astma, som indeholder følgende anbefaling: ”*Der er ikke klinisk relevant forskel i effekt og bivirkninger mellem mepolizumab og reslizumab, som derfor ligestilles til 80 % af populationen. Evidenskvaliteten er meget lav.”*

Med den nuværende viden vurderer fagudvalget, at benralizumab, mepolizumab og reslizumab er klinisk ligeværdige, og kan ligestilles som tillægsbehandling til patienter med svær, eosinofil astma, som opfylder kriterierne for opstart angivet i behandlingsvejledningen for biologiske lægemidler til svær astma (LINK). For benralizumab gælder de samme opmærksomhedspunkter vedrørende monitorering, seponering og skift, som er angivet for mepolizumab og reslizumab i behandlingsvejledningen for biologiske lægemidler til svær astma (LINK).

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12 Bilag 1: Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende svær astma

Formand t.o.m. 31. marts 2018	*Indstillet af*
Uffe Christian Heitmann Bødtger *Forskningslektor*	Lægevidenskabelige selskaber (LVS)
Formand fra 1. april 2018	*Indstillet af*
Bo Chawes *Afdelingslæge, seniorforsker, dr.med., ph.d.*	Dansk Pædiatrisk Selskab
Medlemmer	*Udpeget af*
Kirsten Sidenius *Praktiserende speciallæge*	Inviteret af formanden
Kan ikke udpege	Region Nordjylland
Pernille Hauschildt *Ledende overlæge*	Region Midtjylland
Hanne Madsen *Ledende overlæge, ph.d.*	Region Syddanmark
Niels Maltbæk *Overlæge*	Region Sjælland
Lars Pedersen *Overlæge, klinisk lektor, ph.d.*	Region Hovedstaden
Pernille Printzlau *Farmaceut, cand.pharm.*	Dansk Selskab for Sygehusapoteksledelse (DSS)
Daniel Pilsgaard Henriksen *Læge, ph.d.*	Dansk Selskab for Klinisk Farmakologi (DSKF)
2 patientrepræsentanter	Danske Patienter

Medicinrådets sekretariat

Medicinrådet Dampfærgevej 27-29, 3. 2100 København Ø + 45 70 10 36 00 medicinraadet@medicinraadet.dk
Sekretariatets arbejdsgruppe: Louise Klokker Madsen (projekt- og metodeansvarlig) Pernille Skaarup Arrevad (projektdeltager) Anette Pultera Nielsen (koordinator) Annemette Anker Nielsen (teamleder)

13 Bilag 2: MAIC-analyse og ansøgers anvendelse af denne

Formålet med en MAIC-analyse er at justere for de forskelle i patientpopulation, der kan være mellem studierne i forhold til baselinekarakteristika. MAIC gør det muligt at fremkomme med valide estimater på behandlingseffekter, når en netværksmetaanalyse eller Buchers metode for justeret indirekte sammenligning ikke vurderes som metodisk forsvarlig. I MAIC-analyser vægtes patienterne i de inkluderede studier for det lægemiddel, hvor der findes data på individniveau, således at patientpopulationen i størst mulig grad tilsvarer patientpopulationen i de inkluderede studier for lægemidlet (f.eks. komparator), hvor individdata ikke er tilgængelig (kun adgang til aggregerede data). Metoden giver således kun mening i en sammenligning af to lægemidler, når der findes tilgængelige data på individniveau for mindst det ene lægemiddel.

I Medicinrådets behandlingsvejledning for biologiske lægemidler til svær astma (LINK) blev Buchers metode for indirekte sammenligning anvendt, uden justering for baselinekarakteristika. Denne metode kan anvendes, når de tilgængelige data er aggregerede.

Inklusion af studier i ansøgningens MAIC-analyser er udvalgt på baggrund af studiernes primære endepunkter. SIROCCO [6], CALIMA [7], MENSA [10] og DREAM [9] har alle eksacerbationer som primært endepunkt. ZONDA [8] og SIRIUS [11] har OCS-reduktion (reduktion af peroral kortikosteroid). Ansøger har gennemført MAIC-analysen før publiceringen af et relevant mepolizumabstudie (MUSCA[12]). Analysen er ikke efterfølgende opdateret, hvorfor resultater fra MUSCA ikke er inkluderet i ansøgers MAIC-analyser. Efter aftale med Medicinrådets sekretariat har ansøger derfor foretaget en sensitivitetsanalyse samt inkluderet MUSCA i vurderingen af de effektmål, som ansøgers MAIC ikke dækker.

Ansøger har i deres MAIC-analyse gjort rede for udvælgelsen af de variable, som analysen blev justeret for, på grund af forskelle i baselinedata. De udvalgte variable er vist i Tabel 12.

Tabel 12: Variable der er justeret for i MAIC-analyserne, på grund af forskelle i baselinedata.

Eksacerbationsstudier: SIROCCO/CALIMA vs. MENSA/DREAM	**OCS-reduktionsstudier: ZONDA vs. SIRIUS**
Antal eosinofile (fordeling af patienter med ≥ 300 celler/µL vs. < 300 celler/µL)	Antal eosinofile celler
Behandling med vedligeholdelsesdosis af OCS (andel af patienter)	OCS-dosis
IgE-tal (andel af patienter for hver kategori)	
Køn	
Antal eksacerbationer de seneste 12 måneder	Antal eksacerbationer de seneste 12 måneder
Nasale polypper	Nasale polypper
BMI (gennemsnit)	BMI (gennemsnit)

Udover forskelle i baselinekarakteristika er definitionen af højdosis ICS også forskellig i de inkluderede studier. I benralizumabstudierne er højdosis ICS defineret som behandling med ≥ 500 µg fluticasone propionate (FP) dagligt eller ækvivalent, mens højdosis ICS i mepolizumabstudierne er defineret som ≥ 880 µg FP dagligt eller ækvivalent. Ansøger har på den baggrund udført to MAIC-analyser for effektmålet "eksacerbationsrate", som inkluderer patienter fra benralizumabstudierne i behandling med henholdsvis ≥ 880 µg eller ≥ 500 µg FP dagligt eller ækvivalent. Fagudvalget vurderer, at ICS-dosis ≥ 880 µg FP dagligt eller ækvivalent bedst afspejler danske forhold, hvor behandling med højdosis ICS ifølge dansk guldstandard (ERS [2,4]) er ≥ 1000 µg FP dagligt eller ækvivalent. Derfor baserer Medicinrådets vurdering af effektmålet eksacerbationsrate sig alene på analyserne af ICS-dosis ≥ 880 µg FP dagligt eller ækvivalent.

Fordeling på baggrund af definition af højdosis ICS anvendes ikke i MAIC-analysen af effektmålet "peroral vedligeholdelsesbehandling med kortikosteroid", hvorfor en del af patienterne er i behandling med

højdosis ICS, forstået som ≥ 500 µg FP pr. dag (eller ækvivalent). Fagudvalget vurderer imidlertid, at resultaterne for dette effektmål alligevel kan overføres til danske forhold, idet alle patienterne i disse studier er i behandling med OCS, og deres standard-ICS blev vurderet til ikke at have afgørende indflydelse på effektmålet reduktion af OCS.

14 Bilag 3: Studiekarakteristik

Studiekarakteristika af de inkluderede studier samt karakteristika for populationen som var inkluderet i analyserne, hvor oplysningerne var tilgængelige (i kursiv). For alle studier var det et krav, at deltagerne benyttede second controller (typisk langtidsvirkende beta2-agonist, LABA).

Publikation (klinisk studie)	Antal	Opfølgningstid	Alder	Eosinofil inflammation	Eksacerbationer de seneste år	Inhalations-Steroid**	Oralt steroid	Dosisregime	Primære effektmål
Benralizumab									
Bleeker 2016 (SIROCCO)	1204	48 uger	12-75 år	Blod: < 300 celler/µL eller ≥ 300 celler/µL i det foregående år	≥ 2	Højdosis (patienter mellem 12 og 17 år er mediumdosis tilladt)	Tilladt, men ikke et krav	2 aktive arme, subkutan: 30 mg hver 4. eller 8. uge	Årlige eksacerbationer
*inkluderet i analyser**	*267*			*≥ 300 celler/µL*		*højdosis*		*Hver 8. uge*	
Fitzgerald 2016 (CALIMA)	1306	56 uger	12-75 år	Blod: < 300 celler/µL eller ≥ 300 celler/µL i det foregående år	≥ 2	Medium til højdosis	Tilladt, men ikke et krav	2 aktive arme, subkutan: 30 mg hver 4. eller 8. uge	Årlige eksacerbationer
*inkluderet i analyser**	*239*			*≥ 300 celler/µL*		*højdosis*		*Hver 8. uge*	
Nair 2017 (ZONDA)	220	28 uger	18-75 år	Blod: ≥ 150 til < 300 celler/µL eller ≥ 300 celler/µL i det foregående år	≥1	højdosis	OCS i de seneste 6 måneder. Dosis skal være 7,5 til 40 mg/dag ved besøg 1 og stabil mindst 2 uger før randomisering.	2 aktive arme, subkutan: 30 mg hver 4. eller 8. uge	OCS reduktion
*inkluderet i analyser**	*73*			*≥ 300 celler/µL*		*højdosis*		*Hver 8. uge*	
Mepolizumab									
Pavord 2012 (DREAM)	621	52 uger	12-74 år	I det foregående år: Sputum: ≥ 3 % eller Blod: ≥ 300 celler/µL	≥ 2	Højdosis	Tilladt, men ikke et krav	3 aktive arme, i.v.: 75 mg, 250 mg, 750 mg	Årlige eksacerbationer
*inkluderet i analyser**	*153*					*højdosis*			
Ortega 2014 (MENSA)	576	32 uger	Over 12 år	Blod: ≥ 150 celler/µL ved screening eller ≥ 300 celler/µL i det foregående år	≥ 2	Højdosis	Tilladt, men ikke et krav	2 aktive arme: 100 mg s.c., 75 mg i.v. (placebo i.v.	Årlige eksacerbationer

								og placebo s.c.)	
*inkluderet i analyser**	*385*					*højdosis*			
Bel 2014 (SIRIUS)	135	24 uger	Over 12 år	Blod: ≥ 150 celler/µL ved screening eller ≥ 300 celler/µL i det foregående år	Nej	Højdosis	5-35 mg/dag i de seneste 6 måneder	100 mg s.c.	Årlige eksacerbationer
*inkluderet i analyser**	*69*					*højdosis*			
Chupp 2017 (MUSCA)	551	24 uger	Over 12 år	Blod: ≥ 150 celler/µL ved screening eller ≥ 300 celler/µL i det foregående år	≥ 2	Højdosis	Tilladt, men ikke et krav	100 mg s.c.	Livskvalitet
*inkluderet i analyser**	*274*					*højdosis*			
*kun fra interventionsgrupperne, for benralizumab studierne er antallet før justering i MAIC-analyserne									

15 Bilag 4: Baselinekarakteristik

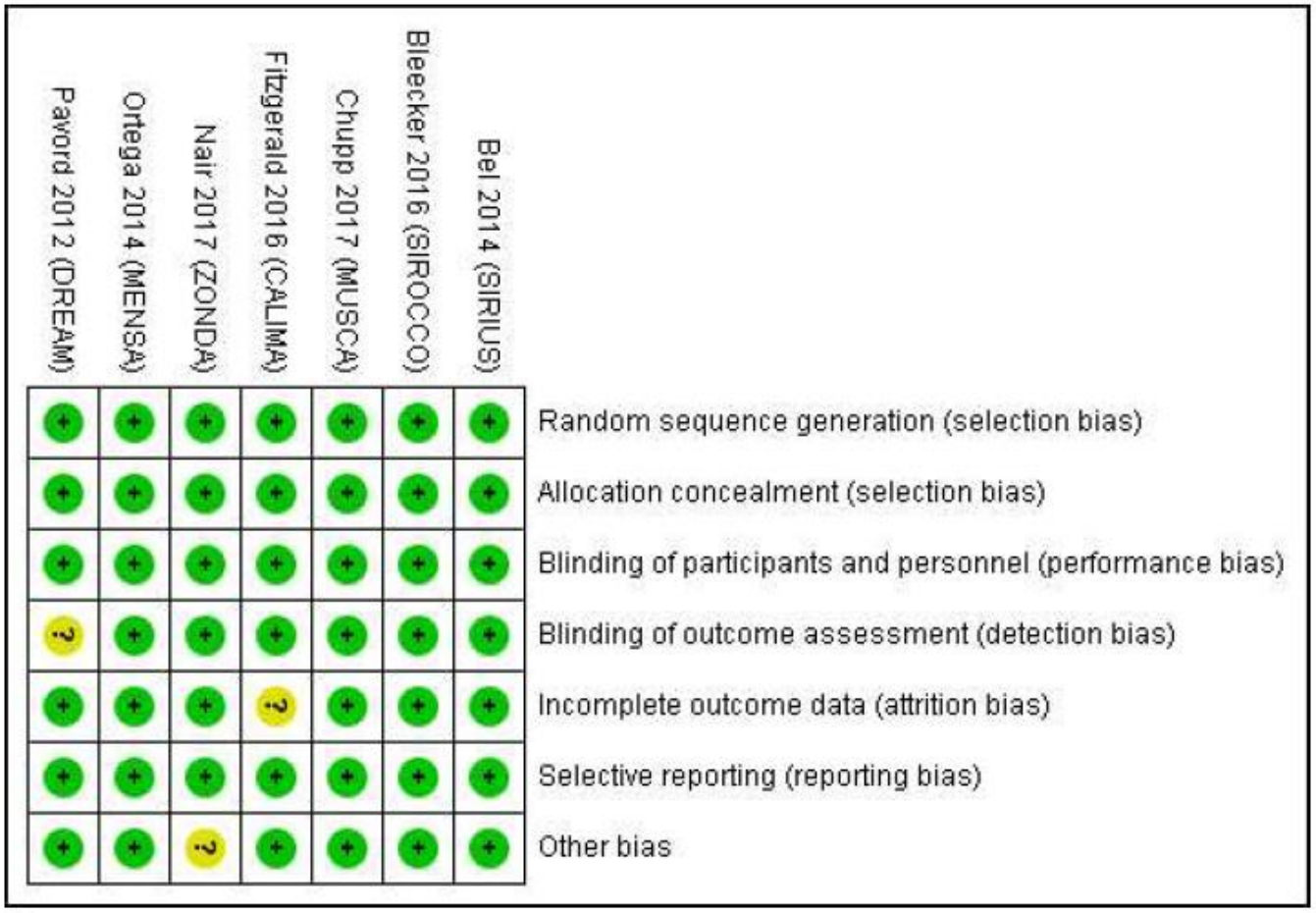
Baselinekarakteristik for de inkluderede studier samt karakteristika for populationen som var inkluderet i analyserne, hvor oplysningerne var tilgængelige (i kursiv).

	Alder (år)	Andel under 18 år (%)	Andel kvinder (%)	FEV1 % forventet (FEV1, L)	Tid siden diagnose (år)	Antal eksacerbationer det seneste år (gennemsnit)	OCS-dosis	Astmakontrol (ACQ)
Benralizumab								
Bleeker 2016 (SIROCCO)	49	4,4	66	56 (1,67)	15	2,9	10-17 mg	2,8-2,9 (for gruppen med blod eosinofili ≥ 300 celler/µL
*inkluderet i analysen**	*48*	*3,7*	*65*	*56 (1,66)*	*15*	*2,8*	*16 mg (2,5-60)*	*2,8 (0,89)*
Fitzgerald 2016 (CALIMA)	49		61,8	(1,76)	16	2,7	7-12 mg	2,7-2,8 (for gruppen med blod eosinofili ≥ 300 celler/µL
*inkluderet i analysen**	*51*	*2,5*	*58*	*57 (1,76)*	*16*	*2,7*	*8 mg (2-25)*	*2,8 (0,95)*
Nair 2017 (ZONDA)	51	-	61	(1,85)	12	2,8	14,7 mg	2,4 - 2,9
*inkluderet i analysen**	*53*	-	*64*	*59 (1,75)*	*16*	*3,1*	*14,3 mg*	*2,42 (1,21)*
Mepolizumab								
Pavord 2012 (DREAM)	49		62	(1,85)	19	3,7	10 mg	2,35
*inkluderet i analysen**	*50*	-	*68*	*50 (1,81)*	*19*	*3,7*	*10 mg (10-20)*	*2,2 (1,1)*
Ortega 2014 (MENSA)	50		57	(1,82)	20	3,6	12-15 mg	2,2
*inkluderet i analysen**	*51*	-	*58*	*60 (1,79)*	*20*	*3,7*	*12 mg (1-50)*	*2,2 (1,2)*
Bel 2014 (SIRIUS)	50		55	(1,95)	19	3,1	11 mg	2,1
*inkluderet i analysen**	*50*	-	*64*	*60 (1,90)*	*17*	*3,3*	*10 mg*	*2,2 (1,3)*
Chupp 2017 (MUSCA)	51		59	(1,75)	20	2,8	13 mg	2,2
*inkluderet i analysen**	*50*	-	*54 %*	*56 %*	*20*	*2,9*	*13 mg (11)*	*2,2 (1,1)*

FEV1: Forced Expiratory Volume (forceret ekspirationsvolumen) på 1 sekund
FEV1 % forventet: FEV1-værdi i % af forventet FEV1-værdi, ud fra normalværdier
OCS: peroral korticosteroid
* Kun fra interventionsgrupperne, for benralizumabstudierne er antallet før justering i MAIC-analyserne

16 Bilag 5: GRADE-evidensprofiler

16.1 Cochrane Risk of Bias



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

Hvilken klinisk merværdi tilbyder benralizumab sammenlignet med mepolizumab ved behandling af patienter med svær, eosinofil astma?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations***	**benralizumab**	**mepolizumab**	**Relative (95 % CI)**	**Absolute (95 % CI)**		
Eksacerbationer pr. år (subgruppe med ≥ 880 µg FP dagligt), MAIC analyse (justeret for forskelle i baselinekarakteristika)												
4	randomised trials	not serious	not serious	serious [a]	not serious	none	-/839	-/345	**RR 0,94** [0,78; 1,13]		⊕⊕⊕◯ MODERAT	CRITICAL
Andel af patienter med mere end 0 eksacerbationer												
5	randomised trials	not serious	not serious	serious [a]	not serious	none	205/579 (35,4 %)	253/538 (47,0 %)	**RR 0,94** [0,73; 1,22]	**3 fewer per 100** (from 10 more to 13 fewer)	⊕⊕⊕◯ MODERAT	CRITICAL
Peroral kortikosteroidbehandling, gennemsnitlig %-reduktion i daglig dosis (follow up: range 24 weeks to 28 weeks)												
2	randomised trials	not serious	not serious	serious [a]	serious [b]	none	73	69	-	MD **5,06 % higher** (22,39 lower to 32,52 higher)	⊕⊕◯◯ LAV	CRITICAL
Peroral kortikosteroidbehandling, andel af patienter som ophører												
2	randomised trials	not serious	not serious	serious [a]	serious [b]	none	16/73 (21,9 %)	10/69 (14,5 %)	**RR 1,48** [0,42; 5,21]	**7 more per 100** (from 8 fewer to 61 more)	⊕⊕◯◯ LAV	CRITICAL
Peroral kortikosteroidbehandling, andel af patienter som opnår 50 % reduktion												
2	randomised trials	not serious	not serious	serious [a]	serious [b]	none	43/73 (58,9 %)	37/69 (53,6 %)	**RR 1,10** [0,65; 1,86]	**5 more per 100** (from 19 fewer to 46 more)	⊕⊕◯◯ LAV	CRITICAL
Lungefunktion, gennemsnitlig reduktion, mL												
4	randomised trials	not serious	not serious	serious [a]	not serious	none	839	345	-	MD **20 mL higher** (60 lower to 100 higher)	⊕⊕⊕◯ MODERAT	IMPORTANT
Lungefunktion, andel af patienter som opnår en forbedring på 200mL - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Astmakontrol, gennemsnitlig ændring												
6	randomised trials	not serious	not serious	serious [a]	serious [b]	none	442	804	-	MD **0,01 higher** (0,2 lower to 0,2 higher)	⊕⊕◯◯ LAV	IMPORTANT
Livskvalitet, gennemsnitlig ændring												
6	randomised trials	not serious	not serious	serious [a]	not serious	none	434	803	-	SMD **0,06 SD higher** (0,3 lower to 0,2 higher)	⊕⊕⊕◯ MODERAT	IMPORTANT
Alvorlige uønskede hændelser (Serious Adverse Events, SAEs), antal hændelser												
6	randomised trials	not serious	not serious	serious [a]	serious [d]	none	99/895 (11,1 %)	65/811 (8,0 %)	**RR 1,18** [0,75; 1,85]	**15 more per 1.000** (from 20 fewer to 68 more)	⊕⊕◯◯ LAV	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations***	**benralizumab**	**mepolizumab**	**Relative (95 % CI)**	**Absolute (95 % CI)**		
Frafald af patienter i studierne, andel												
6	randomised trials	not serious	serious [c]	serious [a]	not serious	none	105/912 (11,5 %)	54/812 (6,7 %)	**RR 1,40** [0,80; 2,43]	**26 more per 1.000** (from 13 fewer to 95 more)	⨁⨁◯◯ LAV	IMPORTANT
Sygefravær - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

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

a. Der nedgraderes et niveau for indirekte sammenligning af de 2 lægemidler

b. Der nedgraderes et niveau for unøjagtighed, da konfidensintervallet er bredt og overskrider den mindste klinisk relevante forskel i begge retninger

c. Der nedgraderes et niveau for inkonsistens, idet der ses betydelig variation i effektestimaterne for de enkelte studier

d. Der nedgraderes et niveau for unøjagtighed, da konfidensintervallet er bredt og overskrider den mindste klinisk relevante forskel i den ene retning

Application for the assessment of clinically added value of Fasenra (benralizumab) as an add on maintenance treatment in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus long acting β agonists.

Contents

1 Basic information

Table 1: Contact information

Name	Anupma Farrington
Title	Medical Affairs Manager
Area of responsibility	Medical
Phone	+45 25971819
E-mail	Anupma.farrington@astrazeneca.com
Name	Søren Clausen
Title	Market Access Director
Area of responsibility	Reimbursement
Phone	+4523615584
E-mail	Soren.clausen@astrazeneca.com
Name	Thomas Kristensen
Title	Health Economists
Area of responsibility	Health economy
Phone	+46722140492
E-mail	Thomas.kristensen@astrazeneca.com

Table 2: Overview of the pharmaceutical

Proprietary name	Fasenra
Generic name	Benralizumab
Marketing authorization holder in Denmark	AstraZeneca A/S
ATC code	R03DX10
Pharmacotherapeutic group	Drugs for obstructive airway diseases, other systemic drugs for obstructive airway diseases.
Active substance(s)	One pre-filled syringe contains 30 mg benralizumab in 1 mL
Pharmaceutical form(s)	Solution for injection. 1 pre-filled syringe
Mechanism of action	Benralizumab is an anti-eosinophil, humanised afucosylated, monoclonal antibody (IgG1, kappa). It binds to the alpha subunit of the human interleukin 5 receptor (IL 5Rα) with high affinity and specificity. The IL 5 receptor is specifically expressed on the surface of eosinophils and basophils. The absence of fucose in the Fc domain of benralizumab results in high affinity for FcγRIII receptors on immune effectors cells such as natural killer (NK) cells. This leads to apoptosis of eosinophils and basophils through enhanced antibody dependent cell mediated cytotoxicity (ADCC), which reduces eosinophilic inflammation.
Dosage regimen	The recommended dose of benralizumab is 30 mg by subcutaneous injection every 4 weeks for the first 3 doses, and then every 8 weeks thereafter. Fasenra is intended for long term treatment. A decision to continue the therapy should be made at least annually based on disease severity, level of exacerbation control and blood eosinophil counts.
Therapeutic indication relevant for assessment (as defined by EMA)	Fasenra is indicated as an add on maintenance treatment in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus long acting β agonists.
Other approved therapeutic indications	No
Will dispensing be restricted to hospitals?	BEGR label. Fasenra is administered as a subcutaneous injection by a healthcare professional. Studies on home administration are ongoing.
Combination therapy and/or co-medication	No formal drug interaction studies have been conducted. An effect of benralizumab on the pharmacokinetics of co-administered medicinal products is not expected. Based on the population pharmacokinetic analysis, commonly co-administered medicinal products (montelukast, paracetamol, proton pump inhibitors, macrolides and theophylline/aminophylline) had no effect on benralizumab clearance in patients with asthma.
Packaging – types, sizes/number of units, and concentrations	Pack containing 1 single use pre-filled syringe. Each pre-filled syringe contains 30 mg benralizumab in 1 ml.
Orphan drug designation	No

2 Abbreviations

ACQ	Asthma Control Questionnaire
AQLQ	Asthma Quality of Life Questionnaire
BENRA	Benralizumab
CDR	CADTH Common Drug Review (CDR) (*Canada)*
CI	Confidence interval
CIQ	Classroom Impairment Questions
CSR	Clinical study report
ECP	Eosinophil cationic protein
eCRF	Electronic case report form
EDN	Eosinophil derived neurotoxin
EOS	Eosinophils
ER	Emergency room
EQ	EuroQol
FAS	Full analysis set
FEV / FEV1	Forced expiratory volume / Forced expiratory volume in one second
FP	Fluticasone propionate
HRU	Healthcare Resource Utilization
ICS	Inhaled Corticosteroids
IgG1	Immunoglobulin G1
IL5	Interleukin 5
IPD	Individual patient data
ITC	Indirect treatment comparison
ITT	Intent-to-Treat
IV	Intravenous
LABA	Long-Acting Beta-Agonists
LCI	Lower confidence interval
LS	Least squares
MAIC	Matching adjusted indirect comparison
MD	Mean difference
MEPO	Mepolizumab
MOA	mechanism of action
NICE	National Institute for Health and Clinical Excellence *(UK)*
OCS	Oral Corticosteroids
PBAC	Pharmaceutical Benefits Advisory Committee (*Australia)*
PEF	Peak expiratory flow
PT	Preferred term
Q4W	Every four weeks
Q8W	Every eight weeks;
QoL	Quality of life
RR	Rate ratio
SAE	Serious adverse event
SC	Subcutaneous
SOC	Standard of care
STC	Simulated treatment comparison
UCI	Upper confidence interval
WPAI Q	Work Productivity and Activity Impairment Questionnaire

3 Summary (dansk)

Tre store fase III studier er grundlaget for EU godkendelsen af benralizumab til voksne med svær eosinofil astma. To eksacerbations-studier CALIMA og SIROCCA samt ZONDA som undersøger reduktion i oral steroid dosis (OCS). Alle studier sammenligner med placebo + standardbehandling (SOC). Studierne viser signifikante fordele for både de primære og sekundære endepunkter. Desuden opnår mange patienter 0 eksacerbationer (60 – 77 % afhængig af studie) og ligeledes opnår 52 % at reducere OCS forbruget til 0 mg ved det sidste besøg.

To biologiske anti-IL5 produkter er allerede markedsført i Danmark og i forhold til dem skiller Fasenra sig ud ved:

- en anderledes virkningsmekanisme som bl.a. betyder, at eosinofil-niveauet reduceres mod 0-værdi efter 24 timer og deraf hurtig indsættende respons.
- at have det største fase 3 program.
- subkutan administration hver 8. uge (efter en initial loading dosis) som medfører færre hospitalskontakter til gavn for patient, sundhedspersonale og deraf relaterede omkostninger

Medicinrådet har valgt mepolizumab som komparator i forbindelse med denne ansøgning. Der er ikke head-to-head studier som sammenligner effekten af de to produkter. Vi har derfor bygget ansøgningens konklusioner på de kritiske/vigtige effektmål op omkring en Matching Adjusted Indirect Comparison (MAIC) af benralizumab vs. mepolizumab. For de effektmål som ikke er dækket af denne analyse er der i stedet anvendt andre statistiske metoder for at besvare de kliniske spørgsmål. For de kritiske/vigtige endepunkter, ses der kun numeriske og ikke signifikant forskelle i mellem benralizumab vs. mepolizumab. Differencerne set i de statistiske modeller møder generelt ikke kravene til effektmålene fra tabel 4 i medicinrådets protokol. En undtagelse er 100 % reduktion i OCS hvor 5 % målet opfyldes.

Der er for tiden 7 hospitalsafdelinger som behandler med anti-IL5 produkter og det vurderes ud fra salgstal og beregninger fra tidligere KRIS ansøgninger, at 200 til 230 patienter her og nu er i behandling med disse produkter. Vi har nedenfor angivet vores bud på en udvikling på nye og igangværende patienter de kommende år. Vi forventer, at flere vil blive tilbudt anti-IL5 produkter fremover men, at der selvfølgelig er en øvre grænse defineret ved, at der er forholdsvis få astma patienter som har svær eosinofil astma.

Patienttype						
	Estimat 2016	Estimat 2017	Produkt	2018	2019	2020
Net nye patienter	0	0	Fasenra**	83	92	88
Net nye patienter	135	63	Nucala	41	24	24
Net nye patienter	0	30	Cinqaero	14	12	12
Net nye patienter	0	0	Dupilumab	0	48	58
Net nye patienter	**135**	**93**	**Total**	**138**	**176**	**182**
Nye og igangværende patienter	0	0	Fasenra	83	175	263
Nye og igangværende patienter	135	198	Nucala	233	257	281
Nye og igangværende patienter	0	30	Cinqaero	41	53	65
Nye og igangværende patienter	0	0	Dupilumab	0	48	106
Nye og igangværende patienter	**135***	**228**	**Total**	**357**	**533**	**715**

* Lancering af Nucala betød at en pulje af patienter blev behandlet

** Udviklingen er baseret på at både Fasenra og senere Dupilumab anbefales som standardbehandling

De gentagne injektioner administreres i dag månedligt på de 7 klinikker. På grund af centraliseringen af behandlingen kan den månedlige administration og anden opfølgning medføre; lang transporttid for nogle patienter, fri fra arbejde og andre udgifter. Disse forhold danner baggrund for omkostningsanalysen som er medsendt til Amgros.

Tidshorisonten er vigtig. Benralizumab studierne løber i højst 56 uger. Medicinrådet og DLS anbefaler, at effekten evalueres efter 12 måneder og fortsætter ved respons og er i princippet livslang.

Mortalitet er ikke behandlet i ansøgningen da død relateret til astma/svær astma er sjælden.

3.1 Introduction

A subset of patients with severe asthma are often uncontrolled with the current standard of care and their treatment remains a significant unmet need. Patients with severe uncontrolled asthma are at a higher risk of exacerbations, hospitalization, and death compared to controlled asthma, and are often dependent on OCS and have severely impaired quality of life (QoL). Although patients with severe uncontrolled asthma comprise a small proportion (3-5%) of the total asthma population, they have substantially more health resource use than patients with moderate or mild asthma. Eosinophils play a central role in the pathogenesis of severe uncontrolled asthma and are correlated with worse outcomes. Patients with severe uncontrolled asthma with an eosinophilic phenotype comprise only a minority (<3%) of the total asthma patients. Increased eosinophil levels are associated with increased disease severity, more exacerbations, less well-controlled disease, decreased lung function, higher mortality, and higher OCS dependency. Severe uncontrolled asthma patients, especially with an eosinophilic phenotype, show frequent or chronic use of OCS, which is associated with short-term and long-term detrimental side effects, including diabetes, osteoporosis, high blood pressure, skeletal complications, ocular complications, and Cushingoid features.

4 Literature search

4.1 Databases and search strategy

Please see Appendix 1 for details.

The systematic literature search and literature selection identified 7 randomized studies (published in 8 articles) that have investigated the effect of benralizumab (Bleecker 2016 [1], FitzGerald 2016 [2], Nair 2017 [3], FitzGerald 2018 [8]) and the effect of mepolizumab (Pavord 2012 [4], Ortega 2014 [5], Bel 2014 [6], Chupp 2017 [7]), all with placebo as comparator. In addition, we have included article on Methods for population-adjusted indirect comparisons in submissions to NICE [10]. Additionally, we have included the GINA guidelines [9], as the GINA guidelines refer to the patient segment, which is comparable with the two replicate primary registration studies (Bleecker 2016 [1] and FitzGerald 2016 [2]) of benralizumab, evaluating patients with uncontrolled asthma and a history of exacerbations still symptomatic despite using high-dose ICS/LABAs with or without OCS or additional controller medications – and eligible for refer for add-on treatment e.g. anti-IL5 (GINA Steps 4 and 5). Moreover, we have included as a reference; Medicinrådets behandlingsvejledning for biologiske lægemidler til svær astma [12], in order to evaluate the current application with reference to this protocol.

In all selected studies, the control arm is placebo and patient continue their ongoing treatment except for SIRIUS and ZONDA (OCS reduction). The benralizumab and mepolizumab studies varied with respect to the primary endpoint. Most trials (SIROCCO, CALIMA, MENSA, DREAM) evaluated the annual rate of clinically significant exacerbations as the primary endpoint while two of the trials (ZONDA, SIRIUS) evaluated OCS sparing as the primary outcome. MUSCA is primarily an asthma score study with exacerbation as “another endpoint “

Depending upon the primary objective of the benralizumab and mepolizumab trials, the studies were classified into two groups:

- Exacerbations trials: trials analysing annual rate of exacerbations as primary endpoint (benralizumab: SIROCCO, CALIMA, mepolizumab: MENSA and DREAM).
    - MUSCA is an asthma score trial with exacerbation as a secondary or "another" endpoint
- OCS sparing trials: trials analysing OCS sparing effect as a primary endpoint (benralizumab: ZONDA and mepolizumab: SIRIUS)

Furthermore, a MAIC (Matching adjusted indirect treatment comparison) report of benralizumab vs. mepolizumab, an external sourced report by AstraZeneca, [11] has been added to the reference list. It includes a detailed description of the MAIC literature search. The MAIC report has been submitted to Medicinrådet for evaluation and has been validated and accepted as roboust. It should be treated as confidential as the report is awaiting publication. For more information around the methods use see section 5.1.26.

The MAIC analysis was started earlier than the publication of the mepolizumab study MUSCA[7]. Therefore, it did not fall into the predefined MAIC search duration (10+ years up to 17th June 2016) in the systematic literature review done for the MAIC analysis.
The MAIC analysis was not updated with MUSCA trial data , mainly due to lack of clinical relevance. Exacerbation reduction rate was the primary endpoint in the two sets pivotal trials of benralizumab (SIROCCO/CALIMA) and mepolizumab (MENSA/DREAM), however, in MUSCA trial, it was included as 'other endpoint' and due to the very short duration of MUSCA trial (24 week), clinical relevance of annualized reporting of exacerbation rate was questioned. Asthma has a seasonality effect on its disease outcome (symptoms and exacerbations) and shorter duration trials may not be adequate to capture this seasonality effect on its outcome. Also, exacerbation and hospitalization is relatively a rare outcome and it may be difficult to observe representative number of exacerbation or hospitalization in a very short duration trial like MUSCA. Therefore, we have considered, only 24-week trial may not be clinically relevant to pool together with a 52 weeks (DREAM) and 32 weeks (MENSA) trials for exacerbation endpoints. However, trial design should not be considered as a reason of excluding any trials in meta-analysis and to meet this point it was agreed with Medicinrådet to do an additional analysis (see below) to compare exacerbation data (both overall exacerbation and ER/Hospitalization) from MAIC without MENSA trial which means SIROCCO/CALIMA (pooled data) vs. DREAM only.

SIROCCO/CALIMA vs DREAM. Overall exacerbation and ER/Hospitalization)

The studies differed in baseline EOS count, definition of the high-dose ICS, prior history of exacerbation, proportion of patients using OCS at baseline, and nasal polyp status. The benralizumab studies recruited a lower proportion of patients with ≥3 exacerbation within the previous year, higher proportion of patients with ≥300 cells/µL EOS count at baseline, and a lower proportion of patients with baseline maintenance OCS use.

The results and model is enclosed as a separate appendix. The conclusion from this additional analysis is that there is no statistically significant difference in efficacy between benralizumab and mepolizumab. The two IL-5 inhibitors may be considered as same in terms of exacerbation reduction in severe asthma patient

For other clinical questions that are not covered by the MAIC we have included MUSCA data if it was possible.

4.2 Relevant studies - benralizumab and mepolizumab

Table 3A: Benralizumab Relevant studies included in the assessment

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date). Patient number	Relevant for clinical question
[1] Bleecker ER, FitzGerald JM, Chanez P, Papi A, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. Lancet. 2016; 388:2115-2127. Supplementary appendix: Supplement to: Lancet 2016; published online Sept 5. http://dx.doi.org/10.1016/ S0140-6736(16)31324-1.	SIROCCO	NCT01928771.	Study start date: September 19, 2013 Study completion date: April 5, 2016 Patient numbers: N= 407 placebo N= 400 benralizumab Q.4W N=398 benralizumab Q8W <u><300 EOS:</u> N= 267 placebo N= 275 Q4 benralizumab N = 267 Q8W benralizumab	Exacerbations, ACQ-6, AQLQ, FEV, OCS discontinuations and productivity loss.
[2] FitzGerald JM, Bleecker ER, Nair P, et al. Benralizumab, an anti–interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2016; 388:2128-2141. Supplementary appendix: Supplement to: Lancet 2016; published online Sept 5. http://dx.doi.org/10.1016/ S0140-6736(16)31322-8.	CALIMA	NCT01914757.	Study start date: August 2013 Study completion date: March 2016 Patient numbers: N= 440 placebo N= 425 benralizumab Q.4W N=441 benralizumab Q8W <u><300 EOS:</u> N= 248 placebo N= 241 Q4 benralizumab N = 239 Q8W benralizumab	Exacerbations, ACQ-6, AQLQ, FEV, OCS discontinuations and productivity loss.
[3] Nair P, Wenzel S, Rabe KF, Bourdin A, et al., Oral Glucocorticoid–Sparing Effect of Benralizumab in Severe Asthma. The New England Journal of Medicine. 2017; 376, 25: 2448-2458.	ZONDA	NCT02075255.	Study start date: April 28, 2014 Study completion date: August 8, 2016	OCS reduction, Exacerbations, FEV, ACQ-6, AQLQ and discontinuations

Supplementary appendix: Supplement to: N Engl J Med 2017;376:2448-58. DOI: 10.1056/NEJMoa1703501			Patient numbers: N= 75 placebo N= 72 benralizumab Q.4W N=73 benralizumab Q8W	

Table 3B: Mepolizumab Relevant studies included in the assessment

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date). Patient numbers	Relevant for clinical question
[4] Pavord ID, Korn S, Howarth P, Bleecker ER et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial Lancet 2012; 380: 651–59 doi: 10.1016/S0140-6736(12)60988-X.	DREAM	NCT01000506	Study start date: November 2009 Study completion date: December 2011 Patient numbers: n= 155 placebo n= 153 mepolizumab, 75mg n= 152 mepolizumab, 250mg n= 156 mepolizumab, 75mg	Exacerbations, ACQ-6, AQLQ, FEV, OCS, SAE and discontinuations
[5] Ortega HG, Liu MC, Pavord ID, Brusselle GG et al. Mepolizumab Treatment in Patients with Severe Eosinophilic Asthma NEJM 2014 Sep 25;371(13):1198-207. doi: 10.1056/NEJMoa1403290.	MENSA	NCT01691521	Study start date: October 2012 Study completion date: January 2014 Patient numbers: n= 191 placebo n= 191 mepolizumab, iv n= 194 mepolizumab, sc	Exacerbations, ACQ-5, SGRQ, FEV_1, AE, SAE and discontinuations
[6] Bel EH, Wenzel SE, Thompson PJ, Prazma CM, et al. Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma NEJM 2014 Sep 25;371(13):1189-97. doi: 10.1056/NEJMoa1403291	SIRIUS	NCT01691508	Study start date: October 2012 Study completion date: December 2013 Patient numbers: n= 66 placebo n= 69 mepolizumab n=73 mepolizumab	OCS reduction, Exacerbations, FEV_1, AE, SAE, ACQ-5, SGRQ and discontinuations

[7] Chupp GL, Bradford ES, Albers FC, Bratton F et al. 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 Lancet Respir Med 2017; 5: 390–400 dx.doi.org/10.1016/ S2213-2600(17)30125-X	MUSCA	NCT02281318	Study start date: December 2012 Study completion date: November 2015 Patient numbers: n= 277 placebo n= 274 mepolizumab	Exacerbations, FEV_1, SGRQ, ACQ-5, AE, SAE

4.3 Main characteristics of included studies

4.3.1 Clinical data for benralizumab, phase 3 study design and end points

An overview of the benralizumab Phase 3 WINDWARD clinical program to support registration/approval in patients with severe uncontrolled asthma is shown in Appendix 2.

Asthma exacerbation studies (SIROCCO and CALIMA) [1]-[2], [8]:

The 2 replicate primary registration studies, SIROCCO and CALIMA, evaluated patients 12 years to 75 years of age with uncontrolled asthma and a history of exacerbations still symptomatic despite using high-dose ICS/LABAs with or without OCS or additional controller medications (GINA Steps 4 and 5, GINA 2017)[9] in 2 dosing regimens (every 4 weeks [Q4W] and every 8 weeks [Q8W]), blood eosinophil counts ≥300 cells/µL, ≥2 exacerbations. Comparison: benralizumab + SOC *vs.* placebo + SOC.

The primary endpoint in each study was the annual rate of asthma-related exacerbations, with key secondary endpoints being FEV1 and asthma symptoms as defined by a daily patient diary. Other secondary endpoints included asthma symptom score and other asthma control metrics (e.g. ACQ-6, QoL (AQLQ(S)+12, EQ-5D), HRU, and productivity loss (WPAIQ+CIQ). A pooled analysis was pre-specified for SIROCCO and CALIMA to assess whether benralizumab reduces asthma-related hospitalization and/or ER/urgent care visits. Study endpoints were evaluated over a 48-week treatment period in SIROCCO and a 56-week treatment period in CALIMA.

Randomized patients were stratified by baseline blood eosinophil counts ≥300 cells/µL and <300 cells/µL at a ratio of 2:1. Both studies were prospectively powered for the primary efficacy analysis of annual rate of asthma-related exacerbations in the stratum of patients on high-dose ICS/LABA with blood eosinophils ≥300/µL. This stratification approach allows for the effect of benralizumab on primary and the 2 key secondary endpoints to be characterized across the full range of baseline blood eosinophil counts, although all multiplicity-protected analyses in both studies were in the primary population of patients on high-dose ICS/LABA with blood eosinophils ≥300 cells/µL.

Oral corticosteroid reduction study (ZONDA) [3]:

ZONDA evaluated patients 18 to 75 years of age with severe asthma who required treatment with high-dose ICS/LABAs and chronic OCS therapy with or without additional controller medications. The same 2 dosing

regimens (Q4W and Q8W) studied in SIROCCO and CALIMA were also studied in ZONDA, and compared with placebo, over a 28-week treatment period. The primary endpoint in this study was the percentage reduction in final OCS dose compared with baseline, while maintaining asthma control. In this study, eligible patients with a peripheral blood eosinophil count of ≥150/µL were randomized. Secondary endpoints included the proportion of patients with ≥50% and 100% reduction in average daily OCS dose while maintaining asthma control; the proportion of patients with an average final OCS dose ≤5.0 mg daily while maintaining asthma control; annual asthma exacerbation rate and other exacerbation parameters; pre-bronchodilator FEV1; asthma symptoms; ACQ-6 score; and AQLQ(S)+12 score.

In the 3 key registration trials (SIROCCO, CALIMA, and ZONDA), patients received SC benralizumab 30 mg, either Q4W, Q8W (following Q4W x 3), or matching placebo. This dosing regimen was chosen based on an exposure-response analysis of data from the phase 2b study with benralizumab involving patients with uncontrolled asthma. While both dosing regimens were studied in the WINDWARD clinical program, the recommended dosing regimen for benralizumab is Q8W, and **only data relating to the approved dosing schedule of Q8W** in adults are presented in this application to Medicinrådet.

The approved indication for Fasenra is indicated as an add on maintenance treatment in adult patients, with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus long acting β agonists. Both SIROCCO and CALIMA trials assessed benralizumab in both adults and adolescents, hence some of data presented in this application includes adolescents, however only a small number of adolescents were included in the trials (4.4% in SIROCCO and 4.2% in CALIMA).

Patient population:

As the primary and key secondary analyses of efficacy endpoints in SIROCCO and CALIMA trials were assessed in patients with blood eosinophil counts ≥300 cells/µL, the base case population used to demonstrate the clinical benefit of benralizumab includes patients receiving high-dose ICS/LABA with ≥2 exacerbations in the previous year and baseline blood eosinophil counts ≥300 cells/µL. Further, for patients on chronic OCS, the base case patient population is consistent with the ZONDA primary population of patients on chronic OCS and baseline blood eosinophil counts ≥150 cells/µL.

Data for patients with ≥2 exacerbations in the previous year and baseline blood eosinophil counts ≥300 cells/µL are presented for two pivotal Phase 3 trials:

1. SIROCCO
2. CALIMA
3. Pooled SIROCCO and CALIMA

Data for patients on chronic OCS and baseline blood eosinophil counts ≥150 cells/µL are presented for three Phase 3 benralizumab trials:

1. ZONDA (≥1 exacerbations in the previous year)
2. Pooled SIROCCO and CALIMA (≥2 exacerbations in the previous year)

4.3.2 Clinical data for mepolizumab, phase 3 study design and end points

Baseline characteristic overview for mepolizumab phase 3 clinical studies (DREAM, MENSA, SIRIUS and MUSCA) is presented, for each study, in Table A2 as part of this application. And a summary overview is presented in Appendix 4, Table 4.16.

Asthma exacerbation studies: DREAM and MENSA [4] - [5]

The DREAM study evaluated patients 12 years to 75 years of age with uncontrolled asthma and a history of exacerbations and signs of eosinophilic inflammation randomly assigned in a 1:1:1:1 ratio to receive one of three doses of intravenous mepolizumab (75 mg, 250 mg, or 750 mg) or matched placebo.
The primary outcome was the rate of clinically significant asthma exacerbations, which were defined as validated episodes of acute asthma requiring treatment with oral corticosteroids, admission, or a visit to an emergency department.
For all participants, demographic information was obtained along with prebronchodilator and postbronchodilator spirometry measurements, and blood eosinophil counts, ACQ, AQLQ, and blood eosinophil counts at screening. Fractional exhaled nitric oxide (FE_{NO}) was measured at either screening or baseline visits. After treatment began, spirometry measurements, blood eosinophil counts, and ACQ scores were obtained every 4 weeks; FE_{NO} and AQLQ were assessed at weeks 4, 16, 32, and 52. A subgroup also had sputum induction and sputum eosinophil counts taken at either screening or baseline, and at weeks 4, 16, and 52.

The MENSA study evaluated patients 12 to 82 years of age with recurrent asthma exacerbations and evidence of eosinophilic inflammation despite high doses of inhaled glucocorticoids to one of three study groups: mepolizumab administered as either a 75-mg intravenous dose, a 100-mg subcutaneous dose, or placebo every 4 weeks for 32 weeks. The primary outcome was the rate of exacerbations. The primary outcome was the annualized frequency of clinically significant exacerbations, which were defined as worsening of asthma such that the treating physician elected to administer systemic glucocorticoids for at least 3 days or the patient visited an emergency department or was hospitalized. Exacerbations were confirmed by objective changes that patients recorded daily in an electronic diary, other outcomes included the forced expiratory volume in 1 second (FEV_1) and scores on the St. George's Respiratory Questionnaire (SGRQ) and the 5-item Asthma Control Questionnaire (ACQ-5). Safety was also assessed.

COPD study: SIRIUS [6]

The SIRIUS trial involved 135 patients aged 12 and older with severe eosinophilic asthma comparing the glucocorticoid-sparing effect of mepolizumab (at a dose of 100 mg) with that of placebo administered subcutaneously every 4 weeks for 20 weeks. The primary outcome was the degree of reduction in the glucocorticoid dose : 90-100% reduction, 75 to < 90% reduction, 50 to < 75% reduction, > 0 to 50% reduction, or no decrease in oral glucocorticoid dose, a lack of asthma control during weeks 20 to 24, or withdrawal from treatment. Other outcomes included the rate of asthma exacerbations, asthma control, and safety.

HRQOL study: MUSCA [7]

The MUSCA study evaluated patients aged 12 years or older with severe eosinophilic asthma and a history of at least two exacerbations requiring treatment in the previous 12 months before screening despite regular use of high-dose inhaled corticosteroids plus other controller medicines. participants (1:1) by country to receive a subcutaneous injection of either mepolizumab 100 mg or placebo, plus standard of care, every 4 weeks for 24 weeks (the final dose was given at week 20). The primary endpoint was the mean change from baseline in the St George's Respiratory Questionnaire (SGRQ) total score at week 24 in the modified intention-to-treat (modified ITT) population (analysed according to their randomly assigned treatment). Safety was assessed in all patients who received at least one dose of trial medication (analyzed according to the actual treatment received).

5 Clinical questions

5.1 Clinical question 1: Annual asthma exacerbation rate reduction

5.1.1 Presentation of relevant studies: Asthma exacerbation studies

The primary analysis population, from the two pivotal Phase 3 trials, SIROCCO and CALIMA (≥2 exacerbations in the previous year and blood eosinophil counts ≥300 cells/µL), is used as a base case to demonstrate the clinical benefit of benralizumab.

For the ZONDA study, the primary analysis population (≥1 exacerbations in the previous year, blood eosinophil counts ≥150 cells/µL, chronic OCS use for prior 6 months) is used as base case to demonstrate the clinical benefit of benralizumab tapering chronic OCS use.

5.1.2 Baseline characteristics

All efficacy analyses were performed using an Intent-to-Treat(ITT) approach based on the FAS. Baseline characteristic overview for benralizumab phase 3 clinical studies is presented, for each study, in Table A2 as part of this application. Demographic and baseline characteristics for patients with blood eosinophil counts ≥300 cells/µL in Q8W group and the placebo group of the SIROCCO, CALIMA and ZONDA study are presented in Appendix 4

SIROCCO:

Demographic characteristics, Patients with baseline blood eosinophil counts ≥300 cells/µL: The majority of patients in the full analysis set (FAS) were White (71.0%) and female (65.1%). The mean age was 48.5 years (range: 12 to 75 years); 30 (3.7%) patients were ≥12 to <18 years (i.e. adolescents), the remaining patients were adults, of whom 87 (10.8%) were ≥65 to 75 years. The mean weight was 77.37 kg (range: 41.0 to 194.5 kg), the mean BMI was 28.43 kg/m2 (range: 15.4 to 61.7 kg/m2).

Respiratory and other baseline disease characteristics:
The key respiratory and other baseline disease characteristics at study entry were similar across groups. All patients in this study had asthma and the median time since asthma diagnosis was 14.36 years (Appendix 4). The majority of patients (60.1%) had 2 exacerbations in the last 12 months (mean [SD]: 3.0 [1.83]); 74.8% of patients had 0 exacerbations resulting in hospitalization in the last 12 months (mean [SD]: 0.4 [0.78]). At study entry, the majority of patients had never smoked (80.7%) or were former smokers (19.0%) and the mean smoking history among smokers was 5.0 pack years.

Of the relevant medical conditions at study entry presented in Appendix 4, the most common were atopic based on phadiatop test (59%) and diagnosis of allergic rhinitis (56%). The incidence of relevant medical conditions at study entry was similar across groups.
The key respiratory and other baseline disease characteristics for all patients in the FAS with a baseline blood eosinophil count ≥300/µL were similar to key respiratory and other baseline disease characteristics in the FAS overall.

The incidence of maintenance asthma medication use at baseline was similar across groups. All patients (100 %) were taking ICS and LABA, whether separately or in combination. A total of 762 (94.2%) patients were taking their ICS/LABA as a fixed dose combination device, with the remainder of the patients taking ICS and LABA in separate inhalers. A total of 127 (15.7%) patients were taking OCS. The incidence of individual maintenance asthma medication use was similar across groups at baseline (Appendix 4).

CALIMA:

Demographic characteristics, Patients with baseline blood eosinophil counts ≥300 cells/µL: The majority of patients in the FAS were White (85.9%) and female (60.7%). The mean age was 49.4 years (range: 12 to 75 years); 16 (2.2%) patients were ≥12 to <18 years (i.e., adolescents), the remaining patients were adults, of whom 87 (12.0%) were ≥65 to 75 years. The mean weight was 79.74 kg (range: 41.0 to 185.9 kg), the mean BMI was 28.90 kg/m2 (range: 15.9 to 79.9 kg/m^2).

Respiratory and other baseline disease characteristics: The key respiratory and other baseline disease characteristics at study entry were similar across groups. Patients with baseline blood eosinophil counts ≥300 cells/µL in this study had asthma and the median time since asthma diagnosis was 16.06 years (Appendix 4). The majority of patients (60.9%) had 2 exacerbations in the last 12 months (mean [SD]: 2.8 [1.57]); 83.5% of patients had 0 exacerbations resulting in hospitalization in the last 12 months (mean [SD]: 0.3 [0.62]). At study entry, the majority of patients had never smoked (77.3%) or were former smokers (22.4%) and the mean smoking history among smokers was 4.6 pack years.

Of the relevant medical conditions at study, the most common were atopic based on phadiatop test (63.7%) and diagnosis of allergic rhinitis (56.%). The incidence of relevant medical conditions at study entry was similar across groups.

The incidence of maintenance asthma medication use at baseline was similar across groups. All patients were to be taking ICS and LABA, whether separately or in combination, per the inclusion criteria. In the FAS, patients with a baseline blood eosinophil count ≥300/µL, 726 (99.7%) patients were taking ICS and 724 (99.5%) patients were taking LABA (Appendix 4). A total of 641 (88.0%) patients were taking their ICS/LABA as a fixed dose combination device, with the remainder of the patients taking ICS and LABA in separate inhalers. A total of 80 (11 %) patients were taking OCS. The incidence of individual maintenance asthma medication use was similar across groups at baseline (Appendix 4).

ZONDA:

Demographic characteristics (full analysis set (FAS)): The majority of patients in were White (93.2%) and female (61.4%) (Appendix 4). The mean age was 51.0 years (range: 20 to 75 years). The mean weight was 83.12 kg (range: 47.0 to 155.2 kg), and the mean BMI was 29.58 kg/m2 (range: 18.6 to 55.2 kg/m^2) (Appendix 4).

The key respiratory and other baseline disease characteristics: were similar across groups at study entry. The median time since asthma diagnosis was 12,18 years. The majority of patients had 1 (31.4%) or 2 (29.1%) exacerbations in the last 12 months (mean [SD]: 2.8 [2.25]). The majority of patients (71.8%) had 0 exacerbations resulting in hospitalization in the last 12 months (mean [SD]: 0.4 [0.96]). At study entry, no patients were current smokers, and the majority of patients had never smoked (79.1%). Of the patients who were former smokers, the mean smoking history was 5.5 pack years.

Maintenance asthma medications at baseline: The incidence of maintenance asthma medication use at baseline was similar across groups. All patients were taking ICS and LABA, whether separately or in combination. The majority of patients (89.5%) were taking their ICS/LABA as a fixed dose combination device, with the remainder of the patients taking ICS and LABA in separate inhalers (Appendix 4).
The mean and median OCS doses at study entry were 15.3 mg and 10.0 mg, respectively, and the mean and median optimized (baseline) OCS doses were 14.7 mg and 10.0 mg, respectively (Appendix 4). These results were similar across groups.

5.1.3 Asthma exacerbations

The primary endpoint was the annual rate of clinically significant asthma exacerbations in patients with baseline blood eosinophil counts ≥300 cells/µL who were taking high-dose ICS and LABA. Clinically significant asthma exacerbation was defined as worsening of asthma requiring use of oral/systemic corticosteroids for at

least 3 days, and/or emergency department visits requiring use of oral/systemic corticosteroids and/or hospitalization. For patients on maintenance OCS, this was defined as a temporary increase in stable oral/systemic corticosteroids for at least 3 days or a single depo-injectable dose of corticosteroids.

5.1.4 Results per study

5.1.5 Efficacy results – SIROCCO study

The primary population of interest for the efficacy analyses was patients with baseline blood eosinophils ≥300/µL. Efficacy results are summarized by various blood eosinophil count categories.

The testing strategy was employed to account for multiplicity to test the primary endpoint, annual asthma exacerbation rate based on electronic case report form (eCRF) recorded data in patients with baseline blood eosinophils ≥300/µL.

5.1.6 Summary of asthma exacerbations (SIROCCO)

In patients with a baseline blood eosinophil count ≥300/µL, fewer patients treated with benralizumab 30 mg Q8W experienced at least 1 asthma exacerbation during the 48-week treatment period compared with patients treated with placebo (34.8%, and 50.6%, respectively) (Appendix 5, Table 5.1).

Across groups, patients experiencing an exacerbation primarily reported between 1 to 3 exacerbations during the treatment period. The total numbers of exacerbations/follow-up years (i.e., crude annual exacerbation rates) were 0.66, and 1.53 for the benralizumab 30 mg Q8W and placebo groups, respectively.

Fewer patients treated with benralizumab 30 mg Q8W experienced at least 1 asthma exacerbation associated with an adjudicated hospitalization or ER visit compared with placebo (6.7% and 13.9%, for the benralizumab 30 mg Q8W and placebo groups, respectively). This lower incidence for the benralizumab 30 mg Q8W group was driven by a lower incidence of at least 1 exacerbation associated with an adjudicated ER visit (2.2%) compared with the placebo (7.5%) group. Similar results to those for the adjudicated events were observed for exacerbation events associated with a hospitalizations or ER visit as assessed by the investigator and recorded in the eCRF.

5.1.7 Annual asthma exacerbation rate (Primary endpoint) - SIROCCO

The primary analysis was to compare the annual asthma exacerbation rate (based on unadjudicated data reported by the investigator in the eCRF) of each benralizumab dosing regimen with placebo in patients with baseline blood eosinophil count ≥300/µL.

In patients with a baseline blood eosinophil count ≥300/µL, the number of asthma exacerbation events over 48 weeks was lower in benralizumab 30 mg Q8W group compared with placebo (156 and 365, respectively; Appendix 5, Table 5.2). The total follow-up time was similar across groups.

Benralizumab 30 mg Q8W statistically significantly reduced the annual asthma exacerbation rate over 48 weeks compared with placebo (51% reduction; $p<0.001$).

The crude annual exacerbation rates differed from the model-estimated rates, as shown in Appendix 5, Table 5.2. Model-estimated rates via a marginal method provided better alignment with the crude rates (0.74 and 1.52 for benralizumab 30 mg Q8W, and placebo groups, respectively).

5.1.8 Proportion of patients with ≥1 asthma exacerbation and time to first asthma exacerbation (Secondary endpoints) - SIROCCO

Results for the proportion of patients with ≥1 asthma exacerbation and the time to first asthma exacerbation were consistent with the primary analysis and supported an improvement in asthma exacerbations for benralizumab compared with placebo. In patients with a baseline blood eosinophil count ≥300/µL, a lower proportion of patients had ≥1 asthma exacerbation over 48 weeks in benralizumab 30 mg Q8W (34.8%) group compared with placebo (50.6%) (odds ratio: 0.62 [0.43, 0.90; nominal p≤0.010). The time to first asthma exacerbation was longer for benralizumab 30 mg Q8W, as indicated by a lower probability of having an asthma exacerbation compared with placebo (hazard ratio: 0.60 [0.46, 0.78]; nominal p<0.001).

A clear separation, for the time to first exacerbation, is observed between benralizumab and placebo that is maintained over time (Appendix 5, Figure 5.3). The cumulative number of exacerbations over time shows continued divergence of benralizumab from placebo, indicating that the reduced annual asthma exacerbation rate for both benralizumab group (Appendix 5, figure 5).

5.1.9 Asthma exacerbations associated with an ER/urgent care visit or hospitalization (Secondary endpoint) – SIROCCO

The annual exacerbation rate associated with an adjudicated ER/urgent care visit or hospitalizations was a supportive analysis to the primary endpoint.

In patients with a baseline blood eosinophil count ≥300/µL, the number of asthma exacerbation events associated with an adjudicated ER/urgent care visit or hospitalization over 48 weeks was lower in the benralizumab 30 mg Q8W group compared with placebo group (20 and 50, respectively) (Appendix 5, Table 5.5). The total follow-up time was similar across groups.

Benralizumab 30 mg Q8W reduced the annual rate of asthma exacerbations associated with an adjudicated ER/urgent care visit or hospitalization over 48 weeks compared with placebo (63% [nominal p<0.001]) reduction. Reductions observed for the benralizumab 30 mg Q8W regimen compared with placebo were driven by the reduction in annual rate of asthma exacerbations associated with adjudicated ER visits (77% [nominal p=0.003]) with reductions also observed in asthma exacerbations associated with adjudicated hospitalizations (52% [nominal p=0.060]).

In patients with a baseline blood eosinophil count ≥300/µL, a lower proportion of patients had ≥1 asthma exacerbation associated with an adjudicated ER visit or hospitalization over 48 weeks in both benralizumab 30 mg Q8W (6.7%) group compared with placebo (13.9%). The time to first asthma exacerbation associated with an adjudicated ER visit or hospitalization was longer for benralizumab 30 mg Q8W, as indicated by a lower probability of having an asthma exacerbation requiring hospitalization or an ER visit compared with placebo (hazard ratio: 0.45 [0.25, 0.78]; nominal p=0.006).

A post-hoc sensitivity analysis was conducted on the annual exacerbation rate for asthma exacerbations associated with an ER visit or hospitalization as assessed by the investigator and recorded in the eCRF, and similar findings were observed as for those reported for adjudicated events.

5.1.10 Proportion of patients with 0 asthma exacerbation - SIROCCO

Number of exacerbations per patient, n (%) is presented in Appendix 5, Table 5.12. Patient with 0 exacerbations per patient; 174 patients (65.2 %) in benralizumab 30 mg Q8W group and 132 patients (49.4 %) in the placebo group.
Mepo

5.1.11 Efficacy results – CALIMA study

The annual asthma exacerbation rate was the primary efficacy variable in this study, the primary analysis was to compare the annual asthma exacerbation rate (based on unadjudicated data reported by the investigator in the eCRF) of each benralizumab dose regimen with placebo in patients with baseline blood eosinophil counts ≥300/µL who were taking high-dose ICS.

Benralizumab 30 mg Q8W achieved statistical significance for the primary endpoint after multiplicity adjustment (nominal p<0.04). Results for all comparisons analyzed for the key secondary endpoints achieved statistical significance as evaluated per the Holm procedure.

5.1.12 Summary of asthma exacerbations - CALIMA

In patients with a baseline blood eosinophil count ≥300/µL who were taking high-dose ICS, fewer patients treated with benralizumab 30 mg Q8W experienced at least 1 asthma exacerbation during the 56-week treatment period compared with patients treated with placebo (39.7% and 50.8%, respectively) (Appendix 5, Table 5.6). Across groups, patients experiencing an exacerbation primarily reported between 1 to 3 exacerbations during the treatment period. The total numbers of exacerbations/follow-up years (i.e., crude annual exacerbation rates) were 0.66 and 1.03 for the

benralizumab 30 mg Q8W and placebo groups, respectively. The proportion of patients with at least 1 asthma exacerbation associated with a hospitalization or ER visit was similar across groups, whether based on adjudicated events or as assessed by the investigator and recorded in the eCRF.

5.1.13 Annual asthma exacerbation rate (Primary endpoint)

In patients with a baseline blood eosinophil count ≥300/µL who were taking high-dose ICS, the number of asthma exacerbation events over 56 weeks was lower for benralizumab 30 mg Q8W regimen compared with placebo (163 and 270, respectively; Appendix 5, Table 5.7). The total follow-up time was similar across groups.
Benralizumab 30 mg Q8W statistically significantly reduced the annual asthma exacerbation rate over 56 weeks compared with placebo (28% reduction; p≤0.019).

5.1.14 Proportion of patients with ≥1 asthma exacerbation and time to first asthma exacerbation (Secondary endpoints) - CALIMA

Results for the proportion of patients with ≥1 asthma exacerbation and the time to first asthma exacerbation were consistent with the primary analysis and supported an improvement in asthma exacerbations for benralizumab regimen compared with placebo. In patients with a baseline blood eosinophil count ≥300/µL who were taking high-dose ICS, a lower proportion of patients had ≥1 asthma exacerbation over 56 weeks in benralizumab 30 mg Q8W (39.7%) regimen compared with placebo (50.8%) (odds ratio: 0.65 [0.45, 0.95]; nominal p≤0.023). The time to first asthma exacerbation was longer for benralizumab 30 mg Q8W, as indicated by a lower probability of having an asthma exacerbation compared with placebo (hazard ratio: 0.73 [0.55, 0.95]; nominal p≤0.018).

A clear separation is observed between benralizumab and placebo group that is maintained over time (Appendix 5, Figure 5.8). The cumulative number of exacerbations over time shows continued divergence of benralizumab from placebo, indicating that the reduced annual asthma exacerbation rate for benralizumab (Appendix 5, Figure 5.9).

5.1.15 OCS use associated with asthma exacerbations - CALIMA

In patients with a baseline blood eosinophil count ≥300/µL who were taking high dose ICS, the total OCS dose and total number of OCS treatment days associated with asthma exacerbations were lower in the benralizumab 30 mg Q8W (29.6 g and 1225 days) group compared with the placebo group (51.9 g and 1910 days). Of the patients using OCS for asthma exacerbations, the total OCS dose and treatment days per patient were generally similar across the benralizumab 30 mg Q8W (0.333 g and 13.764 days) and the placebo groups (0.429 g and 15.785 days).

5.1.16 Asthma exacerbations associated with an ER/urgent care visit or hospitalization (Secondary endpoint) - CALIMA

Given that there is considerable variation across regions in the reasons that patients seek emergency department care for uncontrolled asthma and in the clinical thresholds used to determine the need for hospitalization, all ER/urgent care visits or hospitalizations during this study were adjudicated by an independent adjudication committee, to determine if the event was related to asthma. The annual exacerbation rate associated with an adjudicated ER/urgent care visit or hospitalization was a supportive analysis to the primary endpoint (Appendix 5, Table 5.10).

5.1.17 Proportion of patients with 0 asthma exacerbation - CALIMA

Number of exacerbations per patient, n (%) is presented in Appendix 5, Table 5.6. Patient with 0 exacerbations per patient; 144 patients (60.3 %) in benralizumab 30 mg Q8W group and 122 patients (49.2 %) in the placebo group.

5.1.18 Asthma exacerbations - overview of secondary efficacy variables for ZONDA

Overall, secondary efficacy results showed that benralizumab treatment resulted in improvements related to asthma exacerbation rate (Appendix 5, Table 5.11)

5.1.19 Asthma exacerbations- summary statistics - ZONDA

Fewer patients treated with benralizumab 30 mg Q8W experienced at least 1 asthma exacerbation during the 28-week treatment period compared with patients treated with placebo (23.3% vs 52.0%, respectively) (Appendix 5, Table 5.12)

Fewer patients treated with benralizumab 30 mg Q8W experienced at least 1 asthma exacerbation associated with hospitalization or an ER visit compared with placebo (1.4% vs. 12.0%, for the benralizumab 30 mg Q8W and placebo groups, respectively). This lower incidence for the benralizumab 30 mg Q8W group was driven by a lower incidence of hospilatisations (1.4%) and ER visits (0%) compared with placebo (8.0% and 5.3%, respectively). Cumulative number of asthma exacerbations over 28 weeks are presented in Appendix 5, Figure 5.13.

5.1.20 Annual rate of asthma exacerbations after randomization - ZONDA

The number of asthma exacerbation events over 28 weeks was lower in benralizumab 30 mg Q8W groups compared with placebo (21 and 73, respectively) (Appendix 5, Table 5.14). The total follow-up time was similar across groups. The total number of exacerbations/follow-up years (ie, crude annual exacerbation rate) was lower for the benralizumab Q8W group compared with placebo (0.55 and 1.80, respectively). Benralizumab 30 mg Q8W demonstrated a greater reduction in the annual asthma exacerbation rate over 28 weeks compared with placebo (70% reduction; nominal p≤0.003) (Appendix 5, Table 5.14).

5.1.21 Annual rate of asthma exacerbations that are associated with an emergency room visit or a hospitalization after randomization - ZONDA

The number of asthma exacerbation events associated with ER visit or hospitalization over 28 weeks was lower in benralizumab 30 mg Q8W regimen compared with placebo (1 and 14, respectively; Appendix 5, Table 5.15). The total follow-up time was similar across groups. Benralizumab 30 mg Q8W reduced the annual rate of asthma exacerbations associated with ER visit or hospitalization over 28 weeks compared with placebo (93%; nominal p=0.01)

5.1.22 Proportion of patients with ≥1 asthma exacerbation and time to first asthma exacerbation - ZONDA

A smaller proportion of patients had ≥1 asthma exacerbation over 28 weeks in benralizumab 30 mg Q8W (23.3%) group compared with placebo (52%) (odds ratio: 0.28 [95% CI 0.14, 0.56]; nominal p≤0.001) (Appendix 5, Table 5.16).

The time to first asthma exacerbation was longer for benralizumab 30 mg Q8W, as indicated by a lower probability of having an asthma exacerbation compared with placebo (hazard ratio: 0.32 [95% CI 0.17, 0.57]; nominal p<0.001) (Appendix 5, Table 5.17).

As shown for the time to first exacerbation in Appendix 5, Figure 5.18, a clear separation is observed between both benralizumab group and placebo that is maintained over time.

5.1.23 Proportion of patients with 0 asthma exacerbation - ZONDA

Number of exacerbations per patient, n (%) is presented in Appendix 5, Table 5.12. Patient with 0 exacerbations per patient; 56 patients (76.7 %) in benralizumab 30 mg Q8W group and 36 patients (48.0 %) in the placebo group.

5.1.24 Indirect comparison with other anti-IL-5 products

In the absence of a head-to-head randomized controlled trials comparing benralizumab vs. the other biologics indicated for treatment of patients with severe asthma with an eosinophilic phenotype, an indirect treatment comparison (ITC) can be a valid alternative as it synthesizes all the relevant evidence and provides comparative effectiveness estimates between these treatments. Matching Adjusted Indirect Comparison (MAIC) and simulated treatment comparison (STC) have been endorsed by HTA authorities (e.g. NICE, CDR, PBAC) as alternatives when

traditional indirect comparisons are vulnerable to biases from imbalanced baseline characteristics that may be treatment effect modifiers [10]. The MAIC protocol has been submitted to Medicinrådet and accepted as valid.

5.1.25 Exacerbation annual rates - Comparative analyses, benralizumab vs. mepolizumab

Three studies each assessing benralizumab (SIROCCO, CALIMA, and ZONDA) and mepolizumab (MENSA, DREAM, and SIRIUS) were considered for MAIC analysis.

Prior to analysis, a feasibility assessment was undertaken to assess the homogeneity across the trial populations, which showed that the trials varied in terms of primary study objective (exacerbation reduction and OCS reduction).

Considering the differences in the trial objectives, two different analyses based on study objective were considered:

• Analysis of exacerbation reduction trials: SIROCCO, CALIMA, MENSA and DREAM trials

• Analysis of OCS sparing trials: ZONDA and SIRIUS trials

Another key difference was the definition of high-dose ICS considered at baseline. Benralizumab trials included patients with >500 µg FP fluticasone propionate(FP) daily or equivalent, while mepolizumab studies included patients with ≥880 µg FP daily or equivalent. Given the high-dose ICS definition differences, MAIC was conducted across two scenarios:

• High-dose ICS considered as ≥880 µg FP daily or equivalent (similar to the mepolizumab trial definition)

• High-dose ICS considered as >500 µg FP daily or equivalent (high-dose ICS according to benralizumab studies)

However, for OCS reduction trials, all patients were receiving maintenance OCS, and the background ICS dose was assumed to have no impact on outcomes. Therefore, for OCS reduction trials only definition of high-dose ICS, i.e., >500 µg FP daily or equivalent (as reported in the benralizumab trial) was considered in analyses.

5.1.26 Matching adjusted indirect treatment comparison (MAIC) of benralizumab vs. mepolizumab

A MAIC [11] was undertaken to assess the comparative clinical effectiveness of benralizumab vs. mepolizumab. A MAIC indirectly compares treatment interventions when baseline characteristics are imbalanced between studies and the differences may cause treatment effects. The benralizumab and mepolizumab clinical trials have similarities in their design and patient populations but there are several differences in the recruited populations that create challenges in comparing the 2 treatment options through a conventional ITC. These differences include baseline eosinophil count, the proportion of patients with 2 or more exacerbations in the prior year, baseline maintenance OCS, and the definition of high-dose ICS. A MAIC makes the benralizumab and mepolizumab populations more similar by adjusting the individual trial data from the benralizumab trials to more closely match the aggregate baseline characteristics of the mepolizumab trials.

<u>Potential effect of two included trials has been accounted for.</u>

The post matching statistics do account for the potential effect of two clinical studies. We had used the combined data set from SIROCCO and CALIMA, however, post matching, we did account for clustering of subjects within trials as suggested by Cochrane IPD Meta-analysis Methods Group. As suggested, this adjustment could be performed either by including a separate term for each trial in the model (fixed effect) or a term that varies across trials via a random effect. As we had just two studies, we have used a fixed effects model to combine the estimates post-matching.
To further validate the output of our model, we have provided below a comparison of two results where we had calculated separate estimates for SIROCCO and CALIMA post matching and combined estimates using a fixed effects model as was done in the MAIC.

Analysis: High-dose defined as ICS>500

Pooled-estimates	RR	LCI	UCI	Heterogeneity stats
CALIMA+SIRROCO-pre-matching	0.54	0.47	0.61	I^2= 0.00%
CALIMA+SIRROCO-post matching	0.50	0.45	0.55	I^2= 0.00%
Study	RR	LCI	UCI	
CALIMA	0.50	0.43	0.58	
SIRROCO	0.49	0.43	0.57	
Pooled(using drop down command prompt *metan*)	0.50	0.45	0.55	I^2= 0.00%

The results of the combined model and the separate model are exactly same indicating the output of the meta-analysis using a weighted regression model accounts for clustering of subjects in the trials.

Key areas in which the studies differ include:

- Baseline EOS count: inclusion criteria in mepolizumab studies require that patients have an EOS count of at least 150 cells/µL at baseline or 300 cells/µL in the prior year, which is not a requirement in BENRA studies.
- Cut off for the high-dose ICS: >500 µg of FP) in BENRA studies and ≥880 µg of FP in mepolizumab studies.
- Prior history of exacerbations: mepolizumab studies recruited a more severe population with ~60% of patients with a history of 2 or more exacerbations.
- Baseline OCS use: mepolizumab studies recruited a more severe population with ~23% to 30% of patients using OCS at baseline.
- Duration of follow-up: Benralizumab studies assess patients up to 56 weeks (48 weeks SIROCCO, 56 weeks CALIMA) and
- Mepolizumab studies up to 52 weeks (32 weeks MENSA, 52 weeks DREAM).

5.1.27 Exacerbation trials (SIROCCO/CALIMA vs. MENSA/DREAM)

Benralizumab and mepolizumab trials varied in terms of the definition of high-dose ICS (i.e., >500 µg of FP in benralizumab studies and ≥880 µg of FP in mepolizumab studies). Therefore, to select a similar or more homogeneous population across the two trials, analyses for exacerbation trials were conducted at two different doses (≥880 µg of FP and >500 µg of FP, daily).

Benralizumab was compared with mepolizumab for the following key efficacy outcomes:

- Annual rate of clinically significant exacerbations
- Annual rate of exacerbations resulting in ER visit/hospitalization
- Pre-bronchodilator FEV_1 (L) change from baseline

Treatment differences of each intervention against placebo were used to derive the anchored ITC. Results for benralizumab were obtained by pooling the Individual Patient Data (IPD) from the SIROCCO and CALIMA trials, while aggregated results for mepolizumab were pooled from the MENSA and DREAM trials (mepolizumab 75 mg IV: pooling data from MENSA and DREAM; mepolizumab 100 mg: MENSA trial).

5.1.28 Annual rate of clinically significant exacerbations

Scenario 1: ICS ≥880 µg FP daily

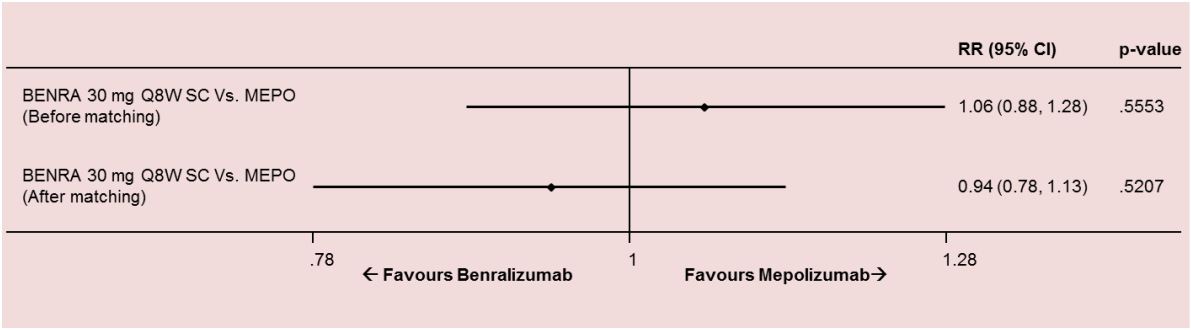
Table I presents the rate ratios for clinically significant exacerbations in benralizumab trials before and after adjustment. There was an improvement in clinically significant exacerbation reduction with benralizumab compared with placebo after adjusting for differences between benralizumab and mepolizumab trials. There was a 46% reduction in the rate of clinically significant exacerbations with benralizumab (RR = 0.54) before adjustment compared with 52% reduction (RR = 0.48) after adjustment.

Table I: Pooled MAIC results for clinically significant exacerbations in subgroup with ≥880 µg FP daily

Comparison	RR	LCI	UCI
BENRA Q8W vs. placebo (SIROCCO/CALIMA), unmatched	0.54	0.47	0.61
MEPO vs. placebo (MENSA/DREAM)	0.51	0.44	0.58
BENRA Q8W vs. placebo (matched for MENSA/DREAM trial)	0.48	0.43	0.55

Unadjusted rate estimates for benralizumab vs. placebo were pooled from SIROCCO and CALIMA IPD. Unadjusted rate estimates for mepolizumab vs. placebo were pooled from MENSA and DREAM CSRs

Figure II: Summary of ITC analysis results for clinically significant exacerbations in subgroup with ≥880 µg FP daily



Conclusion ≥880 µg FP daily:

After adjustment for the differences in MENSA/DREAM trials, the ITC results showed that benralizumab leads to numerically higher reduction in clinically significant exacerbations compared with mepolizumab (6% higher exacerbation reduction, RR = 0.94 after adjustment), although the results were statistically non-significant. The difference does not reach the 25 % reduction set by Medicinrådet.

Scenario 2: ICS >500 µg FP daily (high-dose, as defined in the benralizumab studies)

Table III presents the rate ratio for benralizumab vs. placebo for clinically significant exacerbations in patients receiving >500 µg FP daily or equivalent. An improvement in reduction in clinically significant exacerbations was observed in benralizumab trials after adjusting for differences from MENSA/DREAM trials. There was a 43% reduction in the rate of clinically significant exacerbations with benralizumab (RR = 0.57) before adjustment and 50% reduction (RR = 0.50) after adjustment compared with placebo.

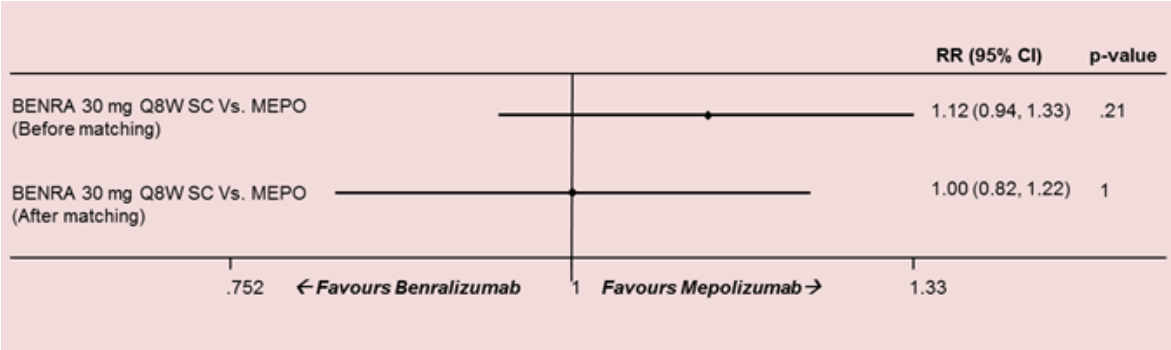
Table III: Pooled MAIC results for clinically significant exacerbations in patients with >500 µg FP daily or equivalent

Comparison	RR	LCI	UCI
BENRA Q8W vs. placebo (SIROCCO/CALIMA), unadjusted	0.57	0.51	0.63
MEPO vs. placebo (MENSA/DREAM), unadjusted	0.51	0.44	0.58
BENRA Q8W vs. placebo (adjusted for MENSA/DREAM trial)	0.50	0.45	0.55

Unadjusted rate estimates for benralizumab vs. placebo were pooled from SIROCCO and CALIMA IPD. Unadjusted rate estimates for mepolizumab vs. placebo were pooled from MENSA and DREAM CSRs.

The results of the ITC in the population receiving >500 µg FP daily or equivalent are presented in Figure IV.

Figure IV: Summary of ITC analysis results for clinically significant exacerbations in patients with >500 µg FP daily or equivalent



Conclusion >500 µg FP:

After adjustment for the differences in MENSA/DREAM trials, the ITC results demonstrated no difference between benralizumab and mepolizumab in reducing clinically significant exacerbations (RR = 1.00 after matching). There was no statistical significance between the two treatments. The difference does not reach the 25 % reduction set by Medicinrådet.

5.1.29 Annual rate of exacerbations resulting in ER visit/hospitalization

Scenario 1: ICS ≥880 µg FP daily

Table V presents the rate ratios for exacerbations resulting in ER visits/hospitalizations in benralizumab trials before and after adjustment. There was a numerically higher reduction in exacerbations leading to ER visit/hospitalization with benralizumab compared with placebo after adjustments. There was 35% reduction in the rate of clinically significant exacerbations leading to ER visit/hospitalization with benralizumab (RR = 0.65) before adjustment compared with 52% reduction (RR = 0.48) after adjustment.

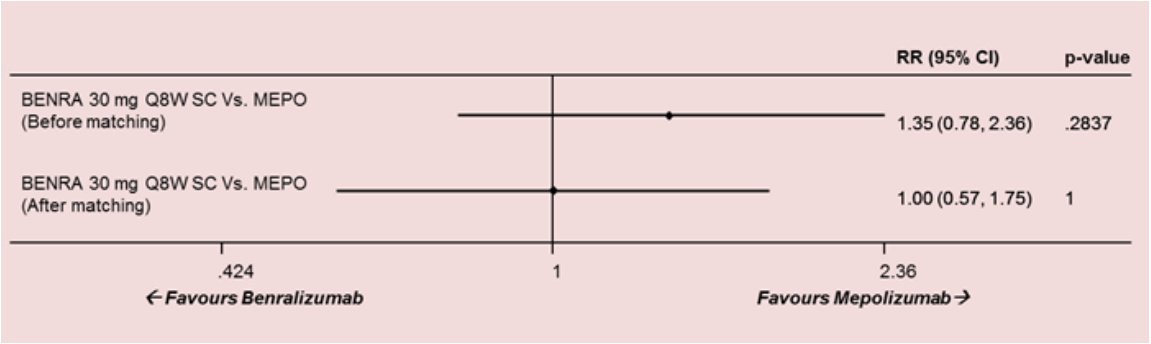
Table V: Pooled MAIC results for exacerbations resulting in ER visit/hospitalization in patients with ≥880 µg FP daily

Comparison	RR	LCI	UCI
Benralizumab Q8W vs. placebo (unadjusted)	0.65	0.46	0.93
Mepolizumab vs. placebo (MENSA/DREAM)	0.48	0.31	0.73
Benralizumab Q8W vs. placebo (adjusted for MENSA/DREAM trial)	0.48	0.33	0.68

Unadjusted rate estimates for benralizumab vs. placebo were pooled from SIROCCO and CALIMA IPD. Unadjusted rate estimates for mepolizumab vs. placebo were pooled from MENSA and DREAM CSRs

The base case ITC results for benralizumab vs. mepolizumab are presented in Figure VI. The rate ratio indicated that benralizumab 30 mg Q8W was comparable to mepolizumab (pooled 75 mg IV and 100 mg SC doses) in reducing exacerbations requiring ER visit/hospitalization after adjusting for baseline severity (RR=1.0).

Figure VI: Summary of ITC analysis results for exacerbations resulting in ER visit/hospitalizations in subgroup with ≥880 µg FP daily



Conclusion ≥880 µg FP:

After adjustment for the differences in MENSA/DREAM trials, the ITC results demonstrated comparable efficacy between benralizumab and mepolizumab in reducing exacerbations leading to ER visit/hospitalization (RR = 1.00 after adjustment). The difference between the two treatments was statistically non-significant.

Scenario 2: ICS >500 µg FP daily (high-dose, as defined in benralizumab studies)

Pooled-population adjusted MAIC results for exacerbations leading to ER visit/hospitalization in patients receiving >500 µg FP daily are presented in Table VII. The rate ratio for benralizumab vs. placebo for exacerbations resulting in ER visit/hospitalization reduced from 32% (RR = 0.68) before adjustment to 42% (RR = 0.58) after adjustment.

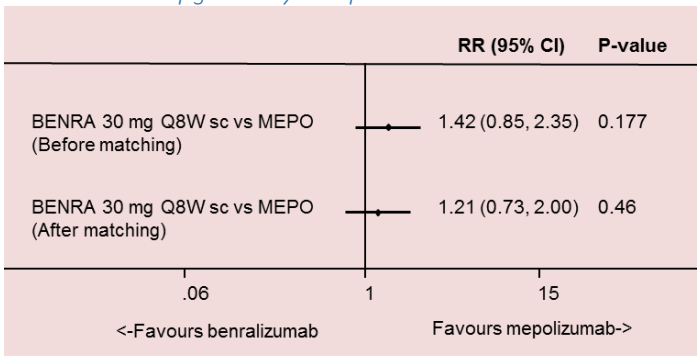
Table VII: Pooled MAIC results for clinically significant exacerbations requiring ER visit/hospitalization in patients with >500 µg FP daily or equivalent

Comparison	RR	LCI	UCI
Benralizumab Q8W vs. placebo (SIROCCO/CALIMA), unadjusted	0.68	0.52	0.89
Mepolizumab vs. placebo (MENSA/DREAM), unadjusted	0.48	0.31	0.73
Benralizumab Q8W vs. placebo (adjusted for MENSA/DREAM trial)	0.58	0.45	0.76

Unadjusted rate estimates for benralizumab vs. placebo were pooled from SIROCCO and CALIMA IPD. Unadjusted rate estimates for mepolizumab vs. placebo were pooled from MENSA and DREAM CSRs.

Figure VII presents the ITC results for benralizumab vs. mepolizumab in the population receiving >500 µg FP daily or equivalent. The ITC results for reduction in the rate of exacerbations leading to ER visit/hospitalization after matching suggested that benralizumab was comparable to mepolizumab in reducing the rate of exacerbations leading to ER visit/hospitalization (RR = 1.21).

Figure VIII: Summary of ITC analysis results for exacerbations resulting in ER visit/hospitalizations in patients receiving >500 µg FP daily or equivalent



Conclusion >500 µg FP:

After matching for the differences MENSA/DREAM trials, benralizumab was comparable to mepolizumab in reducing the rate of exacerbations leading to ER visit/hospitalization (RR after matching = 1.21). The difference between the two treatments was statistically non-significant. Benralizumab vs. mepolizumab cannot show 0,5 less exacerbations.

See also additional calculation in appendix 14.

Overall results per outcome:

Results per outcome		Absolute difference in effect			Relative difference in effect		
	Studies included in the analysis	Difference	CI	*P* value	Hazard/Odds/RR	CI	*P* value
Annual rate of clinically significant exacerbations, in subgroup with ≥880 µg FP daily (Pooled MAIC results)	Comparison: BENRA Q8W vs. Placebo (matched for MENSA/DREAM	-0.031	(-0.112 to 0.066)	NA	Rate ratio: (after matching) 0.94	0.78–1.13	0.5207
Annual rate of clinically significant exacerbations, in subgroup with >500 µg FP daily or equivalent	Comparison: BENRA Q8W vs. Placebo (adjusted for MENSA/DREAM)	0.000	(-0.092 to 0.112)	NA	Rate ratio (after matching): 1.00	0.82–1.22	1
Annual rate of exacerbations resulting in ER visit/hospitalisation in patients with ≥880 µg FP daily (Pooled MAIC results)	Comparison: BENRA Q8W vs. Placebo (adjusted for MENSA/DREAM)	0.000	(-0.206 to 0.360)	NA	Rate ratio (after matching): 1.00	0.57-1.75	1
Annual rate of exacerbations resulting in ER visit/hospitalisation in patients with >500 µg FP daily or equivalent	Comparison: BENRA Q8W vs. Placebo (adjusted for MENSA/DREAM)	0.101	(-0.130 to 0.480)		Rate ratio (after matching): 1.21	0.73 -2.00	0.46

Conclusion rate of exacerbations across patient groups:

After matching for the differences MENSA/DREAM trials, benralizumab was comparable to mepolizumab in reducing the rate of exacerbations and to ER leading to visit/hospitalization. The difference between the two treatments was statistically non-significant. Benralizumab vs. mepolizumab cannot show 0,5 less exacerbations.

5.1.30 Clinical Question: Patients with 0 excacerbations

Below is the RR for benralizumab vs. placebo across trials.

		Comparison between groups		
SIRROCCO Treatment Group	Number(%) of patients with 0 asthma exacerbation	Odds Ratio	95% CI	p-value
Benra 30 mg q.8 weeks (N=267)	174 (65.2)	1.60	(1.11, 2.31)	0.010
Placebo (N=267)	132 (49.4)			

		Comparison between groups		
CALIMA Treatment Group	Numbe(%) of patients with 0 asthma exacerbation	Odds Ratio	95% CI	p-value
Benra 30 mg q.8 weeks (N=239)	144 (60.3)	1.54	(1.06, 2.24)	0.023
Placebo (N=248)	122 (49.2)			

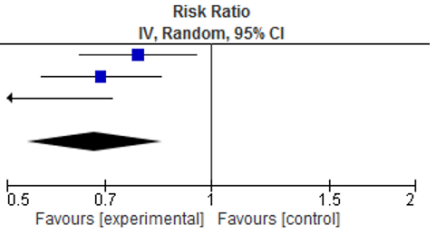
		Comparison between groups		
SIROOCCO/CALIMA pooled Treatment Group	Number(%) of patients with 0 asthma exacerbation	Odds Ratio	95% CI	p-value
Benra 30 mg q.8 weeks (N=506)	318 (62.8)	1.57	(1.21, 2.04)	<.001
Placebo (N=515)	254 (49.3)			

Method for pooling:
Inverse variance method with Random effect. Calculations made using Review Manager v5.3.
Method for indirect comparison:
Bucher method
Events is defined as > 0 exacerbations.

Benralizumab

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Calima	95	239	126	248	41.7%	0.78 [0.64, 0.95]
Sirocco	93	267	135	267	41.2%	0.69 [0.56, 0.84]
Zonda	17	73	39	75	17.1%	0.45 [0.28, 0.72]
Total (95% CI)		**579**		**590**	**100.0%**	**0.67 [0.54, 0.85]**
Total events	205		300			

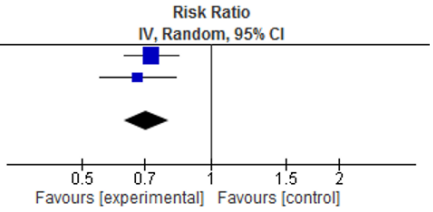
Heterogeneity: Tau² = 0.02; Chi² = 4.69, df = 2 (P = 0.10); I² = 57%
Test for overall effect: Z = 3.36 (P = 0.0008)



Mepolizumab

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Orteag	183	385	125	191	65.8%	0.73 [0.63, 0.84]
Pavord	70	153	105	155	34.2%	0.68 [0.55, 0.83]
Total (95% CI)		**538**		**346**	**100.0%**	**0.71 [0.63, 0.80]**
Total events	253		230			

Heterogeneity: Tau² = 0.00; Chi² = 0.32, df = 1 (P = 0.57); I² = 0%
Test for overall effect: Z = 5.66 (P < 0.00001)



Results per outcome	*Attach forest plots and statistical results as a separate file.* *Results from the comparative analysis should be given in the table below, if possible.*							
		Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	Difference	CI	*P* value	Hazard/Odds/Risk ratio	CI	*P* value	
More than 0 exacerbation	Benralzumab: (Sirocco Calima Zonda) Mepolizumab: (Orteag Pavord)	-2.6%	(-12.7% to 10.3%)	NA	0.944	(0.730 to 1.219)	0.658	Bucher method

Method for calculation of ARR= (RR-1) * event rate for mepolizumab (Orteag and Pavord):
Event rate for Mepolizumab = (183+70)/ (385+153) = 47.0%

Conclusion:

The outcome of the analysis is not significant and the difference seen between benralizumab and mepolizumab does not meet the effect limit of 10 % set by Medicinrådet.

5.2 Clinical question 2: Reduction in average daily OCS dose while maintaining asthma control

The primary endpoint in the ZONDA study was the percentage reduction in final OCS dose compared with baseline, while maintaining asthma control. In the ZONDA study, eligible patients with a peripheral blood eosinophil count of ≥150/µL were randomized. Secondary endpoints included the proportion of patients with ≥50% and 100% reduction in average daily OCS dose while maintaining asthma control; the proportion of patients with an average final OCS dose ≤5.0 mg daily while maintaining asthma control.

5.2.1 Primary variable –percent reduction in daily OCS dose compared with baseline

The median baseline OCS dose was the same across the groups (Appendix, Table 7.1). The benralizumab 30 mg Q8W group demonstrated a statistically significant and clinically relevant median percent reduction from baseline in the final OCS dose at Week 28 compared with placebo using a Wilcoxon rank-sum test ($p<0.001$). A 75% median percent reduction from baseline in final OCS dose was observed for the benralizumab 30 mg Q8W group compared to 25% for the placebo group. This translated to a Hodges-Lehman median treatment difference 37.5% (95% CI 20.8, 50.0) for benralizumab 30 mg Q8W.

Similarly, benralizumab Q8W demonstrated reductions in the daily OCS dose at Week 28 compared with placebo when a proportional odds model was used. Odds ratios of 4.12 (95% CI 2.22, 7.63) for Q8W was observed when analysing the data using this model. In addition, greater proportions of patients in the benralizumab 30 mg Q8W group had a 90% to 100% reduction from baseline in daily OCS dose at Week 28 (37%) compared with those in the placebo group (12%). Greater proportions of patients also had a 75% to <90% reduction in the benralizumab 30 mg group (13.7% for the benralizumab Q8W group and 8.0% for the placebo group). Smaller proportions of patients in the benralizumab 30 mg Q8W group had no change or any increase from baseline in daily OCS dose at Week 28 (20.5%) compared with the placebo group (46.7%). Approximately two-thirds of the patients treated with benralizumab were able to reduce their daily corticosteroid dose by ≥50% compared with approximately one-third of patients receiving placebo. More than one-third of benralizumab treated patients were able to reduce their corticosteroid use by 90% to 100%, compared with 12% of those receiving placebo.

Patients in all groups underwent a forced down-titration at Week 4, at the start of the OCS reduction phase. At Week 8, the CIs were very narrow around the median for the benralizumab group, indicating patients were effectively down titrating their daily OCS dose (Appendix 7, Figure 7.2). The CIs for the placebo group were wider compared with the benralizumab treatment group, indicating that some patients' doses were being increased after the down-titration at Week 4. The median percent change and median percent reduction from baseline in daily OCS dose over time were greater in the benralizumab group compared with placebo starting at Week 12 and were maintained through Week 28 (Appendix 7, Figure 7.2 and Figure 7.3).

In patients with a baseline blood eosinophil level of ≥300/µL, a greater median percent reduction from baseline in final OCS dose was observed for the benralizumab 30 mg Q8W group (50.00% [95% CI 25.00, 66.70]; nominal $p<0.001$) compared with all patients in the Full Analysis Set (FAS) 37.50% [95% CI 20.80, 50.00] for Q8W; $p<0.001$ (Appendix 7, Table 7.1).

The percent reduction from baseline in daily OCS dose at Week 28 by baseline blood eosinophil categories (≥150 to 299/µL, ≥300/µL, 300 to 450/µL, and >450/µL) is presented in Appendix 7, Table 7.4. For all baseline blood eosinophil count categories, the median baseline OCS doses were similar across groups (Appendix 7, Table 7.4).

For the ≥300/µL, 300 to 450/µL, and >450/µL blood eosinophil count categories, the median percent reductions from baseline in daily OCS dose at Week 28 were greater for the benralizumab group compared with those for the placebo group (75.00% vs. 0% for the ≥300/µL category; 63.35% vs. 0% for the 300 to 450/µL category; and 75.00% vs. 0% for the >450/µL category) (Appendix 7, Table 7.4). In addition, the median percent reductions observed for the >450/µL count category for the benralizumab Q8W group was numerically greater than those observed for the 300 to 450/µL count category (75.00% vs. 63.35%, respectively).

For the ≥150 to 299/µL blood eosinophil count category, the median percent reduction from baseline in daily OCS dose at Week 28 for the placebo group was between those for the benralizumab 30 mg group (50.00% vs. 57.50%); however, it is difficult to draw meaningful conclusions from these data because the number of patients randomised in the ≥150 to 299/µL count category was small (n=33).

5.2.2 Secondary variables - daily OCS dose

In line with the primary efficacy analysis results, benralizumab 30 mg Q8W demonstrated consistent improvement over placebo (nominal p≤0.004) for the categorical OCS reduction endpoints (proportion of patients with a ≥25% reduction, ≥50% reduction, 100% reduction, final OCS dose of ≤5.0 mg, or ≥25% reduction with final OCS dose of ≤5 mg) (Appendix 7, Table 7.5).

In addition to the categorical endpoints, an analysis was conducted to assess the proportion of patients with no clinically meaningful reduction from baseline in OCS dose (≤5 mg) at Week 28, which showed a numerically smaller proportion of patients in the benralizumab 30 mg Q8W group compared with the placebo group (34.2% vs 50.7%; nominal p=0.053).

Only patients with an optimized baseline OCS dose of ≤12.5 mg were eligible to achieve a 100% reduction in OCS dose during the study, under the defined titration schedule. Of these eligible patients, 52.4% (22/42: nominal p=0.002) and 19.0% (8/42) achieved a 100% reduction in OCS dose in the benralizumab 30 mg Q8W and placebo groups, respectively.

5.2.3 Comparative analyses – Reduction in average daily OCS dose

5.2.4 OCS sparing trials (ZONDA vs. SIRIUS)

All the patients across the ZONDA and SIRIUS trials were on maintenance OCS and based on clinical opinion. Details for baseline ICS dose across such populations are not judged relevant, as the ICS effect would be overtaken by the OCS. Therefore, only one definition of high-dose ICS was considered for the analysis of OCS sparing trials, i.e., >500 µg FP daily or equivalent (as reported in ZONDA). Considering this high-dose definition, the initial sample size would be sufficiently large for matching across the trials.

Benralizumab was compared with mepolizumab for the following three efficacy outcomes:

- Percentage reduction in OCS dose at 24 weeks and at the end of study
- Proportion of patients with complete reduction in OCS dose at 24 weeks
- Annual rate of clinically significant exacerbations

Treatment differences of each intervention against placebo were used to derive the anchored ITC.
Two analyses including base case and sensitivity analyses were conducted for the OCS sparing trials. The base case analysis included EOS count, exacerbation history, OCS dose, BMI, and nasal polyps for matching, while sensitivity analysis included ACQ-5 score and history of omalizumab use in addition to the above variables.

5.2.5 Percentage reduction in OCS dose

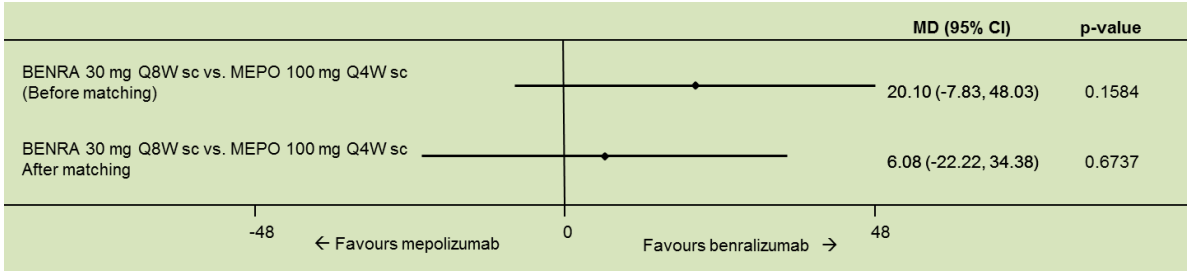
The ZONDA and SIRUS trials varied in terms of study duration. ZONDA was a 28 weeks study, while SIRIUS was a 24 weeks study. In order to have a like-for-like comparison, the mean percentage reduction in OCS dose was analyzed using 24 weeks data from both of the trials. To assess the impact of time-point, an additional analysis was conducted by using the end of study data from both the trials, i.e., 28 weeks from the ZONDA trial and 24 weeks from the SIRIUS trial.

The primary outcome in the ZONDA trial was percentage reduction in OCS dose. The present analysis was performed using mean percentage reduction in OCS dose. For the median treatment differences in percentage reduction in OCS dose in the SIRIUS trial, the results were replicated at 28 weeks using the Hodges Lehman method mentioned in the SIRIUS trial CSR. This is a non-parametric estimation method and doesn't support weights (especially important weights calculated for MAIC). Therefore, it was concluded that creating matched results for median data would not be

feasible. Due to this limitation of the procedure, differences in mean percentage reduction in OCS dose were used for analysis instead of median differences.

5.2.6 Base case analysis

FIGURE IX: BASE CASE: SUMMARY OF ITC RESULTS FOR PERCENT REDUCTION IN OCS DOSE AT 24 WEEKS IN PATIENTS WITH >500 µG FP DAILY OR EQUIVALENT



Conclusion:

The ITC results for benralizumab vs. mepolizumab comparison are presented in Figure IX. The results for the mean percentage reduction in OCS dose from baseline favoured benralizumab before (20% higher reduction) as well as after matching (6% higher reduction) with no statistically significant difference between the two treatments (p-value after matching = 0.67). The difference does not reach the 20 % reduction set by Medicinrådet.

5.2.7 Analysis at the end of study

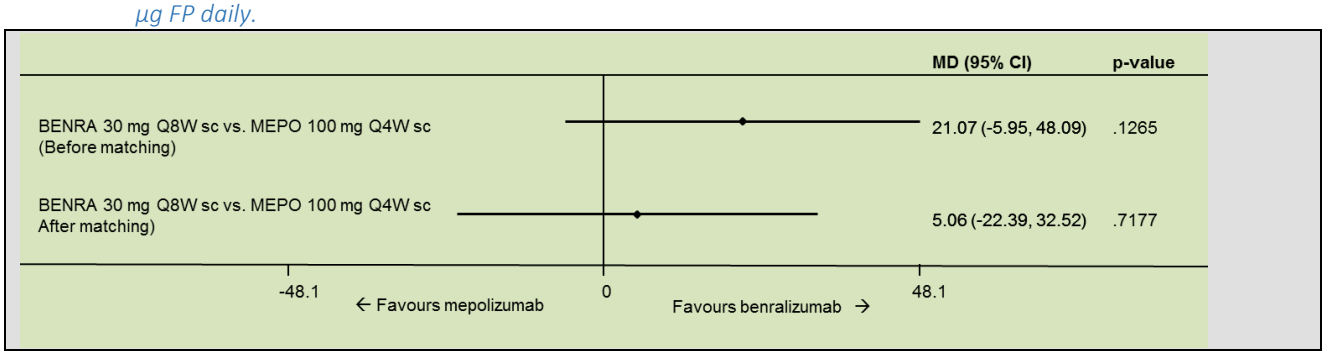
An additional analysis was conducted after considering data at the end of study from both the trials (28 weeks from ZONDA and 24 weeks from SIRIUS). The impact of adjustment on the estimates for benralizumab vs. placebo in ZONDA trial at the end of the study is presented in Table X. The treatment difference for benralizumab vs. placebo in percentage reduction in OCS dose from baseline at the end of the study in ZONDA trial reduced from 37.27% before matching to 21.26% after matching. The difference vs. placebo was statistically significant before as well as after matching the trial populations.

Table X: Base case: MAIC analysis at the end of study in patients with >500 µg FP daily or equivalent

5.2.7.1 Comparison	5.2.7.2 MD (% reduction)	5.2.7.3 LCI	5.2.7.4 UCI
BENRA 30 mg Q8W vs. placebo (ZONDA), unadjusted	37.27	21.47	53.08
MEPO 100 mg SC vs. placebo (SIRIUS), unadjusted	16.20	-5.72	38.12
BENRA 30 mg Q8W vs. placebo (adjusted for SIRIUS trial)	21.26	4.74	37.79

Mean difference for benralizumab vs. placebo were derived from ZONDA trial IPD as the ZONDA trial reported the adjusted estimates. Mean difference for mepolizumab vs. placebo were derived from the reported endpoint values in SIRIUS trial CSR

Figure XI: Base case: Summary of ITC results for percent reduction in OCS dose at the end of study in patients with >500 µg FP daily.



Conclusion:

Figure XI presents the ITC results for the comparison of benralizumab vs. mepolizumab in percentage reduction in OCS dose at the end of the study. The results for the mean percentage reduction in OCS dose favoured benralizumab before (21% higher reduction) as well as after matching (5% higher reduction) with no statistically significant difference between the two treatments (p-value after matching = 0.72). The difference does not reach the 20 % reduction set by Medicinrådet.

5.2.8 Reduction 100% and < 50 % - indirect comparison using Bucher method

Reduction 100 % - indirect comparison using Bucher method

Results per outcome	*Attach forest plots and statistical results as a separate file.* *Results from the comparative analysis should be given in the table below, if possible.*							
		Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	Difference	CI	*P* value	Hazard/Odds/Risk ratio	CI	*P* value	
Reduction 100%	Benralzumab: (Zonda) Mepolizumab: (SIRIUS)	6.9%	-8.4% to 61.0%	NA	1.477	(0.419 to 5.210)	0.544	Bucher method

Method for calculation of ARR= (RR-1) event rate for Mepolizumab (SIRIUS). Event rate for Mepolizumab = 10/69=14.5%

Conclusion:

The difference is not significant but the difference of 6,9 % exceeds the goal of 5 % set by Medicinrådet.

5.2.9 Reduction 50 % - indirect comparison using Bucher method

Results per outcome	*Attach forest plots and statistical results as a separate file.* *Results from the comparative analysis should be given in the table below, if possible.*							
		Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	Difference	CI	*P* value	Hazard/Odds/Risk ratio	CI	*P* value	
Reduction 50%	Benralzumab: (Zonda) Mepolizumab: (SIRIUS)	5.1%	(-19.0% to 45.8%)	NA	1.095	(0.646 to 1.855)	0.736	Bucher method

Method for calculation of ARR= (RR-1). Event rate for Mepolizumab (SIRIUS): Event rate for Mepolizumab = 37/69=53.6%

Conclusion:

The difference between benralizumab and mepolizumab is not significant.

5.3 Clinical question 3: Pre-bronchodilator FEV1

5.3.1 Baseline characteristics SIROCCO – Lung function

Lung function characteristics: Lung function at baseline was similar across groups. In all patients in the FAS, mean pre-bronchodilator lung function tests at baseline showed an FEV1 of 1.665 L, a percent predicted normal FEV1 of 56.7%, and an FEV1/FVC ratio of 61. Mean percent reversibility was 25.7%.

5.3.2 Pre-bronchodilator FEV1 (Key secondary endpoint) - SIROCCO

The change from baseline in pre-bronchodilator FEV1 at Week 48 was a key secondary endpoint in this study; this result achieved significance for benralizumab 30 mg Q8W dosing regimen based on a hierarchical testing procedure to control for multiplicity.

In patients with a baseline blood eosinophil count ≥300/µL, mean baseline FEV1 was similar across groups (Appendix 6, Table 6.1). An improvement in LS mean change from baseline to Week 48 in pre-bronchodilator FEV1 was observed for the benralizumab 30 mg Q8W regimen, as well as placebo (0.398 L and 0.239 L, respectively). Benralizumab 30 mg Q8W demonstrated statistically significant improvements in LS mean change from baseline in pre-bronchodilator FEV1 at week 48 compared with placebo (0.159 L [0.068, 0.249]; p≤0.022).

In patients with a baseline blood eosinophil count ≥300/µL, benralizumab 30 mg Q8W demonstrated greater improvements in LS mean change from baseline in pre-bronchodilator FEV1 compared with placebo at Week 4 that were maintained through Week 48 (nominal p<0.05 for all visits) (Appendix 6, Figure 6.2).

5.3.3 Post-bronchodilator FEV1 (Secondary endpoint) - SIROCCO

In patients with a baseline blood eosinophil count ≥300/µL, an improvement in LS mean change from baseline to Week 48 in post-bronchodilator FEV1 was observed for the benralizumab 30 mg Q8W group, as well as placebo (0.233 L and 0.134 L, respectively). Benralizumab 30 mg Q8W demonstrated greater improvements in LS mean change from baseline in post bronchodilator FEV1 at Week 48 compared with placebo (0.099 L [0.007, 0.192]; nominal p≤0.037) (Appendix 6, Table 6.3).

The LS mean change from baseline to week 48 was lower for post bronchodilator FEV1 compared with pre-bronchodilator FEV1 for benralizumab 30 mg Q8W (0.233 L vs 0.398 L) as well as for placebo (0.134 L vs 0.239 L) (Appendix 6, Table 6.3 and Table 6.1, respectively). Regardless, an improvement in post bronchodilator FEV1 of approximately 0.1 L was observed for benralizumab group over placebo after 48 weeks.

5.3.4 Home lung function (Morning and evening peak expiratory flow (PEF)); secondary endpoints) - SIROCCO

Mean baseline morning and evening peak expiratory flow (PEF) were similar across groups (Appendix 6, Table 6.4). Results for morning and evening PEF at Week 48 in patients with a baseline blood eosinophil count ≥300/µL supported the improvement in pulmonary function demonstrated by benralizumab 30 mg Q8W for the change from baseline in pre-bronchodilator FEV1. Benralizumab 30 mg Q8W demonstrated greater improvements in LS mean change from baseline to Week 48 compared with placebo in morning PEF (16.46 L/min [2.08, 30.83]; nominal p≤0.025) and evening PEF (19.18 L/min [5.09, 33.28]; nominal p≤0.008).

In patients with a baseline blood eosinophil count ≥300/µL, benralizumab 30 mg Q8W demonstrated greater improvements in LS mean change from baseline in morning PEF compared with placebo that were maintained from Week 2 through Week 48 (nominal p<0.05 for all visits) and for evening PEF that were maintained from week 2 through Week 48 (nominal p<0.05 for all visits except Week 4) (Appendix 6, Figure 6.5).

5.3.5 Baseline characteristics CALIMA– Lung function

Lung function at baseline was similar across groups. In all patients in the FAS, mean pre-bronchodilator lung function tests at baseline showed an FEV1 of 1.762 L, a percent predicted normal FEV1 of 58.3%, and an FEV1/FVC ratio of 61 (Table 12). Mean percent reversibility was 26.7%.

5.3.6 Pre-bronchodilator FEV1 (Key secondary endpoint) – CALIMA

The change from baseline in pre-bronchodilator FEV1 at Week 56 was a key secondary endpoint in this study; this result achieved significance for benralizumab 30 mg dose regimen based on a hierarchical testing procedure to control for multiplicity.

In patients with a baseline blood eosinophil count ≥300/µL who were taking high dose ICS, mean baseline FEV1 was similar across groups (Appendix 6, Table 6.6). An improvement in LS mean change from baseline to Week 56 in pre-bronchodilator FEV1 was observed for the benralizumab 30 mg Q8W group, as well as placebo (0.330 and 0.215 L, respectively). Benralizumab 30 mg Q8W demonstrated statistically significantly greater improvements in LS mean change from baseline in pre-bronchodilator FEV1 at Week 56 compared with placebo (0.116 L [0.028, 0.204]; p≤0.010). In patients with a baseline blood eosinophil count ≥300/µL who were taking high-dose ICS, benralizumab 30 mg Q8W demonstrated greater improvements in LS mean change from baseline in pre-bronchodilator FEV1 compared with placebo at Week 4 that were maintained through Week 56 (nominal p<0.05 for all visits for Q8W; Appendix 6, Figure 6.7).

5.3.7 Post-bronchodilator FEV1 (Secondary endpoint) - CALIMA

In patients with a baseline blood eosinophil count ≥300/µL who were taking high-dose ICS, an improvement in LS mean change from baseline to Week 56 in post-bronchodilator FEV1 was observed for the benralizumab 30 mg Q8W grpup, as well as placebo (0.172 L and 0.067 L, respectively). Benralizumab 30 mg Q8W demonstrated greater improvements in LS mean change from baseline in post bronchodilator FEV1 at Week 56 compared with placebo (0.105 L [0.029, 0.180]; nominal p≤0.011) (Appendix 6, Table 6.8).

The LS mean change from baseline to Week 56 was lower for post bronchodilator FEV1 compared with pre-bronchodilator FEV1 for benralizumab 30 mg Q8W (0.172 L vs 0.330 L) as well as for placebo (0.067 L vs 0.215 L)

(Appendix 6, Table 6.8 and Table 6.6, respectively). Regardless, an improvement in post bronchodilator FEV1 of approximately 0.1 L was observed for both benralizumab groups over placebo after 56 weeks.

5.3.8 Home lung function (Morning and evening peak expiratory flow (PEF); secondary endpoints) - CALIMA

Mean baseline morning and evening PEF were similar across groups (Appendix 6, Table 6.9). Results for morning and evening PEF at Week 56 in patients with a baseline blood eosinophil count ≥300/µL who were taking high dose ICS supported the improvement in pulmonary function demonstrated by benralizumab 30 mg Q8W for the change from baseline in pre-bronchodilator FEV1. Benralizumab 30 mg Q8W demonstrated greater improvements in LS mean change from baseline to Week 56 compared with placebo in morning PEF (15.27 L/min [0.90, 29.64]; nominal p≤0.037) and evening PEF (21.22 L/min [6.65, 35.79]; nominal p≤0.018).

In patients with a baseline blood eosinophil count ≥300/µL who were taking high dose ICS, benralizumab 30 mg Q8W demonstrated greater improvements in LS mean change from baseline in morning and evening PEF that were maintained from Week 4 through Week 56 (nominal p<0.05 for all visits) (Appendix 6, Figure 6.12).

5.3.9 Baseline characteristics ZONDA – Lung function

Lung function at baseline was similar across groups. In all patients in the FAS, mean pre-bronchodilator lung function tests at baseline showed an FEV1 of 1.762 L, a percent predicted normal FEV1 of 58.3%, and an FEV1/FVC ratio of 61 (Appendix 4). Mean percent reversibility was 26.7%.

5.3.10 Change from baseline in pre-bronchodilator FEV1 (secondary endpoint) – ZONDA

Mean baseline FEV1 was similar across groups (Appendix 6, Table 6.13). An improvement in least squares (LS) mean change from baseline to Week 28 in pre-bronchodilator FEV1 was observed for the benralizumab 30 mg Q8W group, as well as placebo (0.239 and 0.126 L, respectively), with the LS mean change from baseline in pre-bronchodilator FEV1 at Week 28 favoring benralizumab 30 mg Q8W compared with placebo (0.112 L [95% CI -0.033, 0.258]; nominal p=0.129) – this was a secondary endpoint and that the study was not powered to show a difference.

Benralizumab 30 mg Q8W demonstrated greater improvements in the LS mean change from baseline in pre - bronchodilator FEV1 compared with placebo at Week 4 that were maintained through Week 28 (nominal p<0.05 for most visits) (Appendix 6, Figure 6.14). These results showed that the full magnitude of the treatment effect was observed at the first assessment (Week 4) in benralizumab-treated patients, prior to the OCS reduction phase, and was maintained throughout the treatment period despite OCS dose reduction.

In the placebo group, the LS mean change from baseline in pre- bronchodilator FEV1 for the placebo group was greater (i.e., improved lung function) at Week 28 than all earlier timepoints. This difference was not observed for the benralizumab 30 mg Q4W and Q8W groups.

5.3.11 Change from baseline in home lung function (morning and evening peak expiratory flow (PEF))- ZONDA

Mean baseline morning and evening PEF were similar across groups. Results for morning and evening PEF at Week 28 supported the improvement in pulmonary function demonstrated by benralizumab 30 mg Q8W for the change from baseline in pre-bronchodilator FEV1.

Benralizumab 30 mg Q8W demonstrated greater improvements in the LS mean change from baseline to Week 28 compared with placebo in morning and evening PEF (30.01 L/min [95% CI 4.26, 55.76] and 31.52 L/min [95% CI 6.32, 56.71], respectively; both nominal p≤0.023).

Benralizumab 30 mg Q8W demonstrated greater improvements in the LS mean change from baseline in morning and evening PEF compared with placebo as early as Week 2 that were maintained through Week 28 (nominal p<0.05 for most visits through Week 20) (Appendix 6, Figure 6.13).

5.3.12 Comparative analyses – Lung function

MAIC: results of adjustments - benralizumab vs. mepolizumab are presented in Appendix 12 for scenario 1: ≥880 µg FP daily and Scenario 2: >500 µg FP daily at Pre-bronchodilator FEV1 (L) - change from baseline at 32 weeks, Pre-bronchodilator FEV1 (L) - change from baseline at the end of study and Pre-bronchodilator FEV1 (L) - change from baseline at the end of study (excluding MENSA)

5.3.13 Pre-bronchodilator FEV1 (L), change from baseline

Change from baseline in pre-bronchodilator FEV1 (L) was reported in all the four studies included in the MAIC. The analysis of this outcome was also conducted for two broad scenarios based on the definition of high-dose ICS, i.e., ≥880 µg FP daily or equivalent and >500 µg FP daily or equivalent.

The MENSA trial was of 32 weeks duration, considerably different from the duration of the other three studies, i.e., 52 weeks in DREAM, 48 weeks in SIROCCO, and 56 weeks in CALIMA. Therefore, for each of the above two ICS dose scenarios, pre-bronchodilator FEV1 (L) was analyzed at 32 weeks, end of the studies (including all four trials), and end of the studies (excluding MENSA). The MENSA trial was excluded from the end of study analysis owing to a shorter duration (32 weeks) in comparison to other trials.

Scenario 1: ICS ≥880 µg FP daily

Table XII presents the mean differences between benralizumab or mepolizumab and placebo in change from baseline in pre-bronchodilator FEV1 (L). There was a minor change in mean treatment differences between benralizumab 30 mg Q8W and placebo after adjusting for differences in MENSA/DREAM trials for all the three time-points assessed.

(i) 32 weeks

The mean difference between benralizumab and placebo in change from baseline in pre-bronchodilator FEV1 slightly decreased from 0.11 L to 0.10 L after matching at 32 weeks showing an improvement of 10 mL in favor of benralizumab.

(ii) End of the studies (including MENSA)

When matching was performed at the end of the studies (including MENSA), there was no change in the mean difference between benralizumab and placebo in change from baseline for FEV1. It was 0.11 L before as well as after matching.

(iii) End of the studies (excluding MENSA)

When MENSA trial was excluded from the end of the studies analysis, the mean difference between benralizumab and placebo for change from baseline in FEV1 decreased from 0.11 L to 0.09 L, i.e., an improvement of 20 mL in favour of benralizumab.

Table XII: Pooled MAIC results for change from baseline in pre-bronchodilator FEV_1 (L) in patients with ≥880 µg FP daily

5.3.13.1 Comparison	5.3.13.2 Mean difference in litres (LCI, UCI)		
	5.3.13.3 32 weeks	5.3.13.4 End of study	5.3.13.5 End of study 5.3.13.6 (excluding MENSA)
BENRA Q8W vs. placebo (SIROCCO/CALIMA), unadjusted	0.11 (0.05, 0.18)	0.11 (0.05, 0.18)	0.11 (0.05, 0.18)
MEPO vs. placebo (MENSA/DREAM), unadjusted	0.07 (0.02,0.13)	0.09 (0.04,0.14)	-
BENRA Q8W vs. placebo (adjusted for MENSA/DREAM)	0.10 (0.04, 0.17)	0.11 (0.04, 0.17)	-
MEPO 75 mg IV vs. placebo (DREAM), unadjusted	-	-	0.06 (-0.04, 0.16)
BENRA Q8W vs. placebo (adjusted for DREAM trial)	-	-	0.09 (0.03, 0.14)

End of study for SIROCCO: 48 weeks; CALIMA: 56 weeks; MENSA: 32 weeks; DREAM: 52 weeks
Mean differences for benralizumab vs. placebo were pooled from SIROCCO and CALIMA IPD. Mean differences for mepolizumab vs. placebo were either pooled from MENSA and DREAM CSRs or were used from DREAM trial CSR only

(i) 32 weeks

The mean treatment difference slightly changed when adjusted for MENSA/DREAM pooled population at 32 weeks and the end of the study. Compared with mepolizumab, benralizumab led to an improvement of 30 mL in pre-bronchodilator FEV1 at 32 weeks [(mean difference, 95% CI: 0.03(-0.06, 0.12)].

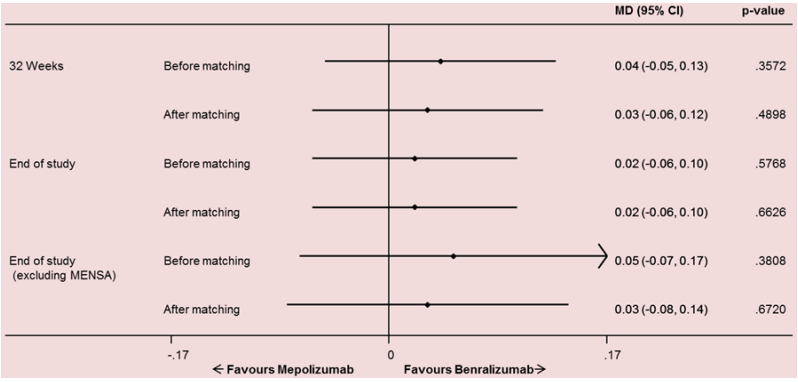
(ii) End of study (including MENSA)

At the end of study analysis including all four trials, benralizumab led to an improvement of
20 mL in pre-bronchodilator FEV1 compared with mepolizumab [(mean difference, 95% CI: 0.02(-0.06, 0.10)]

(iii) End of study (excluding MENSA)

After excluding MENSA trial from the end of study analysis, benralizumab was associated with 30 mL improvement compared with mepolizumab [(mean difference, 95% CI: 0.03 (-0.08, 0.14)].

FigureXIII: Summary of Indirect treatment comparison (ITC) analysis results for change from baseline in pre-bronchodilator FEV_1 (L) in patients with ≥880 µg FP daily



The estimates are mean treatment differences in change from baseline in pre-bronchodilator FEV_1 (L) between benralizumab and mepolizumab

Conclusion:

The Indirect treatment comparison (ITC) results suggested that benralizumab is numerically better in improving pre-bronchodilator FEV1 after matching for differences with mepolizumab trials at all time-points assessed. The difference between the two treatments was statistically non-significant.

Scenario 2: ICS >500 µg FP daily (high-dose, as defined in the benralizumab studies)

Table XIV presents the treatment differences in mean change from baseline in pre-bronchodilator FEV1 (L) between the treatments (benralizumab or mepolizumab) vs. placebo for patients with ICS >500 µg FP daily. There was a slight change in the treatment differences in pre-bronchodilator FEV1 (L), change from baseline for benralizumab 30 mg Q8W vs. placebo after adjusting for differences in MENSA/DREAM trials.

(i) 32 weeks

There was no change in the treatment difference in change from baseline FEV1 between benralizumab and placebo after matching with the MENSA/DREAM trials' pooled population. The mean difference was 0.11 L before as well as after matching.

(ii) End of the studies (including MENSA)

The difference in mean change from baseline in pre-bronchodilator FEV1 (L) between benralizumab and placebo slightly increased from 0.12 to 0.13 at the end of study analysis including all four trials.

(iii) End of the studies (excluding MENSA)

The difference in mean change from baseline in pre-bronchodilator FEV1 (L) between benralizumab and placebo slightly decreased from 0.12 to 0.11 after excluding MENSA trial from the end of study analysis.

Table XIV: Pooled MAIC results for change from baseline in pre-bronchodilator FEV_1 (L) in patients with >500 µg FP daily or equivalent

5.3.13.7 Comparison	5.3.13.8 Mean difference (LCI, UCI)		
	5.3.13.9 32 weeks	5.3.13.10 End of study	5.3.13.11 End of study (excluding MENSA)
BENRA Q8W vs. placebo (SIROCCO/CALIMA), unadjusted	0.11 (0.06, 0.16)	0.12 (0.07, 0.17)	0.12 (0.07, 0.17)
MEPO vs. placebo (MENSA/DREAM), unadjusted	0.07 (0.02, 0.13)	0.09 (0.04,0.14)	-
BENRA Q8W vs. placebo (adjusted for MENSA/DREAM)	0.11 (0.06, 0.16)	0.13 (0.08, 0.19)	-
MEPO vs. placebo (DREAM), unadjusted	-	-	0.06 (-0.04, 0.16)
BENRA Q8W vs. placebo (adjusted for DREAM trial)	-	-	0.11 (0.06, 0.16)

End of study for SIROCCO: 48 weeks; CALIMA: 56 weeks; MENSA: 32 weeks; DREAM: 52 weeks
Mean differences for benralizumab vs. placebo were pooled from SIROCCO and CALIMA IPD. Mean differences for mepolizumab vs. placebo were either pooled from MENSA and DREAM CSRs or were used from DREAM trial CSR only

Figure XV summarizes the ITC results for change from baseline in pre-bronchodilator FEV1 (L) in the patients with >500 µg FP daily or equivalent (high-dose ICS, as defined in benralizumab studies).

Similar to the results for the ≥880 µg FP daily scenario, the improvement in pre-bronchodilator FEV1 (L) after treatment numerically favoured benralizumab when compared with mepolizumab before as well as after matching.

(i) 32 weeks

The mean treatment difference between benralizumab and mepolizumab in change from baseline in pre-bronchodilator FEV1 after matching at 32 weeks was 40 mL favouring benralizumab [(mean difference, 95% CI: 0.04 (-0.03, 0.12)].

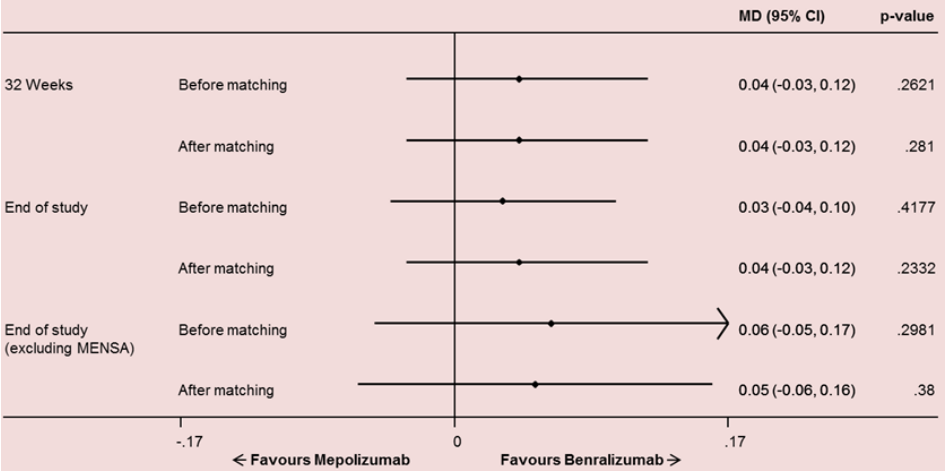
(ii) End of the studies (including MENSA)

At the end of the study analysis including all the four trials, benralizumab led to an improvement of 40 mL in pre-bronchodilator FEV1 compared with mepolizumab after matching [(mean difference, 95% CI: 0.04 (-0.03, 0.12)].

(iii) End of the studies (excluding MENSA)

After excluding MENSA from the end of study analysis, benralizumab was associated with a 50 mL improvement in pre-bronchodilator FEV1 compared with mepolizumab [(mean difference, 95% CI: 0.05 (-0.06, 0.16)].

Figure XV: Summary of ITC analysis results for change from baseline in pre-bronchodilator FEV_1 (L) in patients with >500 µg FP daily or equivalent



The estimates are mean treatment differences in change from baseline in pre-bronchodilator FEV_1 (L) between benralizumab and mepolizumab

Conclusion:

The ITC results suggested that benralizumab was associated with a numerically higher improvement in pre-bronchodilator FEV1, both before and after matching for differences with mepolizumab trials. The difference between the two treatments was statistically non-significant at all the time-points assessed.

5.3.14 Clinical Question 3b: Increase in FEV of 200 ml

Studies included both adult and patients below the age of 18. In the below table XVI, we have listed the number of patients achieving more than 200 ml FEV1. RR is between 1,26 and 1,46 favoring benralizumab vs. placebo.

Due to the lack of data for mepolizumab we cannot perform the indirect comparison (Medicinråd 15 % difference.)

Table XVI Proportion of patients with >=0.2 L FEV1(L) pre-bronchodilator increase from baseline to end of treatment, treatment comparison, Cochran-Mantel Haenzel test (Full analysis set, high-dose ICS, baseline blood eosinophils >=300/µL)

		Comparison between groups		
SIROCCO Treatment Group	Number(%) of patients with >=0.2 L FEV1(L) pre-bronchodilator increase from baseline to end of treatment	Odds Ratio	95% CI	p-value
Benra 30 mg q.8 weeks (N=235)	142 (60.4)	1.46	(1.02, 2.10)	0.037
Placebo (N=233)	115 (49.4)			

		Comparison between groups		
CALIMA Treatment Group	Numbe(%) of patients with >=0.2 L FEV1(L) pre-bronchodilator increase from baseline to end of treatment	Odds Ratio	95% CI	p-value
Benra 30 mg q.8 weeks (N=211)	109 (51.7)	1.26	(0.86, 1.85)	0.234
Placebo (N=221)	100 (45.2)			

		Comparison between groups		
SIROCCO/CALIMA pooled Treatment Group	Number(%) of patients with >=0.2 L FEV1(L) pre-bronchodilator increase from baseline to end of treatment	Odds Ratio	95% CI	p-value
Benra 30 mg q.8 weeks (N=446)	251 (56.3)	1.36	(1.05, 1.78)	0.020
Placebo (N=454)	215 (47.4)			

Conclusion:

Benralizumab vs. placebo will meet the criteria's set by medicinrådet but due to the lack of data for mepolizumab we cannot perform the indirect comparison (Medicinråd 15 % difference).

5.4 Clinical question 4: Asthma control (ACQ-6)

5.4.1 Baseline characteristics, symptom status

Symptom status at baseline was assessed by total asthma symptom score on a range from 0 (best) to 6 (worst). In the population of patients evaluated for efficacy (patients with blood eosinophil counts ≥300/µL).

SIROCCO:

The mean total asthma symptom score ranged from 2.67 to 2.74 units across groups (Appendix 4). Symptom control at baseline was assessed by ACQ-6 on a scale of 0 (totally controlled) to 6 (severely uncontrolled), with a score ≥1.5 being considered not well controlled. In patients with blood eosinophil counts ≥300/µL, mean scores for ACQ-6 at baseline ranged from 2.77 to 2.90 units across groups and most patients (range: 92.4% to 96.3%) were considered not well controlled at baseline.

5.4.2 Change from baseline in Asthma Control Questionnaire (ACQ-6)- SIROCCO

The ACQ-6 is a shortened version of the ACQ that assesses asthma symptoms (nighttime waking, symptoms on waking, activity limitation, shortness of breath, wheezing, and SABA use) omitting the FEV1 measurement from the

original ACQ score. Questions were scored from 0 (totally controlled) to 6 (severely uncontrolled); thus, a decrease in score indicated improvement. In patients with a baseline blood eosinophil count ≥300/µL, mean baseline ACQ 6 scores were similar across groups (Appendix 8, Table 8.1). An improvement in LS mean change from baseline to Week 48 in ACQ 6 scores was observed for the benralizumab 30 mg Q8W group, as well as placebo group (1.46 and 1.17 units, respectively). Benralizumab 30 mg Q8W demonstrated an improvement in LS mean change from baseline in ACQ-6 score at Week 48 compared with placebo (0.29 units [0.48, 0.10]; nominal p=0.003).

In patients with a baseline blood eosinophil count ≥300/µL, benralizumab 30 mg Q8W demonstrated greater improvements in LS mean change from baseline in ACQ 6 score compared with placebo at Week 10 that were generally maintained through Week 48 (nominal p<0.05 at most visits; Appendix 8, Figure 8.2)

5.4.3 Change from baseline in Asthma Control Questionnaire (ACQ-6) - CALIMA

In patients with a baseline blood eosinophil count ≥300/µL who were taking high-dose ICS, mean baseline ACQ-6 scores were similar across groups (Appendix 8, Table 8.3. An improvement in LS mean change from baseline to Week 56 in ACQ-6 scores was observed for the benralizumab 30 mg Q8W group, as well as placebo group. Benralizumab 30 mg Q8W demonstrated greater improvements in LS mean change from baseline in ACQ-6 score at Week 56 compared with placebo (0.25 units [0.44, -0.07]; nominal p≤0.043).

In patients with a baseline blood eosinophil count ≥300/µL who were taking high-dose ICS, benralizumab 30 mg Q8W demonstrated greater improvements in LS mean change from baseline in ACQ-6 score compared with placebo at Week 4 for the Q8W regimen that was maintained through Week 56 (nominal p<0.05 for all visits for Q8W; Appendix 8, Figure 8.4).

5.4.4 Change from baseline in Asthma Control Questionnaire (ACQ-6) -ZONDA

An improvement in LS mean change from baseline to Week 28 in ACQ 6 scores was observed for the benralizumab 30 mg Q8W regimen, as well as placebo. Benralizumab 30 mg Q8W demonstrated an improvement in LS mean change from baseline in ACQ 6 score at Week 28 compared with placebo (-0.55 units [95% CI -0.86, -0.23]; nominal p=0.001).

Benralizumab 30 mg Q8W demonstrated greater improvements in LS mean change from baseline in ACQ 6 score compared with placebo at Week 4 that were generally maintained through Week 28 (nominal p<0.05 at most visits after Week 8) (Appendix 8, Figure 8.5).

MAIC was not undertaken to assess the comparative clinical effectiveness of benralizumab vs. mepolizumab with regards to Asthma Control Questionnaire (ACQ-5 or 6). We have conducted another analysis. Mepolizumab studies used ACQ 5 or 6. Data from SIRIUS is not included in the analysis due to a different study design

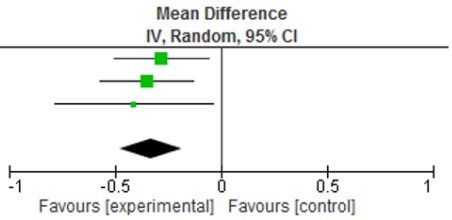
Method for pooling:
Inverse variance method with Random effect. Calculations made using Review Manager v5.3.

Method for indirect comparison:
Bucher method

Benralizumab

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Calima	-1.49	1.13	185	-1.21	1.12	197	41.7%	-0.28 [-0.51, -0.05]
Sirocco	-1.47	1.05	191	-1.12	1.15	186	43.0%	-0.35 [-0.57, -0.13]
Zonda	-1.09	1.09	66	-0.68	1.1	67	15.3%	-0.41 [-0.78, -0.04]
Total (95% CI)			**442**			**450**	**100.0%**	**-0.33 [-0.48, -0.18]**

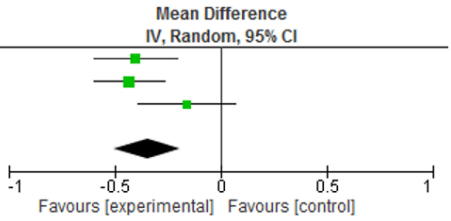
Heterogeneity: Tau² = 0.00; Chi² = 0.40, df = 2 (P = 0.82); I² = 0%
Test for overall effect: Z = 4.44 (P < 0.00001)



Mepolizumab

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Chupp	-0.8	1.1712	266	-0.4	1.1712	261	32.9%	-0.40 [-0.60, -0.20]
Orteag	-0.9301	0.97	385	-0.5	0.9674	191	39.1%	-0.43 [-0.60, -0.26]
Pavord	-0.75	1.0297	153	-0.59	1.0297	155	28.0%	-0.16 [-0.39, 0.07]
Total (95% CI)			**804**			**607**	**100.0%**	**-0.34 [-0.50, -0.19]**

Heterogeneity: Tau² = 0.01; Chi² = 3.72, df = 2 (P = 0.16); I² = 46%
Test for overall effect: Z = 4.34 (P < 0.0001)



ACQ5,6,7 – Bucher

	Attach forest plots and statistical results as a separate file. *Results from the comparative analysis should be given in the table below, if possible.*							
		Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	Difference	CI	*P* value	Hazard/Odds/Risk ratio	CI	*P* value	
ACQ5,6,7	Benralzumab: (Sirocco Calima Zonda) Mepolizumab: (Chupp, Orteag Pavord)	0.01	-0.206 to 0.226	0.928	NA	NA	NA	Bucher method

Conclusion:

There is no significant difference between benralizumab and mepolizumab. The difference does not meet the criteria set by Medicinrådet (ACQ 0,5)

5.5 Clinical question 5: Asthma Quality of Life (AQLQ(S)+12)

5.5.1 Change from baseline in Standardized Asthma Quality of Life Questionnaire for 12 Years and Older (AQLQ[S]+12) – SIROCCO

The AQLQ(S)+12 is a questionnaire that measures the health-related quality of life experienced by asthma patients and is comprised of 4 separate domains (symptoms, activity limitations, emotional function, and environmental stimuli). Patients were asked to recall their experiences during the previous 2 weeks and to score each of the 32 questions on a 7-point scale ranging from 7 (no impairment) to 1 (severe impairment); thus an increase in score indicated improvement.

In patients with a baseline blood eosinophil count ≥300/µL, mean baseline overall AQLQ(S)+12 scores were similar across groups (Appendix 9, Table 9.1). An improvement in LS mean change from baseline to Week 48 in AQLQ(S)+12 scores was observed for the benralizumab 30 mg Q8W regimen, as well as placebo (1.56 and 1.26 units, respectively). Benralizumab 30 mg Q8W demonstrated an improvement in LS mean change from baseline in overall AQLQ(S)+12 score at Week 48 compared with placebo (0.30 units [0.10, 0.50]; nominal p=0.004).

In patients with a baseline blood eosinophil count ≥300/µL, benralizumab 30 mg Q8W demonstrated greater improvements in LS mean change from baseline in AQLQ(S)+12 score compared with placebo at Week 8 that were maintained through Week 48 (nominal p<0.05 for all visits) (Appendix 9, Figure 9.2).

5.5.2 Change from baseline in Standardized Asthma Quality of Life Questionnaire for 12 Years and Older (AQLQ[S]+12) – CALIMA

In patients with a baseline blood eosinophil count ≥300/µL who were taking high-dose ICS, mean baseline overall AQLQ(S)+12 scores were similar across groups (Appendix 9, Figure 9.3). An improvement in LS mean change from baseline to Week 56 in AQLQ(S)+12 scores was observed for the benralizumab 30 mg Q8W regimen, as well as placebo (1.56 and 1.31 units, respectively). Benralizumab 30 mg Q8W demonstrated an improvement in LS mean change from baseline in overall AQLQ(S)+12 score at Week 56 compared with placebo (0.24 units [0.04, 0.45]; nominal p=0.019).

In patients with a baseline blood eosinophil count ≥300/µL who were taking high-dose ICS, both benralizumab 30 mg Q8W demonstrated greater improvements in LS mean change from baseline in AQLQ(S)+12 score compared with placebo at Week 4 that were maintained through Week 56 (nominal p<0.05 for all visits) (Appendix 9, Figure 9.4).

5.5.3 Change from baseline in Standardized Asthma Quality of Life Questionnaire for 12 Years and Older (AQLQ[S]+12) – ZONDA

Mean baseline overall AQLQ(S)+12 scores were similar across groups. An improvement in LS mean change from baseline to Week 28 in AQLQ(S)+12 overall scores was observed for the benralizumab 30 mg Q8W regimen, as well as placebo (1.08 and 0.63 units, respectively). Benralizumab 30 mg Q8W demonstrated an improvement in LS mean change from baseline in overall AQLQ(S)+12 score at Week 28 compared with placebo (0.45 units [95% CI 0.14, 0.76]; nominal p=0.004).

Benralizumab 30 mg Q8W demonstrated greater improvements in the LS mean change from baseline in overall AQLQ(S)+12 score compared with placebo at Week 4 that were maintained through Week 28 (nominal p<0.05 for all visits from Week 8 through Week 28) (Appendix 9, Figure 9.5).

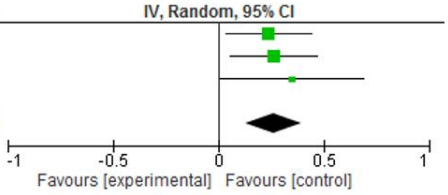
MAIC was not undertaken to assess the comparative clinical effectiveness of benralizumab vs. mepolizumab in AQLQ. We have conducted another analysis. Mepolizumab studies used either AQLQ or SGRQ. Data from SIRIUS is not included in the analysis due to a different study design. Addition of the two studies using SGRQ was done by recalculating to standard mean difference. We did not conduct an analysis of AQLQ studies alone. CALIMA, SIRICCO and ZONDA vs. DREAM.

AQLQ – pooling of studies

Benralizumab

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Calima	1.61	1.24	180	1.32	1.19	191	42.6%	0.24 [0.03, 0.44]
Sirocco	1.56	1.17	187	1.25	1.18	180	42.1%	0.26 [0.06, 0.47]
Zonda	1.05	1.04	67	0.67	1.1	68	15.4%	0.35 [0.01, 0.69]
Total (95% CI)			**434**			**439**	**100.0%**	**0.27 [0.13, 0.40]**

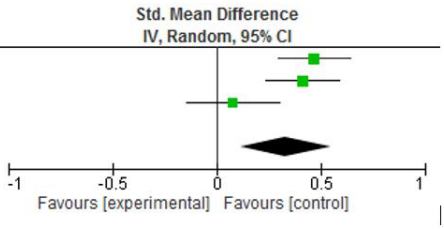
Heterogeneity: Tau² = 0.00; Chi² = 0.32, df = 2 (P = 0.85); I² = 0%
Test for overall effect: Z = 3.92 (P < 0.0001)



Mepolizumab

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Chupp	15.6	16.3659	265	7.9	16.3659	260	34.9%	0.47 [0.30, 0.64]
Orteag	15.7023	15.9424	385	9	16.5843	191	34.7%	0.41 [0.24, 0.59]
Pavord	0.8	1.1193	153	0.71	1.1193	155	30.4%	0.08 [-0.14, 0.30]
Total (95% CI)			**803**			**606**	**100.0%**	**0.33 [0.11, 0.55]**

Heterogeneity: Tau² = 0.03; Chi² = 7.93, df = 2 (P = 0.02); I² = 75%
Test for overall effect: Z = 2.99 (P = 0.003)



AQLQ – Bucher

	Attach forest plots and statistical results as a separate file. *Results from the comparative analysis should be given in the table below, if possible.*							
		Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	Difference	CI	*P* value	Hazard/Odds/Risk ratio	CI	*P* value	
AQLQ	Benralzumab: (Sirocco Calima Zonda) Mepolizumab: (Chupp, Orteag Pavord)	-0.060	-0.3181 to 0.1981	0.649	NA	NA	NA	Bucher method

Conclusion:

The difference is non-significant and does not meet the goal set by Medicinrådet (0,5)

5.6 Clinical question 6: Serious adverse events (SAE)

5.6.1 Serious adverse events, full analysis set – SIROCCO

52 (13.2%) in the benralizumab 30 mg Q8W group and 55 (13.5%) in the placebo group had SAEs (including those with an outcome of death) during the on-treatment period (Appendix 10). The incidences of the most common SAEs were similar across groups, and with the exception of the preferred term (PT) of asthma, the incidence of SAEs was low (<1% in any group).

The most common SAEs by PT (frequency of ≥2 patients in any group) were asthma (24 patients [6.1%] in benralizumab 30 mg Q8W group and 31 patients [7.6%] in the placebo group).

In the post-treatment period, SAEs were reported by 6 patients (5.1%) in the benralizumab 30 mg Q8W group, and 5 (4.2%) in the placebo group. Asthma was the only SAE reported by >1 patient in any group (2 patients [1.7%] in the benralizumab 30 mg Q8W group, and 3 patients [2.5%] in the placebo group).

There were no events of anaphylactic reaction causally related to benralizumab reported in the study.

5.6.2 Serious adverse events, full analysis set – CALIMA

A lower incidence of SAEs was reported by patients in the benralizumab 30 mg Q8W group compared with the placebo group (40 patients [9.3%] vs. 60 patients [13.6%], respectively) (Appendix 10).
The most common SAEs by preferred term (PT) was asthma reported by 18 patients (4.2%) in the benralizumab 30 mg Q8W group and 23 patients (5.2%) in the placebo group. The incidences of the most common SAEs were similar across groups, and with the exception of the PT of asthma, the incidence of SAEs was low (<1% in any group).

In the post treatment period, SAEs were reported by 4 patients (4.0%) in the benralizumab 30 mg Q8W group and 6 (5.6%) in the placebo group. Asthma was the only SAE reported by >1 patient (2 patients each in the benralizumab 30 mg Q8W [2.0%] and placebo [1.9%] groups).

There were no events of anaphylactic reaction causally related to benralizumab reported in the study.

5.6.3 Serious adverse events, full analysis set – ZONDA

A lower incidence of SAEs was reported by patients in the benralizumab 30 mg Q8W group compared with the placebo group (7 patients [9.6%] and 14 patients [18.7%], respectively) (Appendix 10).

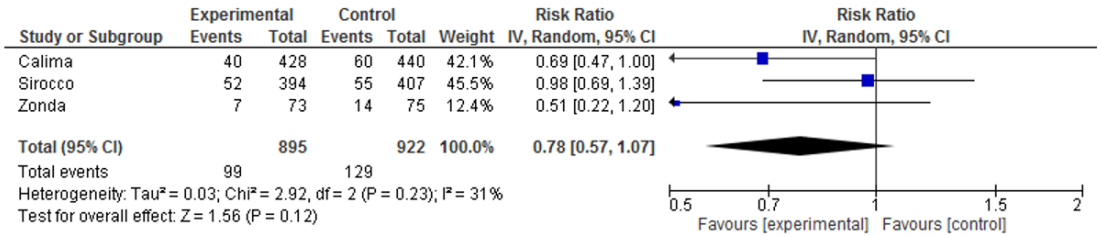
There were no events of anaphylactic reaction causally related to benralizumab reported in the study.

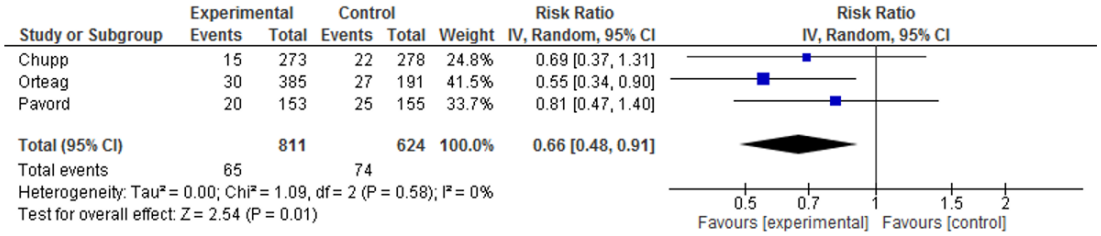
MAIC was not undertaken to assess the comparison of benralizumab vs. mepolizumab with regards to SAE.

We performed another calculation based on the below method and population. It is similar to the analysis made by Medicinrådet:

Method:
Inverse variance method with Random effect. Calculations made using Review Manager v5.3.
Populations
SAE analysis is performed on the safety population (treated patients)

SAE (safety population)





Results per outcome	*Attach forest plots and statistical results as a separate file.* *Results from the comparative analysis should be given in the table below, if possible.*							
		Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	Difference	CI	*P* value	Hazard/Odds/Risk ratio	CI	*P* value	
SAE	Benralzumab: (Sirocco Calima Zonda pooled) Mepolizumab: (Chupp Orteag Pavord pooled)	1.5%	-2.0 to 6.8%	NA	1.1818	(0.7544 to 1.8513)	0.466	Bucher method

*Method for calculation of ARR= (RR-1) * event rate for Mepolizumab (pooled from Chupp, Orteag, Pavord).*
Event rate for Mepolizumab = (15+30+20)/(273+385+153)=8.0%

Conclusion:

There is no significant difference between benralizumab and mepolizumab and the difference do not meet the 5 % criteria set by Medicinrådet. [12]

5.6.4 Anaphylactic reactions:

No anaphylactic reactions were reported in SIROCCO, CALIMA and ZONDA or in the mepolizumab studies

5.7 Clinical question 6: Discontinuation

For all patients with baseline blood eosinophils ≥300/µL included in the primary efficacy population, the proportion of patients who discontinued treatment were similar across the benralizumab 30 mg Q8W and placebo groups (10.1% and 12.0%, respectively) (Appendix 11, Table 11.).

In both the 48-week SIROCCO [1] study and the 56-week CALIMA [2] study, AEs leading to treatment discontinuation were 2% in the Q8W group and <1% in the placebo group (APPENDIX 11). The discontinuation AEs in patients receiving benralizumab were typically single events, without any apparent pattern or trend within a particular system organ class (Safety Evaluation Data D3250C00017 and D3250C00018, Section 12.3. June 2016, in house data, AstraZeneca Pharmaceuticals LP.)

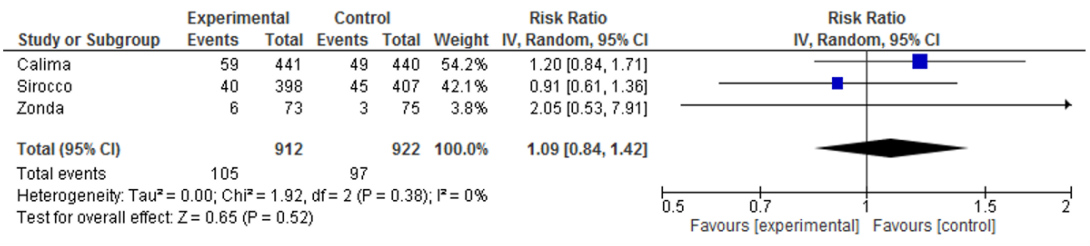
MAIC was not undertaken to assess the comparison of benralizumab vs. mepolizumab with regards to discontinuations.

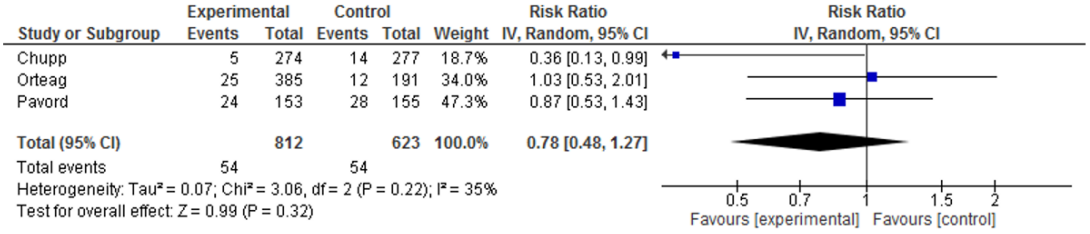
Due to this, we performed another calculation based on the below method and population. It is similar to the analysis made by Medicinrådet [12]:

Method:
Inverse variance method with Random effect. Calculations made using Review Manager v5.3.

Populations
Discontinuation analysis is performed on the FAS population.

Discontinuations (FAS)





Results per outcome	*Attach forest plots and statistical results as a separate file.* *Results from the comparative analysis should be given in the table below, if possible.*							
		Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	Difference	CI	*P* value	Hazard/Odds/Risk ratio	CI	*P* value	
Discontinuation	Benralzumab: (Sirocco Calima Zonda pooled) Mepolizumab: (Chupp Orteag Pavord pooled)	2.6	(-1.3 to 9.5)	NA	1.397	(0.804 to 2.429)	0.235	Bucher method

Method for calculation of ARR= (RR-1) * Event rate for Mepolizumab (pooled from Chupp, Orteag, Pavord).
Event rate for Mepolizumab = (5+25+24)/(274+385+153)=6.7%

Conclusion:

There is no statistical significant difference between the two treatments and the difference do not meet the 10 % difference set by Medicinrådet [12]

5.8 Clinical question 7: Sick leave

Calculated sick leave benralizumab vs. placebo

	Placebo	Benra Q8W	Absolute difference
SIROCCO	27.98	22.49	5.50
CALIMA	29.98	25.72	4.26
Pooled	28.77	24.31	4.45

The clinical trial data demonstrated a reduction in mean weekly work hours loss for patients receiving benralizumab compared to patients on SoC (Appendix 13). Weekly work hour loss was reported in terms of work hour loss due to health-related issues and due to other reasons. The sum of these, the total weekly work hour loss, was converted to mean yearly work days lost as presented above. This was calculated separately for SIROCCO and CALIMA and pooled data.

Conclusion:

The results are close to the target set by Medicinrådet (5 days) when the comparator is placebo. [12] Benralizumab and mepolizumab cannot be compared for this clinical question as no data has been reported in mepolizumab studies.

Overall conclusion:

Benralizumab compared to mepolizumab showed no significant differences across the clinical questions defined by Medicinrådet. The defined efficacy objectives (minimum differences) can be met by both benralizumab and mepolizumab vs. placebo but in the indirect comparisons most criteria's are not achieved. However, for 100 % OCS the 5 % difference was obtained

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6 References

[1] Bleecker ER, FitzGerald JM, Chanez P, Papi A, Weinstein SF, Barker P, Sproule S et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. Lancet. 2016; 388(10056):2115-2127.

Supplementary Appendix; Supplement to: Bleecker ER, FitzGerald JM, Chanez P, Papi A, Weinstein SF, Barker P, Sproule S et al., on behalf of the SIROCCO study investigators. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. Lancet 2016; published online Sept 5. http://dx.doi.org/10.1016/ S0140-6736(16)31324-1.

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Supplementary Appendix; Supplement to: FitzGerald M, Bleecker ER, Nair N, Korn S, Ohta K, Lommatzsch M et al., on behalf of the CALIMA study investigators. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomized, double-blind, placebo-controlled phase 3 trial. Lancet 2016; published online Sept 5. http://dx.doi.org/10.1016/S0140-6736(16)31322-8.

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[10] Phillippo DM, Ades AE, Dias S, Palmer S, Abrams KR, Welton NJ (2016). "NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submissions to NICE." NICE_DSU December 2016.

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7 Main characteristics of included studies

7.1.1 Study characteristics SIROCCO

Table A2: Study characteristics SIROCCO

Trial name	**A Multicentre, Randomized, Double-blind, Parallel Group, Placebo-controlled, Phase III Efficacy and Safety Study of Benralizumab (MEDI-563) Added to High-dose Inhaled Corticosteroid Plus Long-acting β2 Agonist in Patients with Uncontrolled Asthma**
NCT number	NCT01928771
Objective	The purpose of this study is to determine whether benralizumab reduces the number of asthma exacerbations in patients who remain uncontrolled on high doses of ICS-LABA. The objective was to assess the safety and efficacy of benralizumab, a monoclonal antibody against interleukin-5 receptor α that depletes eosinophils by antibody-dependent cell-mediated cytotoxicity, for patients with severe, uncontrolled asthma with eosinophilia.
Publications – title, author, journal, year	Bleecker ER, FitzGerald JM, Chanez P, Papi A, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β2-agonists (SIROCCO): a randomized, multicentre, placebo-controlled phase 3 trial. Lancet. 2016; 388:2115-2127. Includes supplementary appendix, The Lancet, 2016.
Study type and design	Allocation: Randomized; Intervention Model: Parallel Assignment; Masking: Triple (Participant, Care Provider, Investigator). A randomized, double-blind, parallel-group, placebo-controlled phase 3 study at 374 sites in 17 countries. Recruited patients (aged 12–75 years) with a physician-based diagnosis of asthma for at least 1 year and at least two exacerbations while on high-dosage inhaled corticosteroids and long-acting β2-agonists (ICS plus LABA) in the previous year. Patients were randomly assigned (1:1:1) by an interactive web-based voice response system to benralizumab 30 mg either every 4 weeks (Q4W) or every 8 weeks (Q8W; first three doses every 4 weeks apart) with placebo administered at the 4-week interim visits; hereafter referred to as the group that received benralizumab every 8 weeks, or placebo administered every 4 weeks. (all subcutaneous injection). Q4W for 48 weeks as add on to their standard treatment. Patients were stratified 2:1 according to blood eosinophil counts of at least 300 cells per µL and less than 300 cells per µL. All patients and investigators involved in patient treatment or clinical assessment were masked to treatment allocation.
Follow-up time	Data were collected from all patients at enrolment, screening, randomization (week 0), every 4-week interval during the treatment period (weeks 4–48), and follow-up (week 56, for patients not continuing in BORA [NCT02258542], an open-label extension study).
Population (inclusion and exclusion criteria)	Inclusion and exclusion criteria related to NCT number from www.clinicaltrials.gov: **Inclusion Criteria:**

	1.Written informed consent for study participation must be obtained prior to any study related procedures being performed (local regulations are to be followed in determining the assent/consent requirements for children and parent[s]/guardian[s]) and according to international guidelines and/or applicable European Union guidelines. 2.Female and Male aged 12 to 75 years inclusively, at the time of visit 1. For those patients, who are 17 on the day of Visit 1 but will turn 18 after this day, will be considered an adolescent for the purposes of this trial. 3.History of physician-diagnosed asthma requiring treatment with medium-to-high dose ICS (>250µg fluticasone dry powder formulation equivalents total daily dose) and a LABA, for at least 12 months prior to Visit 1 4.Documented treatment with ICS and LABA for at least 3 months prior to Visit 1 with or without oral corticosteroids and additional asthma controllers. ◦For subjects 18 years of age and older, the ICS dose must be >500 mcg/day fluticasone propionate dry powder formulation or equivalent daily. ◦For subjects ages 12-17, the ICS dose must be ≥500 mcg /day fluticasone propionate dry powder formulation or equivalent daily. Exclusion criteria: 1.Clinically important pulmonary disease other than asthma (e.g. active lung infection, COPD, bronchiectasis, pulmonary fibrosis, cystic fibrosis, hypoventilation syndrome associated with obesity, lung cancer, alpha 1 anti-trypsin deficiency, and primary ciliary dyskinesia) or ever been diagnosed with pulmonary or systemic disease, other than asthma, that are associated with elevated peripheral eosinophil counts (e.g. allergic bronchopulmonary aspergillosis/mycosis, Churg- Strauss syndrome, hypereosinophilic syndrome) 2.Any disorder, including, but not limited to, cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, haematological, psychiatric, or major physical impairment that is not stable in the opinion of the Investigator and could: ◦Affect the safety of the patient throughout the study ◦Influence the findings of the studies or their interpretations ◦Impede the patient's ability to complete the entire duration of study 3.Acute upper or lower respiratory infections requiring antibiotics or antiviral medication within 30 days prior to the date informed consent is obtained or during the screening/run-in period 4.Any clinically significant abnormal findings in physical examination, vital signs, haematology, clinical chemistry, or urinalysis during screening/run-in period, which in the opinion of the Investigator, may put the patient at risk because of his/her participation in the study, or may influence the results of the study, or the patient's ability to complete entire duration of the study
Intervention	1. Benralizumab 30 mg either every 4 weeks (Q4W) or 2. every 8 weeks (Q8W; first three doses every 4 weeks) or 3. placebo Q4W for 48 weeks as add on to their standard treatment. Patients with blood eosinophil counts at least 300 cells per µL and with ≥2 exacerbations in the previous year; 267 patients in the placebo group, 275 in the benralizumab 30 mg Q4W group, and 267 in the benralizumab 30 mg Q8W group. All the trial agents were provided by AstraZeneca.

Baseline characteristics	The majority of patients in the full analysis set (FAS) were White (72.6%) and female (66.1%). The mean age was 48.8 years (range: 12 to 75 years); 53 (4.4%) patients were ≥12 to <18 years (i.e., adolescents), the remaining patients were adults, of whom 143 (11.9%) were ≥65 to 75 years. The mean weight was 77.92 kg (range: 40.0 to 194.5 kg), the mean BMI was 28.78 kg/m2 (range: 14.5 to 61.7 kg/m2). In all patients in the full analysis set (FAS), mean pre-bronchodilator lung function tests at baseline showed an FEV1 of 1.665 L, a percent predicted normal FEV1 of 56.7%, and an FEV1/FVC ratio of 61. Mean percent reversibility was 25.7%. The median time since asthma diagnosis was 14.76 years. The majority of patients (62.2%) had 2 exacerbations in the last 12 months (mean [SD]: 2.9 [1.69]); 74.7% of patients had 0 exacerbations resulting in hospitalization in the last 12 months (mean [SD]: 0.4 [0.78]). At study entry, the majority of patients had never smoked (80.4%) or were former smokers (19.1%) and the mean smoking history among smokers was 5.0 pack years. The incidence of individual maintenance asthma medication use was similar across groups at baseline. Of the 1204 patients taking maintenance ICS medications at baseline; the most common individual maintenance ICS medications overall (and mean total daily dose) were fluticasone propionate (596 patients [1007.68 µg]), budesonide (454 patients [951.77 µg]), and beclametasone (145 patients [484.14 µg]). Of the 196 patients taking maintenance OCS medications at baseline; the most common individual maintenance OCS medications overall (and mean total daily dose) were prednisolone (88 patients [17.67 mg]), prednisone (63 patients [13.13 mg]), and methylprednisolone (35 patients [10.09 mg]). The ICS and OCS maintenance asthma medication use for all patients in the FAS with a baseline blood eosinophil count ≥300/µL, as well as for patients with baseline blood eosinophil counts <300/µL, were similar to individual ICS and OCS maintenance asthma medication use in the FAS overall. Symptom status at baseline was assessed by total asthma symptom score on a range from 0 (best) to 6 (worst). In the population of patients evaluated for efficacy (patients with blood eosinophil counts ≥300/µL), the mean total asthma symptom score ranged from 2.67 to 2.74 units across groups. Symptom control at baseline was assessed by ACQ-6 on a scale of 0 (totally controlled) to 6 (severely uncontrolled), with a score ≥1.5 being considered not well controlled. In patients with blood eosinophil counts ≥300/µL, mean scores for ACQ-6 at baseline ranged from 2.77 to 2.90 units across groups and most patients (range: 92.4% to 96.3%) were considered not well controlled at baseline.
Primary and secondary endpoints	The primary endpoint was annual asthma exacerbation rate ratio versus placebo, and key secondary endpoints were prebronchodilator forced expiratory volume in 1 s (FEV1) and total asthma symptom score at week 48, for patients with blood eosinophil counts of at least 300 cells per µL.
Method of analysis	All efficacy analyses were done in the intention-to-treat population; that is, all randomly assigned patients who received any study treatment, regardless of their protocol adherence and continued participation in the study. Safety analyses were

	based on the actual treatment regimen received and included all patients who received at least one dose of study drug. All analyses were done using SAS version 9.2. A data safety monitoring board and two independent adjudication committees (one for asthma-associated emergency department visits and/or hospital admissions; the other for major adverse cardiovascular events or malignancies) oversaw the study.
Subgroup analyses	-

7.1.1.1 Baseline demographics and clinical characteristics (full analysis set) – SIROCCO [1]

	All patients (n=1204)			High-dosage ICS plus LABA with baseline blood eosinophils ≥300 cells per µL (n=809)			High-dosage ICS plus LABA with baseline blood eosinophils <300 cells per µL (n=395)		
	Placebo (n=407)	Benralizumab 30 mg Q4W (n=399)	Benralizumab 30 mg Q8W (n=398)	Placebo (n=267)	Benralizumab 30 mg Q4W (n=275)	Benralizumab 30 mg Q8W (n=267)	Placebo (n=140)	Benralizumab 30 mg Q4W (n=124)	Benralizumab 30 mg Q8W (n=131)
Age (years)	48·7 (14·9)	50·1 (13·4)	47·6 (14·5)	48·6 (14·7)	49·2 (13·1)	47·6 (14·6)	49·0 (15·3)	52·0 (13·9)	47·8 (14·3)
Age group (years)									
≥12 to <18	23 (6%)	11 (3%)	19 (5%)	12 (4%)	8 (3%)	10 (4%)	11 (8%)	3 (2%)	9 (7%)
≥18 to 75	384 (94%)	388 (97%)	379 (95%)	255 (96%)	267 (97%)	257 (96%)	129 (92%)	121 (98%)	122 (93%)
Sex									
Male	138 (34%)	124 (31%)	146 (37%)	87 (33%)	102 (37%)	93 (35%)	51 (36%)	22 (18%)	53 (40%)
Female	269 (66%)	275 (69%)	252 (63%)	180 (67%)	173 (63%)	174 (65%)	89 (64%)	102 (82%)	78 (60%)
Race									
White	302 (74%)	285 (71%)	287 (72%)	191 (72%)	191 (69%)	192 (72%)	111 (79%)	94 (76%)	95 (73%)
Black or African American	16 (4%)	15 (4%)	15 (4%)	10 (4%)	11 (4%)	10 (4%)	6 (4%)	4 (3%)	5 (4%)
Asian	50 (12%)	54 (14%)	50 (13%)	36 (13%)	39 (14%)	35 (13%)	14 (10%)	15 (12%)	15 (11%)
Other*	39 (10%)	45 (11%)	46 (12%)	30 (11%)	34 (12%)	30 (11%)	9 (6%)	11 (9%)	16 (12%)
Ethnic group									
Hispanic or Latino	77 (19%)	73 (18%)	80 (20%)	57 (21%)	52 (19%)	52 (19%)	20 (14%)	21 (17%)	28 (21%)
Not Hispanic or Latino	330 (81%)	326 (82%)	318 (80%)	210 (79%)	223 (81%)	215 (81%)	120 (86%)	103 (83%)	103 (79%)
Body-mass index (kg/m²)	28·9 (7·1)	29·2 (7·1)	28·2 (6·2)	28·7 (7·0)	28·9 (6·9)	27·7 (6·1)	29·3 (7·1)	29·9 (7·3)	29·3 (6·2)
Missing data	0	2	0	0	2	0	0	0	0
Eosinophil count (cells per µL)	370 (0–2690)	390 (0–3440)	360 (0–3100)	500 (300–2690)	500 (300–3440)	500 (300–3100)	130 (0–290)	160 (0–297)	180 (0–290)
Missing data	4	4	6	3	1	4	1	3	2
Central eosinophil count (cells per µL)	350 (0–3580)	360 (0–3170)	325 (0–3110)	480 (70–2220)	470 (40–3170)	460 (10–3110)	130 (0–3580)	160 (0–760)	150 (0–460)
Missing data	12	12	16	9	6	10	3	6	6
Prebronchodilator FEV_1 (L)	1·660 (0·584)	1·655 (0·553)	1·680 (0·582)	1·654 (0·580)	1·673 (0·577)	1·660 (0·574)	1·672 (0·594)	1·615 (0·493)	1·721 (0·597)
Predicted normal (%)	56·6% (15·0)	57·4% (14·1)	56·1% (14·6)	56·4% (14·6)	56·5% (14·4)	55·5% (14·6)	57·0% (15·7)	59·4% (13·2)	57·3% (14·7)
Missing data	7	6	1	5	2	1	2	4	0
Prebronchodilator FEV_1/FVC	61 (13)	62 (12)	61 (13)	61 (13)	62 (12)	60 (13)	62 (13)	63 (12)	62 (14)
Missing data	7	6	1	5	2	1	2	4	0
Reversibility (%)	20% (−26 to 154)	18% (−7 to 136)	22% (−12 to 157)	20% (−26 to 154)	18% (−7 to 136)	21% (−10 to 157)	20% (−7 to 138)	17% (−2 to 96)	22% (−12 to 134)
Missing data	26	24	23	16	13	14	10	11	9
ACQ-6 score†	2·87 (0·94)	2·77 (0·96)	2·80 (0·88)	2·90 (0·95)	2·77 (0·95)	2·81 (0·89)	2·82 (0·93)	2·78 (1·00)	2·78 (0·85)

(Table 1 coninues on next page)

	All patients (n=1204)			High-dosage ICS plus LABA with baseline blood eosinophils ≥300 cells per µL (n=809)			High-dosage ICS plus LABA with baseline blood eosinophils <300 cells per µL (n=395)		
	Placebo (n=407)	Benralizumab 30 mg Q4W (n=399)	Benralizumab 30 mg Q8W (n=398)	Placebo (n=267)	Benralizumab 30 mg Q4W (n=275)	Benralizumab 30 mg Q8W (n=267)	Placebo (n=140)	Benralizumab 30 mg Q4W (n=124)	Benralizumab 30 mg Q8W (n=131)
(Continued from previous page)									
Time since asthma diagnosis (years)	14·2 (1·1–72·4)	15·3 (1·1–70·4)	14·4 (1·1–66·9)	13·4 (1·1–65·2)	14·9 (1·1–62·6)	14·6 (1·1–66·9)	16·8 (1·1–72·4)	17·4 (1·2–70·4)	14·0 (1·2–58·8)
Number of exacerbations in the past 12 months	3·0 (1·8)	2·9 (1·8)	2·8 (1·5)	3·1 (2·0)	3·0 (2·0)	2·8 (1·5)	2·7 (1·5)	2·7 (1·2)	2·6 (1·3)
Number resulting in ED visit	0·3 (0·8)	0·3 (1·0)	0·2 (0·8)	0·3 (0·8)	0·4 (1·0)	0·3 (0·9)	0·2 (0·8)	0·2 (0·9)	0·2 (0·6)
Patients with ≥1 exacerbations resulting in ED visit	67 (16%)	64 (16%)	53 (13%)	48 (18%)	51 (19%)	40 (15%)	19 (14%)	13 (10%)	13 (10%)
Number resulting in hospital admission	0·4 (0·8)	0·4 (0·7)	0·4 (0·8)	0·4 (0·8)	0·3 (0·7)	0·4 (0·9)	0·4 (0·8)	0·4 (0·9)	0·3 (0·8)
Patients with ≥1 exacerbations resulting in hospital admission	107 (26%)	98 (25%)	100 (25%)	67 (25%)	66 (24%)	71 (27%)	40 (29%)	32 (26%)	29 (22%)
Total asthma symptom score	2·68 (1·07)	2·72 (1·02)	2·70 (1·11)	2·74 (1·08)	2·67 (1·01)	2·68 (1·09)	2·57 (1·07)	2·84 (1·02)	2·73 (1·14)
Missing data	0	1	3	0	1	2	0	0	1
Diagnosis of allergic rhinitis	220 (54%)	207 (52%)	219 (55%)	156 (58%)	148 (54%)	150 (56%)	64 (46%)	59 (48%)	69 (53%)
Nasal polyps	79 (19%)	84 (21%)	74 (19%)	62 (23%)	66 (24%)	62 (23%)	17 (12%)	18 (15%)	12 (9%)
Atopic (based on Phadiatop test)	230 (57%)	231 (58%)	244 (61%)	152 (57%)	156 (57%)	169 (63%)	78 (56%)	75 (60%)	75 (57%)
History of omalizumab treatment	31 (8%)	29 (7%)	28 (7%)	22 (8%)	16 (6%)	18 (7%)	9 (6%)	13 (10%)	10 (8%)
Missing data	3	1	1	2	1	1	1	0	0
AQLQ(S)+12 score‡	3·90 (1·02)	3·93 (0·98)	3·94 (1·00)	3·87 (0·99)	3·93 (1·00)	3·93 (0·97)	3·97 (1·07)	3·92 (0·95)	3·97 (1·04)
Missing data	15	17	17	12	12	12	3	5	5
Smoker	5 (1%)	0	1 (<1%)	1 (<1%)	0	1 (<1%)	4 (3%)	0	0
Nicotine pack-years	5·0 (0–9)	5·0 (0–9)	5·0 (0–9)	5·0 (0–9)	6·0 (0–9)	5·0 (0–9)	5·0 (0–9)	5·0 (1–9)	5·0 (0–9)

Data are mean (SD), number (%), or median (range). Some percentages do not add up to 100 because of rounding. ICS=inhaled corticosteroids. LABA=long-acting β_2-agonsists. Q4W=every 4 weeks. Q8W=every 8 weeks (first three doses Q4W). ACQ-6=Asthma Control Questionnaire, six-question version. AQLQ(S)+12=Standardised Asthma Quality of Life Questionnaire for 12 years and older. ED=emergency department. FEV_1=forced expiratory volume in 1 s. FVC=forced vital capacity. *Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, or other. †Low numbers represent better symptom control. ‡High numbers suggest better quality of life. §Current smoker or former smoker with a smoking history of ≥10 packs per year.

Table 1: **Baseline demographics and clinical characteristics (full analysis set)**

7.1.2 Study characteristics CALIMA

Table A2: Study characteristics CALIMA

Trial name	**A Multicenter, Randomized, Double-blind, Parallel Group, Placebocontrolled, Phase 3 Study to Evaluate the Efficacy and Safety of Benralizumab in Asthmatic Adults and Adolescents Inadequately Controlled on Inhaled Corticosteroid Plus Long-acting β2 Agonist (CALIMA)**
NCT number	NCT01914757
Objective	The purpose of this study is to determine whether Benralizumab reduces the exacerbation rate in patients with a history of asthma exacerbations and uncontrolled asthma receiving ICS-LABA with or without oral corticosteroids and additional asthma controllers. The objective was to access the efficacy and safety of benralizumab as add-on therapy for patients with severe, uncontrolled asthma and elevated blood eosinophil counts.
Publications – title, author, journal, year	FitzGerald JM, Bleecker ER, Nair P, et al. Benralizumab, an anti–interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2016; 388:2128-2141. Includes supplementary appendix, The Lancet, 2016.
Study type and design	A randomized, double-blind, parallel-group, placebo-controlled, phase 3 study undertaken at 303 sites in 11 countries, enrolled patients aged 12–75 years with severe asthma uncontrolled by medium dosage to high-dosage inhaled corticosteroids plus long-acting β_2-agonists (ICS plus LABA) and a history of two or more exacerbations in the previous year. Patients were randomly assigned (1:1:1) to receive 56 weeks of benralizumab 30 mg every 4 weeks (Q4W), benralizumab 30 mg every 8 weeks (Q8W; first three doses 4 weeks apart), or placebo (all subcutaneous injection). Patients were stratified (2:1) by baseline blood eosinophil counts 300 cells per µL or greater and less than 300 cells per µL, respectively. Patients and study centre staff were masked to treatment allocation. Patients were randomly assigned (1:1:1) by an interactive web-based voice response system to benralizumab 30 mg either every 4 weeks (Q4W) or every 8 weeks (Q8W; first three doses every 4 weeks apart) with placebo administered at the 4-week interim visits; hereafter referred to as the group that received benralizumab every 8 weeks, or placebo administered every 4 weeks. (all subcutaneous injection). Q4W for 48 weeks as add on to their standard treatment.
Follow-up time	Data were collected from all patients at enrolment, screening, randomization (week 0), 4-weekly intervals during the treatment period (weeks 4–56), and follow-up (week 60).
Population (inclusion and exclusion criteria)	Inclusion and exclusion criteria related to NCT number from www.clinicaltrials.gov: **Inclusion criteria:** 1.Provision of informed consent prior to any study specific procedures 2.Female and male aged 12 to 75 years, inclusively, at the time of Visit 1 3.History of physician-diagnosed asthma requiring treatment with medium-to-high dose ICS (>250µg fluticasone dry powder formulation equivalents total daily dose) and a LABA, for at least 12 months prior to Visit 1. 4.Documented treatment with ICS and LABA for at least 3 months prior to Visit 1 with or without oral corticosteroids and additional asthma controllers. The ICS and LABA can be parts of a combination product or given by separate inhalers. The ICS dose must be greater than or equal to 500 µg/day fluticasone propionate dry powder formulation or equivalent daily. For ICS/LABA combination preparations, the mid-strength approved maintenance dose in the local country will meet this ICS criterion.

	Exclusion criteria: 1.Clinically important pulmonary disease other than asthma (e.g. active lung infection, COPD, bronchiectasis, pulmonary fibrosis, cystic fibrosis, hypoventilation syndrome associated with obesity, lung cancer, alpha 1 anti-trypsin deficiency, and primary ciliary dyskinesia) or ever been diagnosed with pulmonary or systemic disease, other than asthma, that are associated with elevated peripheral eosinophil counts (e.g. allergic bronchopulmonary aspergillosis/mycosis, Churg- Strauss syndrome, hypereosinophilic syndrome) 2.Any disorder, including, but not limited to, cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, haematological, psychiatric, or major physical impairment that is not stable in the opinion of the Investigator and could: ◦Affect the safety of the patient throughout the study ◦Influence the findings of the studies or their interpretations ◦Impede the patient's ability to complete the entire duration of study 3.Acute upper or lower respiratory infections requiring antibiotics or antiviral medication within 30 days prior to the date informed consent is obtained or during the screening/run-in period 4.Any clinically significant abnormal findings in physical examination, vital signs, hematology, clinical chemistry, or urinalysis during screening/run-in period, which in the opinion of the Investigator, may put the patient at risk because of his/her participation in the study, or may influence the results of the study, or the patient's ability to complete entire duration of the study
Intervention	1306 were randomized. All randomized patients received study treatment: 425 patients were randomly assigned to and received benralizumab 30 mg Q4W, 441 patients to benralizumab 30 mg Q8W, and 440 patients to placebo. All 1306 patients randomized were included in the full analysis set and safety analysis set. Within the full analysis set, 728 patients were receiving high-dosage inhaled corticosteroids plus LABA and had baseline blood eosinophil counts ≥300 cells per µL and were eligible for the primary efficacy analysis: 241 patients in the benralizumab Q4W group, 239 patients in the benralizumab Q8W group, and 248 patients in the placebo group. All the trial agents were provided by AstraZeneca.
Baseline characteristics	The majority of patients in the full analysis set (FAS) were White (84.3%) and female (61.8%). The mean age was 49.2 years (range: 12 to 75 years); 55 (4.2%) patients were ≥12 to <18 years (i.e., adolescents), the remaining patients were adults, of whom 177 (13.6%) were ≥65 to 75 years. The mean weight was 79.11 kg (range: 41.0 to 204.4 kg), the mean BMI was 28.77 kg/m2 (range: 15.9 to 79.9 kg/m2). In all patients in the FAS, mean pre-bronchodilator lung function tests at baseline showed an FEV1 of 1.762 L, a percent predicted normal FEV1 of 58.3%, and an FEV1/FVC ratio of 61. Mean percent reversibility was 26.7%. All patients in this study had asthma and the median time since asthma diagnosis was 16.11 years. The majority of patients (65.5%) had 2 exacerbations in the last 12 months (mean [SD]: 2.7 [1.65]); 83.5% of patients had 0 exacerbations resulting in hospitalization in the last 12 months (mean [SD]: 0.3 [0.66]). At study entry, the majority of patients had never smoked (78.3%) or were former smokers (21.4%) and the mean smoking history among smokers was 4.7 pack years. In the FAS, 1304 (99.8%) patients were taking ICS and 1300 (99.5%) patients were taking LABA. A total of 1123 (86.0%) patients were taking their ICS/LABA as a fixed dose combination device, with the remainder of the patients taking ICS and LABA in separate inhalers. A total of 122 (9.3%) patients were taking OCS.

	The incidence of individual maintenance asthma medication use was similar across groups at baseline. Of the 1304 patients taking maintenance ICS medications at baseline; the most common individual maintenance ICS medications overall (and mean total daily dose) were fluticasone propionate (721 patients [895.94 µg]), budesonide (401 patients [889.88 µg]), and ciclisonide (154 patients [635.32 µg]). Of the 120 patients taking maintenance OCS medications at baseline; the most common individual maintenance OCS medications overall (and mean total daily dose) were prednisone (46 patients [12.01 mg]), prednisolone (37 patients [11.59 mg]), and methylprednisolone (28 patients [7.21 mg]). The incidence of individual ICS and OCS maintenance asthma medication use for all patients in the FAS with a baseline blood eosinophil count ≥300/µL who were taking high-dose ICS, as well as for patients with baseline blood eosinophil counts ≥300/µL and <300/µL, were similar to individual ICS and OCS maintenance asthma medication use in the FAS overall. Symptom status at baseline was assessed by total asthma symptom score on a range from 0 (best) to 6 (worst). In the population of patients evaluated for efficacy (patients with blood eosinophil counts ≥300/µL), the mean total asthma symptom score ranged from 2.69 to 2.76 units across groups. Symptom control at baseline was assessed by ACQ 6 on a scale of 0 (totally controlled) to 6 (severely uncontrolled), with a score ≥1.5 being considered not well controlled. In patients with blood eosinophil counts ≥300/µL, mean scores for ACQ-6 at baseline ranged from 2.70 to 2.80 units across groups and most patients (range: 93.3% to 94.8%) were considered not well controlled at baseline.
Primary and secondary endpoints	The primary endpoint was annual exacerbation rate ratio versus placebo for patients receiving high-dosage ICS plus LABA with baseline blood eosinophils 300 cells per µL or greater (intention-to-treat analysis). Key secondary endpoints were pre-bronchodilator forced expiratory volume in 1 s (FEV1) and total asthma symptom score.
Method of analyzis	All efficacy analyses were done using an intention-to-treat approach based on the full analysis set. The full analysis set considered patients according to their assigned treatment regimen and included all randomized patients who received any study treatment, regardless of their protocol adherence and continued participation in the study. The safety analysis set considered patients based on the actual treatment regimen they received and included all patients who received at least one dose of study treatment. All data were analyzed with SAS System version 9.2 (SAS Institute Inc, Cary, NC, USA). The study was overseen by an independent drug safety monitoring board, and two adjudication committees (asthma adjudication, and MACE and malignancy adjudication)
Subgroup analyses	-

7.1.2.1 Baseline demographics and clinical characteristics (full analysis set) – CALIMA [2]

	All patients (n=1306)			High-dosage ICS plus LABA with baseline blood eosinophils ≥300 cells per µL (n=728)			High-dosage ICS plus LABA with baseline blood eosinophils <300 cells per µL (n=363)		
	Placebo (n=440)	Benralizumab 30 mg Q4W (n=425)	Benralizumab 30 mg Q8W (n=441)	Placebo (n=248)	Benralizumab 30 mg Q4W (n=241)	Benralizumab 30 mg Q8W (n=239)	Placebo (n=122)	Benralizumab 30 mg Q4W (n=116)	Benralizumab 30 mg Q8W (n=125)
Age (years)	48·8 (15·1)	50·0 (13·6)	49·0 (14·3)	48·5 (14·1)	50·1 (13·1)	49·6 (13·0)	52·4 (14·4)	51·9 (12·2)	51·1 (13·8)
Age group (years)									
≥12 to <18	23 (5%)	11 (3%)	21 (5%)	7 (3%)	3 (1%)	6 (3%)	5 (4%)	1 (<1%)	4 (3%)
≥18 to 75	417 (95%)	414 (97%)	420 (95%)	241 (97%)	238 (99%)	233 (97%)	117 (96%)	115 (99%)	121 (97%)
Sex									
Male	176 (40%)	155 (36%)	168 (38%)	103 (42%)	82 (34%)	101 (42%)	46 (38%)	45 (39%)	38 (30%)
Female	264 (60%)	270 (64%)	273 (62%)	145 (58%)	159 (66%)	138 (58%)	76 (62%)	71 (61%)	87 (70%)
Race									
White	372 (85%)	360 (85%)	369 (84%)	213 (86%)	209 (87%)	203 (85%)	108 (89%)	99 (85%)	107 (86%)
Black or African American	14 (3%)	10 (2%)	15 (3%)	8 (3%)	5 (2%)	8 (3%)	4 (3%)	3 (3%)	5 (4%)
Asian	53 (12%)	55 (13%)	55 (12%)	27 (11%)	27 (11%)	28 (12%)	10 (8%)	14 (12%)	12 (10%)
Other*	1 (<1%)	0	2 (<1%)	0	0	0	0	0	1 (<1%)
Ethnic group									
Hispanic or Latino	92 (21%)	104 (24%)	104 (24%)	52 (21%)	56 (23%)	52 (22%)	22 (18%)	26 (22%)	27 (22%)
Not Hispanic or Latino	348 (79%)	321 (76%)	337 (76%)	196 (79%)	185 (77%)	187 (78%)	100 (82%)	90 (78%)	98 (78%)
Body-mass index (kg/m²)†	28·9 (6·5)	28·7 (6·8)	28·8 (6·5)	29·0 (6·1)	29·1 (7·3)	28·6 (6·1)	29·7 (7·4)	28·8 (6·5)	29·8 (7·2)
Missing data	1	0	0	0	0	0	1	0	0
Local eosinophil count (cells per µL)†	371 (0–4494)	370 (20–2420)	400 (0–2600)	510 (300–4494)	500 (300–2420)	500 (300–2600)	190 (0–298)	160 (20–293)	180 (0–295)
Missing data	7	7	6	1	4	3	2	0	2
Central eosinophil count (cells per µL)†	370 (0–4150)	350 (0–2800)	350 (0–2260)	490 (30–4150)	470 (0–2800)	475 (10–2260)	170 (0–700)	150 (10–880)	140 (0–440)
Missing data	11	9	9	8	4	5	3	5	2
Prebronchodilator FEV_1 (L)†	1·771 (0·645)	1·757 (0·602)	1·759 (0·641)	1·815 0·648)	1·75 (0·570)	1·758 (0·622)	1·639 (0·615)	1·717 (0·626)	1·665 (0·616)
Missing data	6	5	1	3	2	0	3	2	1
Prebronchodilator FEV_1 (% predicted normal)†	58·0% (14·9)	58·9% (14·8)	57·9% (14·9)	58·2% (13·9)	59·1% (13·7)	57·0% (14·2)	56·1% (16·3)	57·4% (16·2)	56·7% (15·2)
Missing data	6	5	1	3	2	0	3	2	1
FEV_1/FVC prebronchodilator†	61 (13)	61 (12)	60 (13)	60 (12)	61 (12)	60 (13)	60 (13)	59 (13)	60 (14)
Missing data	6	5	1	3	2	0	3	2	1
Reversibility (%)†	20% (–18 to 814)	20% (–24 to 809)	20% (–13 to 171)	20% (–9 to 133)	20% (–24 to 124)	20% (–13 to 171)	18% (–18 to 814)	21% (–9 to 809)	18% (–10 to 154)
Missing data	13	15	8	5	6	3	7	6	4
ACQ-6 score‡	2·69 (0·92)	2·69 (0·91)	2·75 (0·93)	2·75 (0·94)	2·70 (0·91)	2·80 (0·95)	2·68 (0·89)	2·82 (0·89)	2·87 (0·96)
Time since asthma diagnosis (years)	16·2 (1·2–69·9)	15·8 (1·2–69·2)	16·8 (1·1–64·6)	17·0 (1·3–69·9)	15·6 (1·3–66·2)	16·1 (1·2–58·2)	16·3 (1·2–64·9)	15·0 (1·5–69·2)	18·3 (1·1–64·6)

(Table 1 continues on next page)

	All patients (n=1306)			High-dosage ICS plus LABA with baseline blood eosinophils ≥300 cells per µL (n=728)			High-dosage ICS plus LABA with baseline blood eosinophils <300 cells per µL (n=363)		
	Placebo (n=440)	Benralizumab 30 mg Q4W (n=425)	Benralizumab 30 mg Q8W (n=441)	Placebo (n=248)	Benralizumab 30 mg Q4W (n=241)	Benralizumab 30 mg Q8W (n=239)	Placebo (n=122)	Benralizumab 30 mg Q4W (n=116)	Benralizumab 30 mg Q8W (n=125)
(Continued from previous page)									
Number of exacerbations in the past 12 months	2·7 (1·6)	2·7 (1·9)	2·7 (1·4)	2·8 (1·7)	2·8 (1·7)	2·7 (1·3)	2·7 (1·9)	2·6 (1·6)	2·7 (1·7)
Number resulting in emergency department visit	0·3 (1·2)	0·3 (0·8)	0·2 (0·7)	0·4 (1·4)	0·3 (0·9)	0·2 (0·6)	0·2 (0·8)	0·2 (0·5)	0·2 (0·6)
Patients with ≥1 exacerbations resulting in emergency department visit	62 (14%)	60 (14%)	56 (13%)	36 (15%)	35 (15%)	31 (13%)	18 (15%)	15 (13%)	13 (10%)
Number resulting in hospital admission	0·3 (0·8)	0·2 (0·5)	0·3 (0·7)	0·3 (0·7)	0·2 (0·5)	0·3 (0·6)	0·3 (1·0)	0·3 (0·6)	0·2 (0·6)
Patients with ≥1 exacerbations resulting in hospital admission	72 (16%)	65 (15%)	78 (18%)	44 (18%)	42 (17%)	43 (18%)	21 (17%)	20 (17%)	18 (14%)
Total asthma symptom score†	2·71 (1·04)	2·73 (1·02)	2·79 (1·06)	2·71 (1·06)	2·69 (0·98)	2·76 (1·06)	2·69 (1·02)	2·81 (1·09)	2·87 (1·06)
Missing data	1	1	2	1	0	1	0	1	1
Diagnosis of allergic rhinitis	248 (56%)	242 (57%)	227 (51%)	147 (59%)	136 (56%)	125 (52%)	59 (48%)	68 (59%)	58 (46%)
Nasal polyps	73 (17%)	59 (14%)	65 (15%)	55 (22%)	40 (17%)	53 (22%)	12 (10%)	12 (10%)	8 (6%)
Atopic (based on Phadiatop test)	286 (65%)	264 (62%)	278 (63%)	164 (66%)	151 (63%)	149 (62%)	69 (57%)	62 (53%)	75 (60%)
History of omalizumab treatment†	14 (3%)	12 (3%)	12 (3%)	9 (4%)	7 (3%)	7 (3%)	5 (4%)	4 (3%)	3 (2%)
Missing data	1	1	3	0	0	2	1	1	1
AQLQ(S)+12 score†§	3·96 (1·03)	3·98 (0·96)	3·85 (1·02)	3·93 (1·04)	3·99 (0·98)	3·87 (1·05)	4·03 (1·01)	3·95 (0·93)	3·82 (0·97)
Missing data	13	13	13	8	7	7	2	4	2
Smoking history									
Never	349 (79%)	325 (76%)	348 (79%)	203 (82%)	175 (73%)	185 (77%)	89 (73%)	91 (78%)	99 (79%)
Current	2 (<1%)	0	3 (<1%)	1 (<1%)	0	1 (<1%)	0	0	1 (<1%)
Former	89 (20%)	100 (24%)	90 (20%)	44 (18%)	66 (27%)	53 (22%)	33 (27%)	25 (22%)	25 (20%)
Smoking pack year (years)¶	5 (0–9)	5 (0–9)	5 (0–45)	4 (0–9)	5 (0–9)	4·5 (0–45)	5 (0–9)	5 (0–9)	5 (0–9)

Data are mean (SD), median (range), or n (%). ACQ-6=Asthma Control Questionnaire-6. AQLQ(S)+12=Standardised Asthma Quality of Life Questionnaire for 12 years and older. FEV_1=forced expiratory volume in 1 s. FVC=forced vital capacity. ICS=inhaled corticosteroids. LABA=long-acting β_2-agonist. Q4W=once every 4 weeks. Q8W=once every 8 weeks (first three doses Q4W). *Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, and other. †Data not available for all randomised patients. ‡The ACQ-6 is a 6-item questionnaire to assess daytime and night-time symptoms and rescue β_2-agonist use on a 0–6 scale (low numbers represent better control). §The AQLQ(S)+12 is a 32-item questionnaire to assess asthma-related quality of life scored on a 1–7 scale (greater numbers indicate better quality of life). ¶For current and former smokers.

Table 1: **Baseline demographics and clinical characteristics (full analysis set)**

7.1.3 Study characteristics ZONDA

Table A2: Study characteristics ZONDA

Trial name	**A Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled, Phase 3 Efficacy and Safety Study of Benralizumab (MEDI-563) to Reduce Oral Corticosteroid Use in Patients with Uncontrolled Asthma on High Dose Inhaled Corticosteroid Plus Long-acting β2 Agonist and Chronic Oral Corticosteroid Therapy (ZONDA)**
NCT number	NCT02075255
Objective	The purpose of this trial is to confirm if benralizumab can reduce the use of maintenance OCS in systemic corticosteroid dependent patients with severe refractory asthma with elevated eosinophils while asthma control was maintained.
Publications – title, author, journal, year	Nair P, Wenzel S, Rabe KF, Bourdin A, et al., Oral Glucocorticoid–Sparing Effect of Benralizumab in Severe Asthma. The New England Journal of Medicine. 2017; 376, 25: 2448-2458.
Study type and design	This randomized, double-blind, parallel-group, placebo-controlled trial comprised an enrollment visit, a run-in phase that included optimization of the oral glucocorticoid dose, a randomized intervention period, and a follow-up visit. The intervention period consisted of the following: an induction phase, during which patients continued receiving their oral glucocorticoid dose as established during the run-in phase; a dose reduction phase, during which the oral glucocorticoid dose was reduced at regular intervals provided asthma control was maintained; and a dose-maintenance phase, during which the oral glucocorticoid dose was maintained or, in patients in whom oral glucocorticoid therapy was discontinued, no further oral glucocorticoids were received. Patients underwent randomization in a 1:1:1 ratio, with the use of an interactive Web- or voice response system, and were stratified according to eosinophil count (≥150 to <300 cells per cubic millimeter vs. ≥300 cells per cubic millimeter) and country. Investigators and patients were unaware of the trial-group assignments. Patients continued their prescribed high-dose inhaled glucocorticoid and LABA therapies, as well as any other asthma-controller medications aside from oral glucocorticoid therapy (including leukotriene modifiers, long-acting muscarinic antagonists, and theophylline), in an unchanged fashion throughout the trial. Short-acting β2-agonists were permitted as rescue medications.
Follow-up time	A Follow up Visit was conducted at Week 36 (Visit 15) unless the patient decided to continue into a separate extension study.
Population (inclusion and exclusion criteria)	Inclusion and exclusion criteria related to NCT number from www.clinicaltrials.gov: **Inclusion Criteria**: 1.Provision of informed consent prior to any study specific procedures. 2.Female and male aged from 18 to 75 years, inclusively. 3.History of physician-diagnosed asthma requiring treatment with medium dose ICS and LABA. 4.Elevated level of peripheral blood eosinophil 5.Documented treatment with high-dose ICS and LABA for at least 6 months prior to Visit 1

	6.Chronic oral corticosteroid therapy for at least 6 continuous months directly preceding Visit 1. Subjects must be on doses equivalent to 7.5 - 40 mg/day of prednisolone/prednisone at Visit 1 and be on a stable dose for at least 2 weeks prior to randomization. Patients must agree to switch to study required prednisone/prednisolone as their oral corticosteroid for the duration of the study. 7.Patients with documented failures of OCS reduction within 6 months prior to Visit 1 will not be required to proceed through the dose optimization phase during run-in. 8.Morning pre-bronchodilator (Pre-BD) FEV1 of <80% predicted 9.Evidence of asthma as documented by either: Airway reversibility (FEV1 ≥12% and 200 mL) demonstrated at Visit 1, Visit 2, or Visit 3 using the Maximum Post-bronchodilator Procedure OR Documented reversibility in the previous 24 months prior to Visit 1 OR Airway hyperresponsiveness (PC20 FEV1 methacholine concentration ≤8mg/mL) documented in the previous 12 months prior to planned date of randomization OR Airflow variability in clinic FEV1 ≥20% between 2 consecutive clinic visits documented in the 12 months prior to the planned date of randomization (FEV1 recorded during an exacerbation should not be considered for this criterion). All patients must have reversibility testing performed before randomization to establish a baseline characteristic. If patients do not demonstrate airway reversibility at either Visit 1 or Visit 2 and this is needed to qualify the patient for randomization, the site should reiterate the need to withhold short- and long-acting bronchodilators prior to Visit 3 in an effort to meet this inclusion criterion. 10.At least 1 documented asthma exacerbation in the previous 12 months prior to the date informed consent is obtained 11.Optimized OCS dose reached at least 2 weeks prior to randomization 12.Additional asthma controller medication must not have been initiated during run in/optimization period (not applicable for management of exacerbations during screening/ run in optimization phase) 13.At least 70% compliance with OCS use 14.At least 70% compliance with usual asthma controller ICS-LABA 15.Minimum 70% (i.e. 10 of 14 days) compliance with asthma daily diary (morning and evening diary) **Exclusion criteria**: 1.Clinically important pulmonary disease other than asthma or ever been diagnosed with pulmonary or systemic disease, other than asthma, that are associated with elevated peripheral eosinophil counts. 2.Any disorder, including, but not limited to, cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, hematological, psychiatric, or major physical impairment that is not stable in the opinion of the Investigator and could: ◦Affect the safety of the patient throughout the study ◦Influence the findings of the studies or their interpretations

	◦Impede the patient's ability to complete the entire duration of study 3.Acute upper or lower respiratory infections requiring antibiotics or antiviral medication within 30 days prior to the date informed consent is obtained or during the screening/run-in period 4.Any clinically significant abnormal findings in physical examination, vital signs, hematology, clinical chemistry, or urinalysis during run-in/optimization period, which in the opinion of the Investigator, may put the patient at risk because of his/her participation in the study, or may influence the results of the study, or the patient's ability to complete entire duration of the study 5.History of life-threatening asthma 6.Asthma control reached at an OCS dose of ≤5mg during run-in/OCS optimization phase 7.Qualifies for 3 consecutive dose reductions at Visits 2-4 and continues to meet OCS dose reduction criteria at Visit 5 8.Receipt of oral corticosteroids, other than prednisone or prednisolone, as the maintenance oral steroid controller for asthma symptoms from Visit 1 and throughout the study. 9.Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level ≥2.5 times the upper limit of normal (ULN) confirmed during screening period
Intervention	220 patients underwent randomization and started the intervention phase. 75 patients in placebo group, 73 patients in 30 mg Q8W group and 72 patients in 30 mg Q4W group. Patients received subcutaneous injections of benralizumab at a dose of 30 mg every 4 weeks, benralizumab at a dose of 30 mg administered every 4 weeks for the first three doses and then every 8 weeks (with placebo administered at the 4-week interim visits; hereafter referred to as the group that received benralizumab every 8 weeks), or placebo administered every 4 weeks. All the trial agents were provided by AstraZeneca.
Baseline characteristics	The majority of patients in the full analysis set (FAS) were White (93.2%) and female (61.4%). The mean age was 51.0 years (range: 20 to 75 years). The mean weight was 83.12 kg (range: 47.0 to 155.2 kg), and the mean BMI was 29.58 kg/m2 (range: 18.6 to 55.2 kg/m2). Lung function at baseline was similar across groups. Mean pre-bronchodilator lung function tests at baseline showed an FEV1 of 1.846 L, a percent predicted normal FEV1 of 59.5%, and an FEV1/forced vital capacity (FVC) ratio of 60. Mean percent reversibility was 24.1%. The median time since asthma diagnosis was 12.18 years. The majority of patients had 1 (31.4%) or 2 (29.1%) exacerbations in the last 12 months (mean [SD]: 2.8 [2.25]). The majority of patients (71.8%) had 0 exacerbations resulting in hospitalization in the last 12 months (mean [SD]: 0.4 [0.96]). At study entry, no patients were current smokers, and the majority of patients had never smoked (79.1%). Of the patients who were former smokers, the mean smoking history was 5.5 pack years. The maintenance asthma medication use at baseline was similar across groups. All patients were taking ICS and LABA, whether separately or in combination, per inclusion criterion. The majority of patients (89.5%) were taking their ICS/LABA as a fixed dose combination device, with the remainder of the patients taking ICS and LABA in separate inhalers. All patients (220) were taking OCS at study entry. The mean and median OCS doses at study entry were 15.3 mg and 10.0 mg, respectively, and the mean and median optimized (baseline) OCS doses were 14.7 mg and 10.0 mg, respectively. These results were similar across groups.

	Symptom status at baseline was assessed by total asthma symptom score on a range from 0 (best) to 6 (worst). In the population of patients evaluated for efficacy full analysis set (FAS), the mean total asthma symptom score at baseline ranged from 2.34 to 2.47 units across groups. Symptom control at baseline was assessed by ACQ 6 on a scale of 0 (totally controlled) to 6 (severely uncontrolled), with a score ≥1.5 being considered not well controlled. For the FAS, mean scores for ACQ 6 at baseline ranged from 2.42 to 2.68 across groups, and most patients (range: 80.6% to 93.3%) were considered not well controlled at baseline.
Primary and secondary endpoints	The primary end point was the percentage reduction in the oral glucocorticoid dose from baseline (randomization at week 0) to the final dose at the end of the maintenance phase (week 28) while asthma control was maintained. Secondary end points included the percentages of patients who had a reduction in the average daily oral glucocorticoid dose of 25% or more, of 50% or more, or of 100% (discontinuation of oral glucocorticoid therapy) from baseline to end of the maintenance phase and the percentage of patients with an average final oral glucocorticoid dose of 5.0 mg or less per day while asthma control was maintained.
Method of analysis	For the primary end point, benralizumab was compared with placebo by means of a Wilcoxon rank-sum test. To control the overall type I error rate, we accounted for multiple comparisons by means of the Hochberg procedure. A sensitivity analysis for the assessment of the primary end point was conducted with a proportional-odds model, with controls for trial group, geographic region, and baseline oral glucocorticoid dose. A Cochran–Mantel–Haenszel test was used, with adjustment for geographic region, to analyze secondary end points regarding reductions in the oral glucocorticoid dose. A negative binomial model, with adjustment for trial group, geographic region, and number of exacerbations in the previous year, with an offset term of the logarithm of the follow-up time was used to calculate annual exacerbation rates in the trial groups. Treatment effects were described with the use of rate ratios.
Subgroup analyses	Additional subgroup populations (I. patients with ≥2 exacerbations in the previous year and baseline blood eosinophil counts ≥150 cells/µL, and II. patients with ≥3 exacerbations in the previous year and baseline blood eosinophil counts ≥300 cells/µL) are presented in the appendices.

7.1.3.1 Baseline demographics and clinical characteristics (full analysis set) – ZONDA [3]

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Placebo (N=75)	Benralizumab, Every 4 Wk (N=72)	Benralizumab, Every 8 Wk (N=73)
Age — yr	49.9±11.7	50.2±12.0	52.9±10.1
Female sex — no. (%)	48 (64)	40 (56)	47 (64)
Body-mass index†	28.7±5.2	29.8±6.8	30.2±6.5
Median smoking history (range) — pack-yr	6.0 (1 to 9)	5.5 (2 to 9)	5.0 (1 to 8)
Median time since asthma diagnosis (range) — yr	10.5 (1.1 to 54.5)	13.3 (1.2 to 52.3)	16.3 (1.3 to 53.0)
Median oral glucocorticoid dose (range) — mg/day			
At trial entry‡	10.0 (7.5 to 40.0)	10.0 (7.5 to 40.0)	10.0 (7.5 to 40.0)
At end of run-in phase	10.0 (7.5 to 40.0)	10.0 (7.5 to 40.0)	10.0 (7.5 to 40.0)
Mean inhaled glucocorticoid dose (range) — μg/day	1232 (250 to 5000)	1033 (250 to 3750)	1192 (100 to 3250)
Leukotriene-receptor antagonist — no. (%)	25 (33)	28 (39)	29 (40)
No. of exacerbations in previous 12 mo	2.5±1.8	2.8±2.0	3.1±2.8
FEV_1 before bronchodilation			
Value — liters	1.931±0.662	1.850±0.741	1.754±0.635
Percent of predicted normal value	62.0±16.5	57.4±18.0	59.0±17.9
FEV_1:FVC ratio before bronchodilation — %	62±13	59±13	59±12
Median percent reversibility of FEV_1 (range)§	16.4 (–5.4 to 93.4)	18.2 (–3.0 to 126.0)	22.6 (–3.4 to 88.0)
Total asthma symptom score¶	2.4±1.0	2.5±1.0	2.3±1.1
ACQ-6 score‖	2.7±1.0	2.6±1.1	2.4±1.2
AQLQ(S)+12 score**	4.1±1.1	4.2±1.1	4.4±1.2
Blood eosinophil count			
Median count (range) — cells/mm^3††	535 (160 to 4550)	462 (160 to 1740)	437 (154 to 2140)
Distribution — no. (%)			
≥150 to <300 cells/mm^3	11 (15)	10 (14)	12 (16)
≥300 cells/mm^3	64 (85)	62 (86)	61 (84)

* Plus–minus values are means ±SD. Patients were randomly assigned to receive benralizumab either every 4 weeks or every 4 weeks for the first three doses and then every 8 weeks (with placebo administered at the 4-week interim visits; referred to as the group that received benralizumab every 8 weeks), or placebo. Data on the demographic characteristics of the patients, lung-function variables after bronchodilation, asthma (including smoking) history, and local blood eosinophil counts were collected at visit 1, which occurred 10 weeks before the induction phase began. Data on other clinical characteristics were collected at multiple time points from visit 1 to visit 6 (the start of the induction phase). The last recorded value before randomization served as the baseline measurement. Details about the characteristics at baseline are provided in Table S3 in the Supplementary Appendix. FEV_1 denotes forced expiratory volume in 1 second, and FVC forced vital capacity.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ Patients who were taking an oral glucocorticoid other than prednisone or prednisolone at enrollment were switched to an equivalent dose of prednisone or prednisolone at trial entry.

§ The percentage reversibility of the FEV_1 was calculated with the use of FEV_1 values obtained before and after bronchodilation at baseline as follows: ([postbronchodilation FEV_1 – prebronchodilation FEV_1] ÷ prebronchodilation FEV_1) × 100.

¶ The total asthma symptom score is a composite of morning assessments of asthma symptoms, nighttime awakenings, and rescue medication use and an evening assessment of activity impairment. Scores range from 0 to 6, and higher scores indicate a greater symptom burden.

‖ The Asthma Control Questionnaire 6 (ACQ-6)[17] is a six-item questionnaire to assess daytime and nighttime symptoms and rescue use of short-term β_2-agonists. Scores range from 0 to 6, and lower scores indicate better control. Score changes of 0.5 or more points were considered to be clinically meaningful.

** The Asthma Quality of Life Questionnaire (standardized) for persons 12 years of age or older (AQLQ[S]+12)[18] is a 32-item questionnaire to assess asthma-related quality of life. Scores range from 1 to 7, and higher scores indicate better asthma-related quality of life. Score changes of 0.5 or more points were considered to be clinically meaningful.

†† Patients were stratified at randomization according to the local laboratory baseline blood eosinophil count that was defined as the result obtained at visit 1.

Table A2: Study characteristics DREAM

Trial name	Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial
NCT number	NCT01000506
Objective	To establish efficacy, safety, and patient characteristics associated with the response to mepolizumab.
Publications – title, author, journal, year	Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. Pavord ID, Korn S, Howarth P et al. Lancet 2012; 380: 651–59
Study type and design	Allocation: A multicentre, double-blind, placebocontrolled trial at 81 centres in 13 countries between Nov 9, 2009, and Dec 5, 2011. Eligible patients were aged 12–74 years and had a clinical diagnosis of asthma supported by one or more other characteristics: variability in diurnal peak expiratory flow (PEF) of more than 20% for at least 3 days during the 2-week run-in period; improvement in FEV1 of more than 12% and 200 mL after 200 g inhaled salbutamol at visit one or two, or in the 12 months before study entry; a variability in FEV1 of greater than 20% between two consecutive clinic visits in 12 months (not including exacerbation visits); 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 two or more exacerbations requiring systemic corticosteroid treatment in the previous. year. Additionally, they had evidence of eosinophilic inflammation as shown by one or more criteria at study entry or in the previous year: a sputum eosinophil count of 3% or more, an exhaled nitric oxide concentration (FENO) of 50 pb or more, an asthma-related peripheral blood eosinophil count of 0・3×10^9 per L or more, or prompt deterioration of asthma control after a 25% or less reduction in regular maintenance inhaled or oral corticosteroids. Patients were randomly assigned (in a 1:1:1:1 ratio) to receive one of three different doses of intravenous mepolizumab or matched placebo with a computer generated randomly permuted block schedule (block size of eight) and a central telephone-based system. They were stratified on the basis of whether they required daily treatment with oral corticosteroids.
Follow-up time	Data were collected from all patients at enrolment, screening, randomization (week 0), every 4-week interval during the treatment period (weeks 4–52)

Population (inclusion and exclusion criteria)	Inclusion and exclusion criteria related to NCT number from www.clinicaltrials.gov: Male or female, aged 12 to 65 years inclusive, minimum weight 45kg, clinical features of severe refractory asthma, well documented requirement for high dose inhaled corticosteroids (ICS) [i.e. >= 880mcg/day fluticasone propionate or equivalent daily] for at least 12 months, using additional controller medication in addition to high dose ICS for at least 12 months, persistent airflow obstruction indicated by a prebroncho-dilator FEV1<80% predicted at visit 1 or 2 or peak flow diurnal variability of >20% on 3 or more days during the run-in, airway inflammation which is likely to be eosinophilic in nature demonstrated by either raised peripheral blood eosinophils (>=300/microL), sputum eosinophils (>=3%), exhaled nitric oxide (>=50ppb) or prompt deterioration of asthma control following a <=25% reduction in regular maintenance dose of inhaled or oral corticosteroids (OCS),history of 2 or more exacerbations requiring systemic corticosteroids in the previous 12 months, evidence of asthma documented by airway reversibility, airway hyperresponsiveness or airflow variability, ECG assessment demonstrating QTc<450msec or QTc<480msec for patients with bundle branch block, liver function tests demonstrating ALT<2xUpper Limit of Normal (ULN), AST<2xULN, Alk Phos <=1.5xULN, bilirubin <=1.5xULN,female of non-child-bearing potential or child-bearing potential with a negative pregnancy test at screening and prepared to agree to an acceptable method of contraception, able to give written informed consent, able to read, comprehend and write at a sufficient level to complete study materials. Exclusion criteria: Current smokers or smoking history of >=10 pack years, clinically important lung condition other than asthma, diagnosis of malignancy or in the process of investigation, unstable liver disease, Churg-Strauss syndrome, using methotrexate, troleandomycin, oral gold, cyclosporine, azathioprine or any experimental anti-inflammatory therapy within 3 months of screening, Omalizumab (Xolair) or any other biological for the treatment of inflammatory disease within 6 months of Visit 1, regular use of oral or systemic corticosteroids for diseases other than asthma within 12 months or any intra-articular, short-acting intramuscular corticosteroid within 1 month or intramuscular, long-acting depot corticosteroid within 3 months, allergy/intolerance to the excipients in the mepolizumab formulation, any investigational drug within 30 days or 5 terminal half-lives, whichever is longer, pregnant or breastfeeding or planning to become pregnant, clinically significant disease which is uncontrolled with standard treatment, history of alcohol misuse or substance abuse, parasitic infestation within previous 6 months, known immunodeficiency, unable to follow instructions, use the electronic diary or peak flow meter, known evidence of lack of adherence to controller medications and/or follow physician's recommendations, previous participation in a study of mepolizumab and received study medication within 90 days.

7.1.3.2 Baseline characteristics of the intention-to-treat population – DREAM study [4]

	Placebo group (n=155)	75 mg mepolizumab group (n=153)	250 mg mepolizumab group (n=152)	750 mg mepolizumab group (n=156)
Women	97 (63%)	104 (68%)	93 (61%)	93 (60%)
Age (years)	46·4 (11·3)	50·2 (10·8)	49·4 (11·6)	48·6 (11·1)
White ethnic origin	140 (90%)	139 (91%)	135 (89%)	140 (90%)
Body-mass index (kg/m^2)	28·3 (6·1)	28·4 (6·0)	28·3 (5·9)	28·9 (5·8)
Former smoker	34 (22%)	31 (20%)	31 (20%)	37 (24%)
Duration of asthma (years)	17·9 (13·7)	19·0 (14·1)	20·4 (13·9)	19·1 (15·3)
Use of longacting β-agonists	150 (97%)	143 (93%)	145 (95%)	151 (97%)
Maintenance use of oral corticosteroids	45 (29%)	46 (30%)	50 (33%)	47 (30%)
Daily dose (mg)*	10 (10–20)	10 (10–20)	10 (8–20)	13 (10–20)
Nasal polyps†	16 (10%)	11 (7%)	22 (14%)	13 (8%)
Atopy‡	81 (52%)	78 (51%)	76 (50%)	76 (49%)
Prebronchodilator FEV_1 (mL)	1900 (653)	1810 (637)	1850 (672)	1950 (670)
Postbronchodilator FEV_1 (mL)	2290 (773)	2150 (695)	2220 (732)	2260 (784)
Percentage of predicted prebronchodilator FEV_1	59% (15)	60% (16)	59% (17)	61% (16)
Postbronchodilator FEV_1/FVC	67% (12)	68% (12)	66% (13)	68% (20)
Score on asthma control questionnaire	2·5 (1·1)	2·2 (1·1)	2·4 (1·1)	2·3 (1·2)
Score on asthma quality of life questionnaire	4·1 (1·2)	4·2 (1·2)	4·2 (1·2)	4·2 (1·2)
Blood eosinophil count (×10^9/L)§¶	0·28 (1·01)	0·25 (0·95)	0·23 (1·20)	0·25 (0·93)
Sputum eosinophil count (%)§¶	6·8% (2·01); n=24	13·9% (1·47); n=18	8·1% (1·79); n=23	5·8% (2·15); n=21
FE_{NO} (ppb)§¶	33·7 (0·79)	29·2 (0·76)	31·4 (0·80)	31·6 (0·81)
Severe exacerbations in previous year	3·7 (3·8)	3·7 (3·1)	3·4 (2·4)	3·5 (2·8)
Exacerbations requiring admission in previous year	40 (26%)	35 (23%)	36 (24%)	39 (25%)

Data are n (%), mean (SD), or median (IQR), unless otherwise stated. *Prednisolone equivalent. †Self reported. ‡Positive atopic status was defined as a positive radioallergosorbent test for any of four specified aeroallergens. §Values below lower limit of quantification were replaced by half the lower limit of quantification. ¶Geometric mean on $\log_e$ scale.

Table A2: Study characteristics MENSA

Trial name	Mepolizumab Treatment in Patients with Severe Eosinophilic Asthma
NCT number	NCT01691521
Objective	To establish efficacy, safety, and patient characteristics associated with the response to mepolizumab in patients with severe asthma have frequent exacerbations associated with persistent eosinophilic inflammation despite continuous treatment with high-dose inhaled glucocorticoids with or without oral glucocorticoids.
Publications – title, author, journal, year	Mepolizumab Treatment in Patients with Severe Eosinophilic Asthma Ortega HG, Liu MC, Pavord ID et al. NEJM 2014 Sep 25;371(13):1198-207
Study type and design	Allocation: A randomized, double-blind, double-dummy study in 576 patients between 12 and 82 years of age with recurrent asthma exacerbations and evidence of eosinophilic inflammation despite high doses of inhaled glucocorticoids to one of three study groups. conducted from October 2012 through January 2014. Patients were assigned to receive mepolizumab, a humanized monoclonal antibody against interleukin-5, which was administered as either a 75-mg intravenous dose or a 100-mg subcutaneous dose, or placebo every 4 weeks for 32 weeks. All enrolled patients were required to have received a clinical diagnosis of asthma by a physician and to have a forced expiratory volume in 1 second (FEV1) of less than 80% of the predicted value (in the case of adults) or an FEV1 of less than 90% of the predicted value or a ratio of the FEV1 to the forced vital capacity (FVC) of less than 0.8 (in the case of adolescents under the age of 18 years). In addition, patients were required to have one or more of the following three test results: FEV1 reversibility of more than 12%, positive results on methacholine or mannitol challenge at visit 1 or 2 or during the previous year, and FEV1 variability (≥20%) between two clinic visits in the past 12 months. All patients had to have had at least two asthma exacerbations in the previous year that were treated with systemic glucocorticoids while they were receiving treatment with at least 880g of fluticasone propionate or the equivalent by inhalation per day and at least 3 months of treatment with an additional controller. In addition, all patients had to have an eosinophil count of at least 150 cells per microliter in the peripheral blood at screening or at least 300 cells per microliter at some time during the previous year. Patients were allowed to continue their current antiasthma therapy throughout the study. All patients provided written informed consent. The primary outcome was the rate of exacerbations. Other outcomes included the forced expiratory volume in 1 second (FEV1) and scores on the St. George's Respiratory Questionnaire (SGRQ)and the 5-item Asthma Control Questionnaire (ACQ-5). Safety was also assessed.
Follow-up time	The study consisted of a run-in period of 1 to 6 weeks, which was followed by a 32-week treatment phase and a follow-up 8-week safety phase

Population (inclusion and exclusion criteria)	Inclusion and exclusion criteria related to NCT number from www.clinicaltrials.gov: Inclusion Criteria: Able to give written informed consent prior to participation in the study, at least 12 years of age at visit 1 and a minimum weight of 45 kilogram (kg),a well-documented requirement for regular treatment with high dose inhaled corticosteroid (ICS) in the 12 months prior to Visit 1 with or without maintenance oral corticosteroids (OCS),current treatment with an additional controller medication, besides ICS, for at least 3 months or a documented failure in the past 12 months of an additional controller medication for at least 3 successive months, prior documentation of eosinophilic asthma or high likelihood of eosinophilic asthma, at Visit 1, a pre-bronchodilator FEV1 <80% (for subjects >= 18 years of age), a pre-bronchodilator FEV1 <90% or FEV1:FVC ratio <0.8 (for subjects 12-17 years of age),previously confirmed history of two or more exacerbations requiring treatment with systemic CS, male or Eligible Female (females of childbearing potential must commit to consistent and correct use of an acceptable method of birth control),French subjects will be included only if either affiliated to or a beneficiary of a social security category. Exclusion Criteria: Current smokers or former smokers with a smoking history of >=10 pack years, presence of a known pre-existing, clinically important lung condition other than asthma, a current malignancy or previous history of malignancy in less than 12 months, known, pre-existing, unstable liver disease cirrhosis and known biliary abnormalities, known, pre-existing severe or clinically significant cardiovascular disease, known, pre-existing other concurrent clinically significant medical conditions that are uncontrolled with standard treatment, subjects with any eosinophilic diseases, QTc(F) ≥450msec or QTc(F) ≥480 msec, a history of alcohol/substance abuse, subject with known immunodeficiency, subjects who have received omalizumab within 130 days of Visit 1 or any monoclonal antibody (other than Xolair) to treat inflammatory disease within 5 half-lives of Visit 1, subjects who have received treatment with an investigational drug within the past 30 days or five terminal phase half-lives of the drug whichever is longer, subjects with allergy/intolerance to a monoclonal antibody or biologic, subjects who are pregnant or breastfeeding, subjects who have known evidence of lack of adherence to controller medications and/or ability to follow physician's recommendations, previously participated in any study with mepolizumab and received investigational product (including placebo).

7.1.3.3 Baseline characteristics of the intention-to-treat population – MENSA study [5]

Table 1. Characteristics of the Patients at Baseline in the Intention-to-Treat Population.*

Characteristic	Placebo (N=191)	Mepolizumab	
		Intravenous (N=191)	Subcutaneous (N=194)
Mean age (range) — yr	49 (12–76)	50 (13–82)	51 (12–81)
Female sex — no. (%)	107 (56)	106 (55)	116 (60)
Body-mass index†	28.0±5.6	27.7±5.7	27.6±6.2
Former smoker — no. (%)	57 (30)	52 (27)	50 (26)
Duration of asthma — yr	19.5±14.6	19.8±14.0	20.5±12.9
Use of oral glucocorticoids			
Maintenance use — no. (%)	44 (23)	48 (25)	52 (27)
Mean daily dose (range) — mg‡	15.1 (5–80)	12.0 (1–40)	12.6 (2–50)
Allergic rhinitis — no. (%)	95 (50)	91 (48)	95 (49)
FEV_1			
Before bronchodilation — liters§	1.86±0.63	1.86±0.70	1.73±0.66
Percent of predicted value before bronchodilation¶	62.4±18.1	61.4±18.3	59.3±17.5
Reversibility — %	27.4±20.8	25.4±19.6	27.9±24.0
FEV_1:FVC ratio — %‖	64±13	64±13	63±13
Morning peak expiratory flow — liters/min	277±106	269±112	255±108
Score on Asthma Control Questionnaire**	2.28±1.19	2.12±1.13	2.26±1.27
Score on St. George's Respiratory Questionnaire††	46.9±19.8	44.4±19.4	47.9±19.4
Geometric mean IgE on $\log_e$ scale — U/ml	150±1.5	180±1.5	150±1.5
Geometric mean blood eosinophil count on $\log_e$ scale — cells/μl‡‡	320±938	280±987	290±1050
Asthma exacerbations			
Severe episodes in previous year — no./patient	3.6±2.8	3.5±2.2	3.8±2.7
Necessitating hospitalization in previous year — no. (%)	35 (18)	41 (21)	33 (17)
History of asthma-related intubation — no. (%)	3 (2)	10 (5)	8 (4)

* Plus–minus values are means (or geometric means) ±SD. There were no significant between-group differences at baseline. More detailed data are provided in Table S3 in the Supplementary Appendix. FEV_1 denotes forced expiratory volume in 1 second, and FVC forced vital capacity.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ The listed value is the prednisone equivalent.
§ Reversibility was measured at baseline.
¶ The percent of the predicted value before bronchodilation was assessed at the screening visit.
‖ The FEV_1:FVC ratio was calculated by dividing the FEV_1 by the FVC and then multiplying by 100 to express the value as a percentage.
** Scores on the Asthma Control Questionnaire range from 0 to 6, with higher scores indicating worse control; a change of 0.5 points is the minimal clinically important difference.
†† Scores on St. George's Respiratory Questionnaire range from 0 to 100, with higher scores indicating worse function; a change of 4 points is considered to be clinically relevant.
‡‡ Values below the lower limit of quantification (LLQ) were replaced by a value that was 50% of the LLQ.

Table A2: Study characteristics SIRIUS

Trial name	Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma
NCT number	NCT01691508
Objective	To compare the effect of mepolizumab adjunctive subcutaneous therapy with that of placebo in reducing the use of maintenance oral glucocorticoids while maintaining asthma control in patients with severe eosinophilic asthma.
Publications – title, author, journal, year	Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma Bel EH, Wenzel SE, Thompson PJ et al. NEJM 2014 Sep 25;371(13):1189-97.
Study type and design	Allocation: A multicenter, randomized, placebo-controlled, double-blind, parallel-group study. The study consisted of four phases: optimization of the oral glucocorticoid regimen, induction, reduction in the oral glucocorticoid dose, and maintenance in 135 patients. The optimization phase was designed to establish the lowest dose of maintenance oral glucocorticoids associated with acceptable asthma control. During this phase, the oral glucocorticoid dose was reduced weekly until there was an exacerbation in asthma symptoms or an increase of at least 0.5 points from the visit 1 score on the Asthma Control Questionnaire 5 (ACQ-5). After optimization of the oral glucocorticoid regimen, patients underwent randomization in a 1:1 ratio to receive mepolizumab (at a dose of 100 mg) or placebo by subcutaneous injection and entered the induction phase (weeks 0 to 4), during which they received the assigned study drug and continued to receive their optimized dose of oral glucocorticoids. During the reduction phase (weeks 4 to 20), the oral glucocorticoid dose was reduced according to a prespecified schedule by 1.25 to 10 mg per day every 4 weeks on the basis of asthma control and symptoms of adrenal insufficiency. During the maintenance phase (weeks 20 to 24), no further adjustment was made in the oral glucocorticoid dose. In addition, a follow-up safety visit was scheduled at week 32. Throughout the study, patients continued to receive the same maintenance regimen of asthma drugs that they were receiving during the optimization phase. Patients recorded data on peak expiratory flow, asthma symptoms, and ACQ-5 scores in an electronic diary (eDiary, PHT).
Follow-up time	32 weeks- A follow-up safety visit was scheduled at week 32.

Population (inclusion and exclusion criteria)	Inclusion and exclusion criteria related to NCT number from www.clinicaltrials.gov: Inclusion Criteria: Informed Consent and Study Compliance: Subjects must be able to give written informed consent prior to participation in the study, which will include the ability to comply with the requirements and restrictions listed in the consent form, systemic corticosteroids: Requirement for regular treatment with maintenance systemic corticosteroids in the 6 months prior to Visit 1 and using a stable oral corticosteroid dose for 4 weeks prior to Visit 1. Subjects must be taking 5.0 to 35 mg/day of prednisone or equivalent at Visit 1 and must agree to switch to study required prednisone/prednisolone as their oral corticosteroid and use it per protocol for the duration of the study, inhaled Corticosteroids: Requirement for regular treatment with high dose inhaled corticosteroid in the 6 months prior to Visit 1. For 18 years of age and older: inhaled corticosteroid (ICS) dose must be >=880 microgram (µg)/day fluticasone propionate (FP) (ex-actuator) or equivalent daily. For ICS/ long acting beta2 agonist (LABA) combination preparations, the highest approved maintenance dose in the local country will meet this ICS criterion. For ages 12 to 17: ICS dose must be >=440 µg/day FP (ex-actuator) or equivalent daily, controller medication: Current treatment with an additional controller medication for at least 3 months OR documentation of having used and failed an additional controller medication for at least 3 successive months during the prior 12 months [e.g., LABA, leukotriene receptor antagonist (LTRA), or theophylline],eosinophilic Asthma: Prior documentation of eosinophilic asthma or high likelihood of eosinophilic asthma,FEV1: Persistent airflow obstruction as indicated by a pre-bronchodilator FEV1 <80% predicted, asthma: Evidence of asthma indicated by airway reversibility, hyperresponsiveness or airway variability. Exclusion Criteria: Smoking history: Current smokers or former smokers with a smoking history of >=10 pack years, concurrent Respiratory Disease: Presence of a clinically important lung condition other than asthma, malignancy: A current malignancy or previous history of cancer in remission for less than 12 months prior screening, liver Disease: Unstable liver disease, cardiovascular: Subjects who have severe or clinically significant cardiovascular disease uncontrolled with standard treatment, other Concurrent Medical Conditions: Subjects who have known, pre-existing, clinically significant endocrine, autoimmune, metabolic, neurological, renal, gastrointestinal, hepatic, haematological or any other system abnormalities that are uncontrolled with standard treatment, eosinophilic Diseases: Subjects with other conditions that could lead to elevated eosinophils such as hypereosiniophilic syndromes, including Churg-Strauss Syndrome, or eosinophilic esophaghitis. Subjects with a known, pre-existing parasitic infestation within 6 months prior to Visit 1 are also to be excluded,ECG: ECG assessment QTcF >=450 milliseconds (msec) or QTcF >= 480 msec for subjects with Bundle Branch Block, immunodeficiency: A known immunodeficiency (e.g. human immunodeficiency virus - HIV), other than that explained by the use of corticosteroids taken as therapy for asthma, omalizumab Use: Subjects who have received omalizumab [Xolair] within 130 days of Visit 1, other monoclonal antibodies: Subjects who have received any monoclonal antibody (other than Xolair) to treat inflammatory

	disease within 5 half-lives of Visit 1, investigational medications: Subjects who have received treatment with an investigational drug within the past 30 days or five terminal phase half-lives of the drug whichever is longer, prior to Visit 1 (this also includes investigational formulations of marketed products), hypersensitivity: Subjects with a known allergy or intolerance to a monoclonal antibody or biologic, pregnancy: Subjects who are pregnant or breastfeeding. Patients should not be enrolled if they plan to become pregnant during the time of study participation. Alcohol/Substance Abuse: A history (or suspected history) of alcohol misuse or substance abuse within 2 years prior to Visit 1, adherence: Subjects who have known evidence of lack of adherence to controller medications and/or ability to follow physician's recommendations, previous participation: Subjects who have previously any study of mepolizumab and received Investigational Product.

7.1.3.4 *Baseline characteristics of the intention-to-treat population – SIRIUS study [6]*

Table 1. Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	Placebo (N=66)	Mepolizumab (N=69)
Mean age (range) — yr	50 (28–70)	50 (16–74)
Female sex — no. (%)	30 (45)	44 (64)
Body-mass index†	29.5±6.0	27.8±5.9
Former smoker — no. (%)	25 (38)	28 (41)
Duration of asthma — yr	20.1±14.4	17.4±11.8
Median daily oral glucocorticoid dose — mg‡		
At screening	15.0	12.5
During optimization phase	12.5	10.0
Duration of oral glucocorticoid use ≥5 yr — no. (%)	31 (47)	34 (49)
FEV_1 before bronchodilation		
Mean — liters	2.00±0.82	1.90±0.66
Percent of predicted value	57.8±18.5	59.6±17.0
FEV_1:FVC ratio before bronchodilation — %§	61±11.7	63±12.4
Percent reversibility of FEV_1	24.8±18.1	27.3±17.4
ACQ-5 score¶	2.0±1.2	2.2±1.3
SGRQ score‖	45±18	50±18
Geometric mean IgE on $\log_e$ scale — U/ml	114±1	117±1
Geometric mean blood eosinophil count on $\log_e$ scale — cells/μl**	230±1001	250±1245
Severe exacerbations in previous year — no./patient	2.9±2.8	3.3±3.4
Exacerbations in the previous year requiring hospitalization — no. (%)	9 (14)	14 (20)
History of asthma-related intubation — no. (%)	3 (5)	2 (3)

* Plus–minus values are means (or geometric means) ±SD unless otherwise stated. There were no significant between-group differences at baseline with the exception of sex (P=0.04). Percentages may not total 100 because of rounding. More details about baseline characteristics are provided in Table S4 in the Supplementary Appendix. FEV_1 denotes forced expiratory volume in 1 second, and FVC forced vital capacity.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ Doses are provided as prednisone equivalents.

§ The FEV_1:FVC ratio was calculated by dividing the FEV_1 by the FVC and then multiplying by 100 to express the value as a percentage.

¶ Scores on the Asthma Control Questionnaire 5 (ACQ-5) range from 0 to 6, with higher scores indicating worse control of asthma; a change of 0.5 points is the minimal clinically important difference.

‖ Scores on St. George's Respiratory Questionnaire (SGRQ) range from 0 to 100, with higher scores indicating worse function; a change of 4 units is considered to be clinically relevant.

** Values below the lower limit of quantification (LLQ) were replaced by 50% of the LLQ.

Table A2: Study characteristics MUSCA

Trial name	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
NCT number	NCT02281318
Objective	To assess mepolizumab in patients with severe eosinophilic asthma by examining its effect on health-related quality of life (HRQOL).
Publications – title, author, journal, year	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, Bradford ES, Albers FC et al. Lancet Respir Med 2017;5: 390–400.
Study type and design	Allocation: A randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3b trial in 146 hospitals or research centres in 19 countries worldwide. Eligible participants were patients aged 12 years or older with severe eosinophilic asthma and a history of at least two exacerbations requiring treatment in the previous 12 months before screening despite regular use of high-dose inhaled corticosteroids plus other controller medicines. Participants were assigned 1:1 to receive a subcutaneous injection of either mepolizumab 100 mg or placebo, plus standard of care, every 4 weeks for 24 weeks. The primary endpoint was the mean change from baseline in the St George's Respiratory Questionnaire (SGRQ) total score at week 24 in the modified intention-to-treat (modified ITT) population (analysed according to their randomly assigned treatment). Safety was assessed in all patients who received at least one dose of trial medication (analysed according to the actual treatment received).
Follow-up time	The patients were followed for 24 weeks.
Population (inclusion and exclusion criteria)	Inclusion and exclusion criteria related to NCT number from www.clinicaltrials.gov: Inclusion Criteria: At least 12 years of age at the time of signing the informed consent/assent (For those countries where local regulations permit enrolment of adults only, participant recruitment will be restricted to those who are >=18 years of age), inhaled corticosteroid: A well-documented requirement for regular treatment with high dose inhaled corticosteroid (ICS) in the 12 months prior to Visit 1 with or without maintenance oral corticosteroids (OCS). For participants >=18 years old: ICS dose must be >=880 micrograms (mcg)/day fluticasone propionate (FP) (exactuator) or equivalent daily. For ICS/long-acting beta-2-agonist (LABA) combination preparations, the highest approved maintenance dose in the local country will meet this ICS criterion. For participants >=12 to <=17 years old: ICS dose must be >=440 mcg/day FP (ex-actuator) or equivalent daily. For ICS/LABA combination preparations, the mid-strength approved maintenance dose in the local country will meet this ICS criterion, controller

	medication: Current treatment with an additional controller medication, besides ICS, for at least 3 months or a documented failure in the past 12 months of an additional controller medication for at least 3 successive months (e.g. LABA, leukotriene receptor antagonist [LTRA], or theophylline),eosinophilic asthma: Prior documentation of eosinophilic asthma or high likelihood of eosinophilic asthma as per randomisation Criteria 1 and 2, FEV1: Persistent airflow obstruction as indicated by: For participants >=18 years of age at visit 1, a pre-bronchodilator FEV1 <80% predicted (National Health and Nutrition Examination Survey [NHANES III]) recorded at Visit 1. For participants 12-17 years of age at Visit 1: A pre-bronchodilator FEV1 <90% predicted (NHANES III) recorded at Visit 1 OR FEV1:FVC ratio <0.8 recorded at Visit 1, exacerbation history: Previously confirmed history of two or more exacerbations requiring treatment with systemic Corticosteroid (CS) (intramuscular, intravenous, or oral), in the 12 months prior to visit 1, despite the use of high-dose inhaled corticosteroids (ICS). For participants receiving maintenance CS, the CS treatment for the exacerbations must have been a two-fold dose increase or greater, gender: Male or Eligible Female. To be eligible for entry into the study, females of childbearing potential must commit to consistent and correct use of an acceptable method of birth control listed in the protocol for the duration of the trial and for 4 months after the last study drug administration,informed Consent/Assent: Able to give written informed consent/assent prior to participation in the core study, which will include the ability to comply with the requirements and restrictions listed in the consent/assent form and in this protocol. Participants must be able to read, comprehend, and write at a level sufficient to complete study related materials. Written informed consent must be obtained from ALL patients/legally authorized representative(s); for patients 12-17 years old, written informed assent must be obtained in addition to the legally authorized representative(s)' consent, French participants: In France, a participant will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category.

	Exclusion Criteria: Smoking history: Current smokers or former smokers with a smoking history of >=10 pack years (number of pack years = (number of cigarettes per day/20) x number of years smoked). A former smoker is defined as a participant who quit smoking at least 6 months prior to Visit 1, concurrent respiratory disease: Presence of a known pre-existing, clinically important lung condition other than asthma. This includes current infection, bronchiectasis, pulmonary fibrosis, bronchopulmonary aspergillosis, or diagnoses of emphysema or chronic bronchitis (chronic obstructive pulmonary disease other than asthma) or a history of lung cancer. Malignancy: A current malignancy or previous history of cancer in remission for less than 12 months prior to screening (Participants that had localized carcinoma of the skin which was resected for cure will not be excluded). Liver Disease: Known, pre-existing, unstable liver disease (as defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, esophageal or gastric varices or persistent jaundice), cirrhosis, and known biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones). Cardiovascular: Participants who have severe or clinically significant cardiovascular disease uncontrolled with standard treatment. Including but not limited to: (a) known ejection fraction of <30% OR (b) severe heart failure meeting New York Heart Association Class IV classification OR (c) hospitalised in the 12 months prior to Visit 1 for severe heart failure meeting New York Heart Association Class III OR (d) angina diagnosed less than 3 months prior to Visit 1 or at Visit 1. Other Concurrent Medical Conditions: Participants who have known, pre-existing, clinically significant endocrine, autoimmune, metabolic, neurological, renal, gastrointestinal, hepatic, haematological or any other system abnormalities that are uncontrolled with standard treatment. Eosinophilic Diseases: Participants with other conditions that could lead to elevated eosinophils such as Hypereosinophilic Syndromes, including Churg-Strauss Syndrome (Eosinophilic Granulomatosis with Polyangiitis [EGPA]), or Eosinophilic Esophagitis. Participants with a known, pre-existing parasitic infestation within 6 months prior to Visit 1 are also to be excluded. Electrocardiogram (ECG) Assessment: QT interval corrected for heart rate by Fridericia's formula (QTc(F)) >=450 milliseconds (msec) or QTc(F) >=480 msec for participants with Bundle Branch Block at Visit 1. Alcohol/Substance Abuse: A history (or suspected history) of alcohol misuse or substance abuse within 2 years prior to Visit 1. Immunodeficiency: A known immunodeficiency (e.g. human immunodeficiency virus [HIV]), other than that explained by the use of corticosteroids taken as therapy for asthma. Xolair: Participants who have received omalizumab (Xolair) within 130 days of Visit 1. Other Monoclonal Antibodies: Participants who have received any monoclonal antibody (other than Xolair) to treat inflammatory disease within 5 half-lives of Visit 1. Investigational Medications: Participants who have received treatment with an investigational drug within the past 30 days or five terminal phase half-lives of the drug whichever is longer, prior to Visit 1 (this also includes investigational formulations of marketed products). Hypersensitivity: Participants with allergy/intolerance to a monoclonal antibody or biologic. Pregnancy: Participants who are pregnant or breastfeeding. Patients should not be enrolled if they plan to become pregnant during the time of study participation. A urine pregnancy test is required of

	all women of child bearing potential. This test will be performed at the time points specified in the Time and Events Schedule in protocol. Adherence: Participants who have known evidence of lack of adherence to controller medications and/or ability to follow physician's recommendations. Previous participation: Previously participated in any study with mepolizumab and received investigational product (including placebo)

7.1.3.5 *Baseline characteristics of the intention-to-treat population – MUSCA study [7]*

	Placebo (n=277)	Mepolizumab 100 mg (n=274)
Age (years)	52·1 (12·9)	49·8 (14·0)
Sex		
Female	176 (64%)	149 (54%)
Male	101 (36%)	125 (46%)
Body-mass index (kg/m²)	27·9 (6·2)	28·5 (6·6)
Former smoker	76 (27%)	71 (26%)
Duration of asthma (years)	19·6 (15·0)	19·5 (14·7)
Number of exacerbations in the 12 months before screening	2·7 (1·5)	2·9 (1·9)
Patients with ≥1 exacerbation requiring ER visit or admission to hospital in the 12 months before screening	92 (33%)	87 (32%)
Patients with ≥1 exacerbation requiring admission to hospital in the 12 months before screening	68 (25%)	69 (25%)
Current oral corticosteroid use	67 (24%)	64 (23%)
Oral corticosteroid dose (mg/day)	13·4 (10·8)	12·6 (11·0)
Current inhaled corticosteroid use	277 (100%)	273 (>99%)
Current LABA use	274 (99%)	273 (>99%)
Current LRA use	114 (41%)	108 (39%)
Current xanthine derivative use	56 (20%)	59 (22%)
Current LAMA use	63 (23%)	51 (19%)
Measures of lung function		
Pre-bronchodilator FEV_1 (L)	1·7 (0·6)	1·8 (0·6)
Percentage of predicted pre-bronchodilator FEV_1	55·2% (14·6)	55·5% (14·4)
Percentage of FEV_1 reversibility	20·5% (21·6)	22·0% (23·2)
Pre-bronchodilator FVC (L)	2·9 (0·9)	3·1 (0·9)
Pre-bronchodilator FEF_{25-75} (mL/s)	869 (505)	919 (529)
Baseline blood eosinophil count		
Baseline geometric mean (10^9/L)	0·35	0·30
≥150 per µL at screening	240 (87%)	234 (85%)
≥300 per µL in 12 months before screening	165 (60%)	186 (68%)
Total SGRQ score	46·3 (18·9)	47·4 (18·1)
ACQ-5 score	2·2 (1·2)	2·2 (1·1)
Baseline presence of nasal polyps	47 (17%)	58 (21%)
Positive atopic status	124 (45%)	127 (46%)

Data are mean (SD) or n (%). ER=emergency room. LABA=long-acting β-2 agonist. LRA=leukotriene receptor antagonist. LAMA=long-acting muscarinic agonist. FVC=forced vital capacity. FEF_{25-75}=forced expiratory flow at 25–75% of FVC. SGRQ=St George's Respiratory Questionnaire. ACQ=Asthma Control Questionnaire.

***Table 1*: Baseline characteristics of the modified intention-to-treat population**

8 Results per study – Table A3

8.1 Table A3a Results of study SIROCCO

Trial name:	**A Multicentre, Randomized, Double-blind, Parallel Group, Placebo-controlled, Phase III Efficacy and Safety Study of Benralizumab (MEDI-563) Added to High-dose Inhaled Corticosteroid Plus Long-acting β2 Agonist in Patients with Uncontrolled Asthma**									
NCT number:	NCT01928771									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome (over 48 weeks)	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value	
Annual exacerbation rate [1]	Benralizumab (30 mg Q8W)	267	Rate estimate (95% CI): 0.65 (0.53–0.80)	Absolute difference estimate: -0.68	(–0.95 to –0.41)	<0.001	Rate ratio vs. placebo: 0.49	0.37-0.64	<0.0001	Estimates calculated using a negative binomial model, with adjustment for treatment, region, oral corticosteroid use at time of randomisation, and previous exacerbations.
	Placebo	267	Rate estimate (95% CI): 1.33 (1.12–1.58)							
Pre-bronchodilator FEV1 (L) [1]	Benralizumab (30 mg Q8W)	264	LS mean change (number of Patients): 0.398 L (235)	LS mean difference vs. placebo: 0.159 L	0.068 to 0.249	0.0006	NA	NA	NA	Estimates calculated using a mixed-effects model for repeated measures analysis, with adjustment for treatment, baseline value, region, oral corticosteroid use at time of randomisation, visit, and visit × treatment.
	Placebo	261	LS mean change (number of Patients): 0.239 L (233)							
Total asthma symptom score [1]	Benralizumab (30 mg Q8W)	263	LS mean change (number of Patient): −1.30 (178)	LS mean difference vs.	–0·45 to –0·06	0.0118	NA	NA	NA	Estimates calculated using a mixed-effects model for repeated measures analysis, with adjustment

	Placebo	267	LS mean change (number of Patient): −1.04 (180)	placebo: -0.25						for treatment, baseline value, region, oral corticosteroid use at time of randomisation, visit, and visit × treatment.
ACQ-6 score [1]	Benralizumab (30 mg Q8W)	263	LS mean change (number of Patient): −1.46 (191)	LS mean difference vs. placebo: -0.29	-0.48 to -0.10	0.0028	NA	NA	NA	Estimates calculated using a mixed-effects model for repeated measures analysis, with adjustment for treatment, baseline value, region, oral corticosteroid use at time of randomisation, visit, and visit × treatment. *Low numbers represent better control. Patients with a baseline and at least one post-baseline assessment.*
	Placebo	267	LS mean change (number of Patient): −1.17 (186)							
AQLQ(S)+12 score [1]	Benralizumab (30 mg Q8W)	252	LS mean change (number of Patient): 1.56 (187)	LS mean difference vs. placebo: 0.30	0.10-0.50	0.0036	NA	NA	NA	Estimates calculated using a mixed-effects model for repeated measures analysis, with adjustment for treatment, baseline value, region, oral corticosteroid use at time of randomisation, visit, and visit × treatment. *High numbers suggest better quality of life.*
	Placebo	254	LS mean change (number of Patient): 1.26 (180)							
Exacerbations resulting in adjudicated ED visit, urgent care visit, or hospitalisation [1]	Benralizumab (30 mg Q8W)	267	Rate estimate (95% CI): 0.06 (0.04, 0.11)	Absolute difference estimate: -0.11	–0.18 to –0·05	<0.001	Rate ratio vs. placebo: 0.37	(0.20-0.67)	0.0010	Estimates via negative binomial model adjusting for treatment, region, oral corticosteroid use at time of randomisation, and prior exacerbations associated with ER visits or hospitalizations.
	Placebo	267	Rate estimate (95% CI): 0.18 (0.13 - 0.25)							

8.2 Table A3a Results of study CALIMA

Trial name:	**A Multicenter, Randomized, Double-blind, Parallel Group, Placebocontrolled, Phase 3 Study to Evaluate the Efficacy and Safety of Benralizumab in Asthmatic Adults and Adolescents Inadequately Controlled on Inhaled Corticosteroid Plus Long-acting β2 Agonist (CALIMA)**									
NCT number:	NCT01914757									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome (over 56 weeks)	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value	
Annual exacerbation rate [2]	Benralizumab (30 mg Q8W)	239	Rate estimate (95% CI): 0.66 (0.54–0.82)	Absolute difference estimate: -0.26	(–0.48 to –0.04)	0.0190	Rate ratio vs. placebo: 0.72	0.54-0.95	0.0188	Estimates calculated using a negative binomial model with adjustment for treatment, region, oral corticosteroid use at time of randomisation, and previous exacerbations
	Placebo	248	Rate estimate (95% CI): 0.93 (0.77–1.12)							
Pre-bronchodilator FEV1 (L) [2]	Benralizumab (30 mg Q8W)	238	LS mean change (number of Patients): 0.330 L (211)	LS mean difference vs. placebo: 0.116 L	0.028 to 0.204	0.0102	NA	NA	NA	Estimates calculated using a mixed-effects model for repeated measures analysis with adjustment for treatment, baseline value, region, oral corticosteroid use at time of randomisation, visit, and visit × treatment.
	Placebo	244	LS mean change (number of Patients): 0.215 L (221)							
Total asthma symptom score [2]	Benralizumab (30 mg Q8W)	237	LS mean change (number of Patient): −1.40 (185)	LS mean difference vs.	–0·43 to –0·04	0.0186	NA	NA	NA	Estimates calculated using a mixed-effects model for repeated measures analysis with adjustment for treatment, baseline value,

	Placebo	247	LS mean change (number of Patient): −1.16 (187)	placebo: -0.23					region, oral corticosteroid use at time of randomisation, visit, and visit × treatment. Key secondary endpoint; composite of daytime and night-time symptoms scored 0–6 overall (a decrease in score indicates improvement).
ACQ-6 score [2]	Benralizumab (30 mg Q8W)	239	LS mean change (number of Patient): −1.44 (185)	LS mean difference vs. placebo: -0.25	-0.44 to -0.07	0.0082	NA	NA	NA	Estimates calculated using a mixed-effects model for repeated measures analysis with adjustment for treatment, baseline value, region, oral corticosteroid use at time of randomisation, visit, and visit × treatment. The ACQ-6 is a 6-item questionnaire to assess daytime and night-time symptoms and rescue β2-agonist use on a 0–6 scale *(low numbers represent better control)*.
	Placebo	247	LS mean change (number of Patient): −1.19 (197)						
AQLQ(S)+12 score [2]	Benralizumab (30 mg Q8W)	230	LS mean change (number of Patient): 1.56 (180)	LS mean difference vs. placebo: 0.24	0.04-0.45	0.0194	NA	NA	NA	Estimates calculated using a mixed-effects model for repeated measures analysis with adjustment for treatment, baseline value, region, oral corticosteroid use at time of randomisation, visit, and visit × treatment. The AQLQ(S)+12 is a 32-item questionnaire to assess asthma-related quality of life scored on a 1–7 scale *(high numbers indicate better quality of life*).
	Placebo	240	LS mean change (number of Patient): 1.31 (191)						

Exacerbations resulting in adjudicated ED visit, urgent care visit, or hospitalisation [2]	Benralizumab (30 mg Q8W) Placebo	239 248	Annual exacerbation rate estimate (95% CI): 0.05 (0.03–0.08) Rate estimate (95% CI): 0.04 (0.02 - 0.07)	Absolute difference estimate: 0.01	-0.02 to 0·04	0.5420	Rate ratio vs. placebo: 1.23	0.64-2.35	0.5381	Estimates via negative binomial model adjusting for treatment, region, oral corticosteroid use at time of randomisation, and any prior exacerbations associated with ED visits or hospitalisations.

*In the previous year.

8.3 Table A3a Results of study ZONDA

Trial name:	**A Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled, Phase 3 Efficacy and Safety Study of Benralizumab (MEDI-563) to Reduce Oral Corticosteroid Use in Patients with Uncontrolled Asthma on High Dose Inhaled Corticosteroid Plus Long-acting β2 Agonist and Chronic Oral Corticosteroid Therapy (ZONDA)**									
NCT number:	NCT02075255									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome (over 28 weeks)	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value	
Median reduction from baseline (range) — % of baseline value [3]	Benralizumab (30 mg Q8W) Placebo	73 75	75.0(-50 to 100) 25.0(-150 to 100)	37.5	20.8-50.0	<0.001	Odds ratio vs. placebo: 4.12	2.22-7.63	<0.001	Negative values indicate an increase in the final oral glucocorticoid dose from baseline. The P values were calculated with the use of a Wilcoxon rank-sum test.

Reduction from baseline in final oral glucocorticoid dose, according to percentage reduction [3]	Benralizumab (30 mg Q8W)	73	100% Reduction — no./total no. (%)**: 22/42(52)	33.3	14.1-52.5	<0.001	Odds ratio vs. placebo: 4.19	1.58 - 11.12	0.002	Source table for absolute difference in effect: Covance table 4.2.42.1.1.3.1
	Placebo	75	100% Reduction — no./total no. (%)**: 8/42(19)							
	Benralizumab (30 mg Q8W)	73	≥50% Reduction — no. (%): 48(66)	28.4	13.0-43.9	<0.001	Odds ratio vs. placebo: 3.03	1.57 – 5.86	<0.001	Source table for absolute difference in effect: Covance table 4.2.13.1.1.3.1
	Placebo	75	≥50% Reduction — no. (%): 28(37)							
Reduction from baseline in final oral glucocorticoid dose, according to percentage reduction [3]	Benralizumab (30 mg Q8W)	73	≥25% Reduction — no. (%)**: 57(78)	27.4	12.6-42.2	<0.001	Odds ratio vs. placebo: 3.25	1.62 – 6.52	<0.001	The table for absolute difference in effect was not previously produced by Covance, but we used the same methods as in the 100% and 50% OCS reductions.
	Placebo	75	≥25% Reduction — no. (%)**: 38(51)							

Final oral glucocorticoid dose of ≤5.0 mg/day — no. (%)* ** [3]	Benralizumab (30 mg Q8W)	73	43(59)	25.6	10.0-41.1	0.001	Odds ratio vs. placebo: 2.74	1.41 – 5.31	0.002	Source table for absolute difference in effect: Covance table 4.2.14.1.1.3.1
	Placebo	75	25(33)							
Percentage of patients with ≥1 asthma exacerbation after randomization [3]	Benralizumab (30 mg Q8W)	73	Patients— no. (%): 17(23)	-28.7	-43.6 to -13.8	<0.001	Odds ratio vs. placebo: 0.28	0.14-0.56	<0.001	The source table for absolute difference in effect: Covance table 4.2.01.1.1.3.1. The odds ratio estimate was determined from the Cochran–Mantel–Haenszel test, with control for region.
	Placebo	75	Patients— no. (%): 39(52)							
Annual asthma exacerbation rate ratio [3]	Benralizumab (30 mg Q8W)	73	Marginal rate estimate: 0.54 (0.34–0.88)	Marginal absolute difference estimate: –1.28	–1.92 to –0.64	<0.001	Rate ratio vs. placebo: 0.30	0.17-0.53	<0.001	The annual exacerbation rate ratios were calculated with the use of a negative binomial model with a log-link function and an offset term of log–follow-up time. The model included covariates of treatment group, region, and number of exacerbations in the previous year.
	Placebo	75	Marginal rate estimate: 1.83 (1.33–2.50)							
Time to first exacerbation [3]	Benralizumab (30 mg Q8W)	73	Percentage of patients with ≥1 asthma exacerbation after randomization: 17 (23 %)	NA	NA	NA	Hazard ratio vs. placebo: 0.32	0.17-0.57	<0.001	The hazard ratio estimate was determined using a Cox proportional hazards model, which included covariates of treatment group, region, and number of exacerbations in the previous year.
	Placebo	75	Percentage of patients with ≥1 asthma exacerbation after							

			randomization: 39 (52 %)						
Annual exacerbation rate ratio associated with an emergency department visit or hospitalisation [3]	Benralizumab (30 mg Q8W)	73	Marginal rate estimate: 0.02 (0.00–0.18)	Marginal absolute difference estimate: -0.30	–0.53 to –0.07	0.011	Rate ratio vs. placebo: 0.07	0.01–0.63	0.018	The annual exacerbation rate ratios were calculated with the use of a negative binomial model with a log-link function and an offset term of log–follow-up time. The model included covariates of treatment group, region, and number of exacerbations that required an emergency department visit or hospitalization in the previous year. Confidence intervals for marginal rates and absolute differences were estimated via the delta method. Rate ratios, confidence intervals, and P values were estimated directly from SAS GENMOD procedure. ‖The hazard ratio estimate was determined using a Cox proportional hazards model, including covariates of treatment group, region, and number of exacerbations that required an emergency department visit or hospitalization in the previous year.
	Placebo	75	Marginal rate estimate: 0.32 (0.16–0.65)							

Time to first exacerbation associated with an emergency department visit or hospitalization [3]	Benralizumab (30 mg Q8W)	73	Percentage of patients with ≥1 asthma exacerbation after randomization: 17 (23 %)	NA	NA	NA	Hazard ratio vs. placebo: 0.12	0.01–0.63	0.042	The hazard ratio estimate was determined using a Cox proportional hazards model, including covariates of treatment group, region, and number of exacerbations that required an emergency department visit or hospitalization in the previous year.
	Placebo	75	Percentage of patients with ≥1 asthma exacerbation after randomization: 39 (52 %)							
Change from baseline in pre bronchodilator FEV1 at Week 28 [3]	Benralizumab (30 mg Q8W)	68	LS mean change: 0.239	LS mean difference vs. placebo: 0.112	-0.033 to 0.258	0.129	NA	NA	NA	The model was: Change from baseline in pre-bronchodilator FEV1 = Treatment + baseline pre-bronchodilator FEV1 + region + visit + treatment*visit. The number of patients in the repeated measures analysis represents all patients with baseline and at least 1 post-baseline assessment. Baseline was defined as the last non-missing value prior to the first dose of study treatment. Estimate of the mean change from baseline at each week in the 2 treatment groups was compared to the placebo group using a repeated measures analysis. Estimates were least squares means

	Placebo	73	LS mean change: 0.126		

*The baseline oral glucocorticoid dose was the daily dose at which the patient's asthma was stabilized at randomization (after the run-in phase), and the final oral glucocorticoid dose was the final daily dose at week 28.
**Patients with a baseline oral glucocorticoid dose of 12.5 mg or less per day at the end of the run-in phase were eligible for a 100% dose Reduction (discontinuation of oral glucocorticoid therapy).
***All the patients with a final oral glucocorticoid dose of 5.0 mg or less per day also had a reduction of at least 25% from baseline in the final oral glucocorticoid dose.

[redacted]

[redacted]				
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	
	[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]	
	[redacted]			

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9 Results per PICO, Table A4

9.1 Annual rate of clinically significant exacerbations & Annual rate of exacerbations resulting in ER visit/hospitalisation

Table A4 Results referring to Annual rate of clinically significant exacerbations & Annual rate of exacerbations resulting in ER visit/hospitalisation

Results per outcome	*Attach forest plots and statistical results as a separate file.* *Results from the comparative analysis should be given in the table below, if possible.*							
		Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	Difference	CI	*P* value	Hazard/Odds/Risk ratio	CI	*P* value	
Annual rate of clinically significant exacerbations, in subgroup with ≥880 µg FP daily (Pooled MAIC results) (Ref.: Fig. 31 in [9])	Comparison: BENRA Q8W vs. Placebo: (SIROCCO/CALIMA trial), unmatched MEPO vs. Placebo (MENSA/DREAM trial) BENRA Q8W vs. Placebo (matched for MENSA/DREAM trial)	-0.031	(-0.112 to 0.066)	NA	Rate ratio: 0.94	0.78–1.13	0.5207	A MAIC indirectly compares treatment interventions when baseline characteristics are imbalanced and the imbalances may cause treatment effects. The benralizumab and mepolizumab clinical trials have similarities in their design and patient populations but there are several differences in the recruited populations that create challenges in comparing the 2 treatment options through a conventional ITC. These differences include baseline eosinophil count, the proportion of patients with 2 or more exacerbations in the prior year, baseline maintenance OCS, and the definition of high-dose ICS. A MAIC makes the benralizumab and mepolizumab populations more similar by adjusting the individual trial data from the benralizumab trials (BENRA) to more closely match the aggregate baseline

								characteristics of the mepolizumab trials (MEPO) (please see MAIC report).
Annual rate of clinically significant exacerbations, in subgroup with >500 µg FP daily or equivalent (Summary of ITC analysis) (Ref.: Fig. 32 in [9])	Comparison: BENRA Q8W vs. Placebo: (SIROCCO/CALIMA trial), unadjusted MEPO vs. Placebo (MENSA/DREAM trial), unadjusted BENRA Q8W vs. Placebo (adjusted for MENSA/DREAM trial)	0.000	(-0.092 to 0.112)	NA	Rate ratio (After matching): 1.00	0.82–1.22	1	
Annual rate of exacerbations resulting in ER visit/hospitalisation in patients with ≥880 µg FP daily (Pooled MAIC results) (Ref.: Fig. 33 in [9])	Comparison: BENRA Q8W vs. Placebo: (SIROCCO/CALIMA trial), unadjusted MEPO vs. Placebo (MENSA/DREAM trial), unadjusted BENRA Q8W vs. Placebo (adjusted for MENSA/DREAM trial)	0.000	(-0.206 to 0.360)	NA	Rate ratio (After matching): 1.00	0.57-1.75	1	
Annual rate of exacerbations	Comparison: BENRA Q8W vs. Placebo:	0.101	(-0.130 to 0.480)	NA	Rate ratio (after matching): 1.21	0.73 -2.00	0.46	

resulting in ER visit/hospitalisation in patients with >500 µg FP daily or equivalent (Summary of ITC analysis) (Ref.: Fig. 34 in [9])	(SIROCCO/CALIMA trial), unadjusted MEPO vs. Placebo (MENSA/DREAM trial), unadjusted BENRA Q8W vs. Placebo (adjusted for MENSA/DREAM trial)							

* The MENSA trial was of 32 weeks duration, considerably different from the duration of the other three studies, i.e., 52 weeks in DREAM, 48 weeks in SIROCCO, and 56 weeks in CALIMA. Therefore, for each of the above two ICS dose scenarios, pre-bronchodilator FEV1 (L) was analysed at 32 weeks, end of the studies (including all four trials), and end of the studies (excluding MENSA). The MENSA trial was excluded from the end of study analysis owing to a shorter duration (32 weeks) in comparison to other trials.

9.2 Results per PICO - Pre-bronchodilator FEV1 (L), change from baseline

Table A4 Results referring to Pre-bronchodilator FEV1 (L), change from baseline

Results per outcome	*Attach forest plots and statistical results as a separate file.* *Results from the comparative analysis should be given in the table below, if possible.*							
		Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	Difference	CI	*P* value	Hazard/Odds/Risk ratio	CI	*P* value	
change from baseline in pre-bronchodilator FEV1 (L), in patients with ≥880 µg FP daily (Pooled MAIC results) (Ref.: Fig. 35 in [9])	Comparison*: BENRA Q8W vs. Placebo (SIROCCO/CALIMA), unadjusted MEPO vs. Placebo (MENSA/DREAM), unadjusted BENRA Q8W vs. Placebo (adjusted for MENSA/DREAM) MEPO 75 mg IV vs. Placebo (DREAM), unadjusted BENRA Q8W vs. Placebo (adjusted for DREAM trial)	Rate ratio – 32 Weeks (after matching): 0.03	-0.06 to 0.12	0.4898	Not applicable			
		Rate ratio – end of study (after matching): 0.02	-0.06 to 0.10	0.6626	Not applicable			
		Rate radio - End of study excluding MENSA (after matching): 0.03	-0.08 to 0.14	0.6720	Not applicable			
Pooled MAIC results for change from baseline in	Comparison*: BENRA Q8W vs. Placebo	Rate ratio – 32 Weeks	-0.03 to 0.12	0.281				

pre-bronchodilator FEV1 (L) in patients with >500 µg FP daily or equivalent (Ref.: Fig. 36 in [9])	(SIROCCO/CALIMA), unadjusted MEPO vs. Placebo (MENSA/DREAM), unadjusted BENRA Q8W vs. Placebo (adjusted for MENSA/DREAM) MEPO 75 mg IV vs. Placebo (DREAM), unadjusted BENRA Q8W vs. Placebo (adjusted for DREAM trial)	(after matching): 0.04						
		Rate ratio – end of study (after matching): 0.04	-0.03 to 0.12	0.2332	Not applicable			
		Rate radio - End of study excluding MENSA (after matching): 0.05	-0.06 to 0.16	0.38	Not applicable			

* The MENSA trial was of 32 weeks duration, considerably different from the duration of the other three studies, i.e., 52 weeks in DREAM, 48 weeks in SIROCCO, and 56 weeks in CALIMA. Therefore, for each of the above two ICS dose scenarios, pre-bronchodilator FEV1 (L) was analysed at 32 weeks, end of the studies (including all four trials), and end of the studies (excluding MENSA). The MENSA trial was excluded from the end of study analysis owing to a shorter duration (32 weeks) in comparison to other trials.

9.3 Results per PICO - Percentage reduction in OCS dose

Table A4 Results referring to Percentage reduction in OCS dose

Results per outcome	*Attach forest plots and statistical results as a separate file.* *Results from the comparative analysis should be given in the table below, if possible.*							
		Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	Difference	CI	*P* value	Hazard/Odds/Risk ratio	CI	*P* value	
Summary of ITC results for percent reduction in OCS dose at 24 weeks in patients with >500 µg FP daily or equivalent (Ref.: Fig. 37 in [9])	Comparison: BENRA 30 mg Q8W vs. Placebo: (ZONDA), unadjusted MEPO 100 mg vs. Placebo (SIRIUS), unadjusted BENRA 30 mg Q8W vs. Placebo (adjusted for SIRIUS trial)	Percent reduction (after matching): 6.08	-22.22 to 34.38	0.6737	Not applicable			
Summary of ITC results for percent reduction in OCS dose at the end of study in patients with >500 µg FP daily (Ref.: Fig. 38 in [9])	Comparison: BENRA 30 mg Q8W vs. Placebo: (ZONDA), unadjusted. MEPO 100 mg vs. Placebo (SIRIUS), unadjusted. BENRA 30 mg Q8W vs. Placebo (adjusted for SIRIUS trial)	Percent reduction (after matching): 5.06	-22.39 to 32.52	0.7177	Not applicable			

9.4 Results per PICO – Percentage reduction in OCS dose, Sensitivity analysis: adding ACQ score and prior omalizumab use for matching

Table A4 Results referring to percentage reduction in OCS dose - adding ACQ score and prior omalizumab use for matching

Results per outcome	*Attach forest plots and statistical results as a separate file.* *Results from the comparative analysis should be given in the table below, if possible.*							
		Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	Difference	CI	*P* value	Hazard/Odds/Risk ratio	CI	*P* value	
Sensitivity analysis: Summary of ITC results for percentage reduction in OCS dose at 24 weeks in patients with >500 µg FP daily (Ref.: Fig. 39 in [9])	Comparison: BENRA 30 mg Q8W vs. Placebo: (ZONDA), unadjusted MEPO 100 mg vs. Placebo (SIRIUS), unadjusted BENRA 30 mg Q8W vs. Placebo (adjusted for SIRIUS trial)	Percent reduction (after matching): 11.94	-17.20 to 41.08	0.4219				
Sensitivity analysis: Summary of ITC results for percentage reduction in OCS dose at the end of study in patients with >500 µg FP daily (Ref.: Fig. 40 in [9])	Comparison: BENRA 30 mg Q8W vs. Placebo: (ZONDA), unadjusted MEPO 100 mg vs. Placebo (SIRIUS), unadjusted	Percent reduction (after matching): 14.80	-12.38 to 41.98	0.2858				

	BENRA 30 mg Q8W vs. Placebo (adjusted for SIRIUS trial)							

9.5 Results per PICO - Patients with complete reduction in OCS dose at 24 weeks

Table A4 Results referring to Patients with complete reduction in OCS dose at 24 weeks

Results per outcome	*Attach forest plots and statistical results as a separate file.* *Results from the comparative analysis should be given in the table below, if possible.*							
		Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	Difference	CI	*P* value	Hazard/Odds/Risk ratio	CI	*P* value	
Base case: Summary of ITC results for proportion of patients with complete reduction in OCS dose at 24 weeks in patients >500 µg FP daily (Ref.: Fig. 41 in [9])	Comparison: BENRA 30 mg Q8W vs. Placebo: (ZONDA), unadjusted MEPO 100 mg vs. Placebo (SIRIUS), unadjusted BENRA 30 mg Q8W vs. Placebo (adjusted for SIRIUS trial)	Percent reduction (after matching): 2.32	0.48 to 11.15	0.2931				

9.6 Results per PICO - Patients with complete reduction in OCS dose at 24 weeks, Sensitivity analysis: adding ACQ score and prior omalizumab use for matching

Table A4 Results referring to Patients with complete reduction in OCS dose at 24 weeks, Sensitivity analysis: adding ACQ score and prior omalizumab use for matching

Results per outcome	*Attach forest plots and statistical results as a separate file.* *Results from the comparative analysis should be given in the table below, if possible.*							
		Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	Difference	CI	*P* value	Hazard/Odds/Risk ratio	CI	*P* value	
Sensitivity analysis: Summary of ITC results for proportion of patients with complete reduction in OCS dose at 24 weeks in patients >500 µg FP daily (Ref.: Fig. 42 in [9])	Comparison: BENRA 30 mg Q8W vs. Placebo: (ZONDA), unadjusted MEPO 100 mg vs. Placebo (SIRIUS), unadjusted BENRA 30 mg Q8W vs. Placebo (adjusted for SIRIUS trial)	Percent reduction (after matching): 3.02	0.52 to 17.49	0.2175				

9.7 Results per PICO – Annual rate of clinically significant exacerbations (ZONDA & SIRIUS trials)

Table A4 Results referring to Annual rate of clinically significant exacerbations (ZONDA & SIRIUS trials)

Results per outcome	*Attach forest plots and statistical results as a separate file.* *Results from the comparative analysis should be given in the table below, if possible.*							
		Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	Difference	CI	*P* value	Hazard/Odds/Risk ratio	CI	*P* value	
Base case: Summary of ITC analysis results for annual rate of clinically significant exacerbations in patients with >500 µg FP daily (Ref.: Fig. 43 in [9])	Comparison: BENRA 30 mg Q8W vs. Placebo: (ZONDA), unadjusted MEPO 100 mg vs. Placebo (SIRIUS), unadjusted BENRA 30 mg Q8W vs. Placebo (adjusted for SIRIUS trial)	Rate vs placebo reduction) -0.299	(-0.490 to 0.088)	NA	Rate ratio (After matching): 0.56	0.28 to 1.13	0.1086	

9.8 Results per PICO – Annual rate of clinically significant exacerbations (ZONDA & SIRIUS trials), Sensitivity analysis: adding ACQ score and prior omalizumab use for matching

Table A4 Results referring to Annual rate of clinically significant exacerbations (ZONDA & SIRIUS trials), Sensitivity analysis: adding ACQ score and prior omalizumab use for matching

Results per outcome	*Attach forest plots and statistical results as a separate file.* *Results from the comparative analysis should be given in the table below, if possible.*							
		Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	Difference	CI	*P* value	Hazard/Odds/Risk ratio	CI	*P* value	
Sensitivity analysis: Summary of ITC analysis results for annual rate of clinically significant exacerbations in patients with >500 µg FP daily (Ref.: Fig. 44 in [9])	Comparison: BENRA 30 mg Q8W vs. Placebo: (ZONDA), unadjusted MEPO 100 mg vs. Placebo (SIRIUS), unadjusted BENRA 30 mg Q8W vs. Placebo (adjusted for SIRIUS trial)	Rate vs placebo reduction): -0.265	-0.483 to 0.190	NA	Rate ratio (After matching): 0.61	0.29 to 1.28	0.1881	

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Protokol for vurdering af den kliniske merværdi af benralizumab til behandling af svær, eosinofil astma

Handelsnavn	Fasenra
Generisk navn	Benralizumab
Firma	AstraZeneca AB
ATC-kode	R03DX10
Virkningsmekanisme	Benralizumab er et monoclonalt antistof rettet mod interleukin 5 (IL-5) receptor. 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 receptorer medfører dermed en reduktion i antallet af eosinofile granulocytter, resulterende i bedre sygdomskontrol.
Administration/dosis	Benralizumab administreres ved en forfyldt injektionssprøjte. Den anbefalede dosis er 30 mg ved subkutan injektion hver 4. uge for de første 3 doser, dernæst hver 8. uge.
Forventet EMA-indikation	Tillægsvedligholdelsesbehandling til voksne patienter med svær, eosinofil astma, der er ukontrolleret trods højdosis inhalationssteroid samt langtidsvirkende β2-agonist. *("Fasenra is indicated as an add-on maintenance treatment in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus long-acting β-agonists.")*
Godkendelsesdato Offentliggørelsesdato Dokumentnummer Versionsnummer (Fagudvalgets sammensætning og sekretariatets arbejdsgruppe se bilag 1)	13. december 2017 13. december 2017 11402 1.0

Indhold

Forkortelser

ACQ 5:	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
FEV1:	Forced Expiratory Volume (forceret ekspirationsvolumen) på 1 sekund
GINA:	Global Initiative of Asthma
GRADE:	Grading of Recommendations Assessment, Development and Education System (System til vurdering af evidens)
HR:	Hazard Ratio
ICS:	Inhaleret corticosteroid
IL5:	Interleukin 5
LABA:	Long-acting beta2-agonist
LTRA:	Leukotrinreceptor antagonist
MD:	Mean Difference (gennemsnitlig forskel)
NO:	Nitrogenoxid
OCS:	Oral kortikosteroid
OR:	Odds Ratio
PICO:	Population, Intervention, Comparator (sammenligning) og Outcome (effektmål)
RR:	Relativ Risiko
SABA:	Short-acting beta2-agonist
SAEs:	Serious adverse events (alvorlige bivirkninger)
SD:	Standardafvigelse
SMD:	Standardized Mean Difference (standardiseret gennemsnitlig forskel)

1 Formål

Protokollen har til formål at definere de kliniske spørgsmål, der ønskes belyst i vurderingen af benralizumab med henblik på generel ibrugtagning til patienter med svær, eosinofil astma. I protokollen angives en definition af populationer, komparator og effektmål, der skal præsenteres i den endelige ansøgning samt de metoder, der ønskes anvendt til den komparative analyse. Arbejdet med protokollen er igangsat på baggrund af den foreløbige ansøgning vedrørende benralizumab modtaget den 15. november 2017.

Protokollen danner grundlaget for den endelige ansøgning for vurderingen af den kliniske merværdi af benralizumab sammenlignet med dansk standardbehandling. Alle effektmål, der er opgivet i denne protokol, skal besvares med en sammenlignende analyse mellem benralizumab vs. mepolizumab af både absolutte og relative værdier for de udspecificerede populationer i de angivne måleenheder (se tabel 2). Litteratursøgning og databehandling udføres som beskrevet i protokollen.

2 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). Symptomer kan optræde hele døgnet, og de kan svinde spontant eller efter specifik behandling. Fysiologisk er astma kendetegnet ved en reversibel, obstruktiv lungefunktionsnedsættelse, hvor lungefunktionen meget ofte vil være normal, når patienten ikke har symptomer. Stor astmasymptombyrde medfører generelle symptomer som påvirket søvn, træthed, uoplagthed, koncentrationsbesvær og nedsat selvværd og livskvalitet [1]. Astma kan debutere i alle aldre, men oftest i barndom eller ungdom. Debut før puberteten er associeret med en større sandsynlighed for, at astmaen har en allergisk komponent. Både arvelige og miljømæssige faktorer er af betydning for udvikling af astma [1]. Astma er hyppigst en selvstændig sygdom, men kan optræde som element i systemsygdomme.

Astma er en hyppigt forekommende kronisk sygdom i Danmark hos både børn og voksne. I dag vurderes det, at 7-11 % af den danske population har astma [1]. Prævalensen af **svær astma** er estimeret til at udgøre 5-15 % af alle patienter med astma [2]. Der indlægges ca. 1.500 patienter med akut astma om året i Danmark. Mildere tilfælde af akut astma, som håndteres af vagtlæge eller skadestue, er langt hyppigere [3].

Astmadiagnosen stilles på baggrund af karakteristiske symptomer og påvisning af variabel luftvejsobstruktion. Der findes ikke en gylden standard, som i alle sammenhænge kan stille diagnosen astma. Almindeligvis anvendes spirometri med reversibilitet, dvs. stigning i lungefunktionen efter enten hurtigvirkende, inhaleret betaagonist eller behandlingsforsøg med inhaleret eller systemisk kortikosteroid eller induktion af luftvejsobstruktion ved bronkiale provokationstest med anstrengelse, hyperventilation eller inhalation af metacholin eller mannitol. Der er mange differentialdiagnoser, hvor hyppigheden varierer med patientens alder og symptombillede [1,4]. Når astmadiagnosen stilles, skal omfanget og betydningen af eventuelle komorbiditeter og triggers (f.eks. allergi, røg, irritanter) beskrives. Sammenfattet bør alle astmapatienter udover farmakologisk behandling tilbydes astmauddannelse, behandles for og rådgives om komorbiditeter og modificérbare risikofaktorer samt udredes og behandles for allergi.

To adskilte begreber er centrale i håndteringen af astma. **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, behov for anfaldsmedicin, mens den fremtidige risiko vurderes ud fra bl.a. lungefunktion og evt. tidligere eksacerbationer [5]. 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. En patient kan således godt have mild, ukontrolleret astma.

Eosinofil astma er en undertype af astma, som er forbundet med øget antal eosinofile celler i luftvejsslimhinder. Der findes ingen tilgængelige metoder til direkte påvisning heraf i daglig klinisk praksis. I forskningssammenhæng kan eosinofil luftvejsinflammation påvises ved kikkertundersøgelse (bronkoskopi) med vævsprøver eller ved induceret sputum, hvor luftvejssekret analyseres for eosinofilkoncentration. Eosinofil luftvejsinflammation er positivt associeret til antallet af eosinofile celler i perifert blod og til koncentration af nitrogenoxid (NO) i udåndingsluft, som dermed kan bruges som proxyvariable [4]. Til svær, refraktær, eosinofil astma er en yderligere behandlingsmulighed tillægsterapi med mepolizumab (Nucala) eller reslizumab (Cinqaero), som begge er antistoffer rettet mod interleukin 5 (IL-5) [5]. 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 medfører dermed en reduktion i antallet af eosinofile granulocytter, resulterende i bedre sygdomskontrol.

2.1 Nuværende behandling

Global Initiative of Asthma (GINA) opdeler den medikamentelle astmabehandling i fem trin (se tabel 1) [5]. Der justeres op og ned i trin afhængig af astmakontrol. Inhalationssteroider udgør hjørnestenen i astmabehandlingen (trin 2-5), og man skelner mellem tre dosisintervaller: lav dosis, middel dosis og høj dosis. Inhalationsbehandling står helt centralt i den farmakologiske behandling af astma, og korrekt anvendelse er derfor af stor betydning.

Tabel 1: Behandlingstrin ved astma, oversat fra Global Initiative for Asthma 2017 report [5]

	Trin 1	***Trin 2***	***Trin 3***	***Trin 4***	***Trin 5*** *(Specialistopgave)*
Foretrukne forebyggende medicin		Overvej lav dosis ICS	Lav dosis ICS/LABA**	Medium/høj dosis ICS/LABA	Tillæg: Tiotropium*Ŧ, anti-IgE, anti-IL5*
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*Ŧ Høj dosis ICS + LTRA (eller + langsomt absorberbart teofyllin*)	Tillæg lav dosis OCS
Anfaldsmedicin	SABA		SABA pn eller lav dosis ICS/formoterol$^{\pi}$		

ICS: Inhaleret corticosteroid, LABA: Long-acting beta2-agonist, LTRA: Leukotrinreceptorantagonist, OCS: Oral corticosteroid, SABA: Short-acting beta2-agonist.

**: Ikke for børn under 12 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.

Ŧ: Tiotropium som Respimat er en tillægsbehandling for patienter med en historie med exacerbationer, ikke indiceret til børn under 12 år.

Dansk Lungemedicinsk Selskab (DLS) definerer **svær astma** i overensstemmelse med ERS (European Respiratory Society)/ATS (American Thoracic Society) guidelines [2,4]: 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 anbefales for at sikre diagnosen, og at den manglende sygdomskontrol ikke skyldes forkert diagnose, manglende adhærens med den ordinerede behandling, behandlelige komorbiditeter eller undgåelige triggers [2].

De fleste patienter med svær astma kan opnå kontrol med behandling på GINA trin 4, eksempelvis med tillæg af LAMA, LTRA og/eller theofyllin. I forbindelse med justering af behandlingen bør det også overvejes, om bedre behandlingseffekt og lavere bivirkningsrisiko, herunder ikke mindst bivirkninger ved systemisk steroid behandling, kan opnås ved valg/tillæg af andre lægemidler inden for samme gruppe af lægemidler, herunder primært valg af inhalationssteroid [4]. Dette kan kræve et intensivt forløb med justering af medicin samt afdækning af modificérbare risikofaktorer og komorbiditet (f.eks. rhinitis, rygning, overvægt, allergeneksposition), sikring af adhærens og oplæring i korrekt inhalationsteknik. Det er vigtigt, at der er fokus på denne del af astmabehandlingen, når rammerne for behandling af svær astma udstikkes [2].

Der vil dog være en mindre andel af patienter, som ikke opnår tilstrækkelig sygdomskontrol trods ovenstående tiltag, og som derfor har svær, refraktær astma. For patienter med eosinofil, svær, refraktær astma er der mulighed for tillægsterapi i form af de biologiske lægemidler mepolizumab og reslizumab.

2.2 Benralizumab

Benralizumab er et monoclonalt antistof rettet mod interleukin 5 (IL-5) receptor [5]. 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-receptorer medfører dermed en reduktion i antallet af eosinofile granulocytter, resulterende i bedre sygdomskontrol. Benralizumab er indiceret som tillægsbehandling ved svær, refraktær, eosinofil astma, som er ukontrolleret trods behandling med højdosis inhalationssteroid samt langtidsvirkende β2-agonist.

Benralizumab administreres ved en forfyldt injektionssprøjte. Den anbefalede dosis er 30 mg ved subkutan injektion hver 4. uge for de første 3 doser, dernæst hver 8. uge. Benralizumab anvendes som langtidsbehandling, og bør administreres af en sundhedsprofessionel. Fortsat behandling bør revurderes mindst en gang årligt, baseret på astmasværhedsgrad og eksacerbationskontrol. Benralizumab skal opbevares ved 2-8°C.

3 Klinisk spørgsmål

Nedenfor beskrives det kliniske spørgsmål, som danner grundlag for Medicinrådets vurdering af den kliniske merværdi af benralizumab til behandling af svær, eosinofil astma. Der er valgt én komparator, mepolizumab, da evidensen for dette lægemiddel er baseret på studier hvor populationen bedst relaterer sig til danske forhold.

Da benralizumab er en tillægsbehandling til svær refraktær 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.

Der findes ikke en generel definition for svær, refraktær astma, og derfor vil der fremadrettet i denne protokol benyttes udtrykket "svær astma" om den patientpopulation, der undersøges.

3.1 Hvilken klinisk merværdi tilbyder benralizumab sammenlignet med mepolizumab ved behandling af patienter med svær, eosinofil astma?

Population
Patienter > 18 år med svær, eosinofil astma.

Intervention
Benralizumab 30 mg ved subkutan injektion hver 4. uge for de første 3 doser, dernæst hver 8. uge (+ standardbehandling).

Komparator
Mepolizumab (+ standardbehandling).

3.2 Valg af effektmål

Valg af de kliniske effektmål og dertilhørende vigtighed og mindste kliniske relevante forskelle er truffet på baggrund af fagudvalgets vurdering af relevans for sygdommen og behandlingen for patienter med svær astma. For alle effektmål vurderes forskellen i opnået effekt mellem intervention og komparatorer.

Tabel 2 summerer de valgte effektmål, deres vigtighed, mindste klinisk relevante forskel og kategori. For alle effektmål ønskes både absolutte og relative værdier, jævnfør ansøgningsskemaet. For de relative værdier vurderes den kliniske relevans (merværdi), jævnfør væsentlighedskriterierne beskrevet i Medicinrådets metodehåndbog for vurdering af nye lægemidler. De relative effektestimater kan angives i relativ risiko (RR), rate ratio, odds ratio (OR) eller hazard ratio (HR). Det skal begrundes i ansøgningen, hvis der afviges fra de ønskede effektmål.

Tabel 2: Oversigt over valgte effektmål. For hvert effektmål er angivet deres vigtighed. For kritiske og vigtige effektmål er desuden angivet den mindste klinisk relevante forskel.

Effektmål*	Vigtighed	Måleenhed	Mindste klinisk relevante forskel
Mortalitet[§]	Kritisk		
Eksacerbationsrate	Kritisk	1. Gennemsnitlig reduktion i årlige antal eksacerbationer	1. Minimum reduceret med 0,5 årlig eksacerbation
		2. Andel af patienter som opnår 0 årlige eksacerbationer	2. 10 procentpoint
Peroral vedligeholdelses-behandling med kortikosteroid	Kritisk	1. Gennemsnitlig %-reduktion i daglig dosis (vedligeholdelsesbehandling)	1. 20 % (dog minimum 2,5 mg prednisolon ækvivalent)
		2. Andel af patienter som bliver helt fri for vedligeholdelsesbehandling med peroral kortikosteroid	2. 5 procentpoint
		3. Andel af patienter som opnår ≥ 50 % reduktion af peroral kortikosteroid	3. 10 procentpoint

Lungefunktion FEV_1	Vigtig	1. Gennemsnitlig ændring i lungefunktion	1. 200 ml for voksne
		2. Andelen af patienter der opnår en forbedring på 200 ml (voksne)	2. 15 procentpoint
Astmakontrol	Vigtig	Gennemsnitlig ændring i astmakontrol. I prioriteret rækkefølge ønskes data fra: • ACQ 5 (Asthma Control Questionnaire) • ACT (Asthma Control Test) • Andre lignende spørgeskemaer	ACQ: 0,5 ACT: 3
Livskvalitet	Vigtig	Gennemsnitlig ændring i livskvalitet. I prioriteret rækkefølge ønskes data fra: • Astma Quality of Life Questionnaire (AQLQ) • Øvrige skemaer	AQLQ: 0,5
Serious adverse events (SAEs)	Vigtig	Den samlede forekomst (antal) af SAEs	5 procentpoint for den samlede forekomst af SAEs
		Specifikke undertyper af SAEs, herunder anafylaksi, vurderes, ift. om det præsenterer sig ensartet mellem grupperne	Der angives ikke en klinisk relevant forskel for forekomsten af specifikke SAEs (se afsnit 3.5)
Frafald af patienter i studier	Vigtigt	Andel af patienter som er frafaldet ved studiets afslutning (forskel mellem "intention to treat"-populationen og afsluttede patienter)	10 procentpoint
Sygefravær	Vigtigt	Gennemsnitligt antal sygedage pr. år – dage hvor pt. ikke kan gå i skole eller på arbejde	5 dage per år
Eosinofil count	Mindre vigtigt		
Adverse events	Mindre vigtigt		

** For alle effektmål ønskes data med længst mulig opfølgningstid.*

§ Mortalitet anses altid for at være et kritisk effektmål, om end ikke et effektivt effektmål i vurderingen af biologiske lægemidler inden for svær astma. Astmarelateret død indtræder sjældent, og det anslås derfor ikke, at dette effektmål vil give nogen relevant information til vurderingen af et nyt lægemiddel. I forhold til sikkerhed indgår det i effektmålet vedr. alvorlige uønskede hændelser (SAEs). Mortalitet vil derfor ikke optræde som et særskilt effektmål i vurderingen af lægemidlet.

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 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 [6]. Den mindste klinisk relevante forskel i absolutte tal skal dog være en forskel på minimum 0,5 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.

En forskel på 10 procentpoint betyder, at man vil anse det for at være klinisk relevant, hvis f.eks. > 20 % bliver helt fri for eksacerbationer i interventionsgruppen, mens det kun er tilfældet for < 10 % i komparatorgruppen. I det tilfælde, at man har 100 patienter, vil det svare til 10 personer i absolutte tal.

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 per 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.

En forskel på 5 procentpoint betyder, at man vil anse det for at være klinisk relevant, hvis f.eks. > 15 % bliver helt fri for oral steroid vedligeholdelsesbehandling i interventionsgruppen, mens det kun er tilfældet for < 10 % i komparatorgruppen. I det tilfælde, at man har 100 patienter, vil det svare til 5 personer i absolutte tal.

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.

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 [7,8]. 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 5 (ACQ5) 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 ACQ5-data ikke er til rådighed. Data fra øvrige astmakontrolspørgeskemaer medtages, hvis ACQ5 eller ACT ikke er anvendt. Mindste klinisk relevante forskelle er defineret i de enkelte måleredskaber og er 0,5 for ACQ [5]. For ACT er den klinisk relevante forskel 3 point [5]. 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). Den mindste kliniske forskel er defineret i redskabet og er 0,5 [9]. Der ønskes data på den gennemsnitlige forskel i ændringen af livskvalitet mellem intervention og komparator.

Serious adverse events (SAEs) er i sagens natur alvorlige. Fagudvalget har vurderet, at SAEs er et vigtigt effektmål for behandling af svær astma med biologiske lægemidler. SAEs 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 SAEs 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 SAEs anses en forskel mellem grupperne på 5 procentpoint for at være klinisk relevant. Fagudvalget vil desuden vurdere forekomsten af specifikke undertyper af SAEs, 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.

Mindre vigtige effektmål

Eosinofil count i blodet er en surrogatmarkør og anses for mindre vigtigt.

Adverse events er i denne forbindelse vurderet af fagudvalget til at være mindre vigtigt.

4 Litteratursøgning

Vurderingen af klinisk merværdi baseres på data fra publicerede fuldtekstartikler og data fra EMAs EPAR – Public assessment report. Data skal derudover stemme overens med protokollens beskrivelser. Upublicerede data, og data fra f.eks. abstracts kan fremsendes og vil indgå i vurderingen, såfremt Medicinrådet finder, at de er nødvendige for at sikre en fair sammenligning. Data skal i så fald stamme fra

de forsøg, hovedpublikationerne rapporterer fra, og ansøger skal acceptere, at Medicinrådet offentliggør dem i ansøgningsskemaet og i rapporten vedr. klinisk merværdi.

Databaser for søgningen

Relevant litteratur søges i databaserne MEDLINE (via PubMed eller Ovid) og CENTRAL (via Cochrane Library). Derudover skal EMAs European public assessment reports (EPAR) konsulteres for både det aktuelle lægemiddel og dets komparator(er).

For alle databaser gælder, at der søges i den senest tilgængelige udgave. For MEDLINE indebærer dette, at også en særlig database med endnu ikke indekserede artikler bliver inkluderet.

Søgetermer

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

Søgningen skal som minimum indeholde termer, som er beskrivende for de områder, der angivet i tabellen herunder. Både indekseret (f.eks. Medical Subject Headings, MeSH) og fritekstsøgning skal anvendes.

Sygdommen afgrænses til det overordnede *asthma* og ikke f.eks. *severe asthma*, da denne betegnelse ikke anvendes konsistent i den internationale litteratur. Stoffernes generiske navne *benralizumab*, *mepolizumab* inkluderes i søgningen sammen med deres handelsnavne: *Fasenra*, *Nucala*. Vær opmærksom på forskellige stavemåder. Hvor der er relevante indekseringstermer (f.eks. Medical Subject Headings, MeSH), inkluderes disse i søgningen, ligesom der tages højde for alternative stavemåder og forskellige ordendelser.

<table>
<tr>
<td>Lægemiddel

• Benralizumab
• Fasenra

Udover termer for det generiske navn, handelsnavn og alternative stavemåder og eventuelle MeSH/Supplementary Concepts kombineres med OR. AND kan bruges, hvor flere termer skal forekomme samtidigt for at beskrive lægemidlet korrekt, f.eks. ved coformuleringer.</td>
<td rowspan="3">Blokkene til venstre og højre kombineres med AND</td>
<td rowspan="3">Indikation

• Astma

Termer for indikationen, alternative stavemåder og eventuelle MeSH kombineres med OR. AND kan bruges, hvor flere termer skal forekomme samtidigt for at beskrive indikationen korrekt.</td>
</tr>
<tr>
<td>Ovenstående og nedenstående blokke kombineres med OR</td>
</tr>
<tr>
<td>Komparator

• Mepolizumab
• Nucala</td>
</tr>
</table>

De anvendte søgetermer, og hvordan de er blevet kombineret, dokumenteres separat for hver af de to databaser.

Kriterier for udvælgelse af litteratur

Der ekskluderes først på titel- og abstractniveau, dernæst ved gennemlæsning af fuldtekstartikler. Artikler, der ekskluderes ved fuldtekstlæsning, skal fremgå med forfatter, årstal og titel i en eksklusionsliste, hvor eksklusionen begrundes kort. Den samlede udvælgelsesproces skal afrapporteres ved brug af et PRISMA-flowdiagram (http://prisma-statement.org/PRISMAStatement/FlowDiagram.aspx).

Ved usikkerheder om hvorvidt en artikel på titel- og abstract-niveau lever op til inklusions- og eksklusionskriterierne, skal der anvendes et forsigtighedsprincip til fordel for artiklen, hvorved fuldtekstartiklen vurderes.

Studier ekskluderes på baggrund af de PICO-beskrivelser, der er angivet under hvert klinisk spørgsmål. Studierne skal rapportere mindst ét af de kritiske eller vigtige effektmål. Hvis der findes randomiserede kontrollerede studier, som kan besvare de kliniske spørgsmål, inkluderes data fra disse. Hvis der ikke findes randomiserede kontrollerede studier, kan data fra ukontrollerede kliniske studier inddrages.

Data kan også ekstraheres fra EMAs EPAR, selvom denne ikke identificeres i litteratursøgningen.

5 Databehandling/analyse

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

Alt relevant data skal som udgangspunkt ekstraheres ved brug af Medicinrådets ansøgningsskema. Der skal udføres en komparativ analyse for hvert enkelt effektmål på baggrund af relevant data fra inkluderede studier. For hvert effektmål og studie angives analysepopulation (f.eks. intention-to-treat (ITT), per-protocol) samt metode. Resultater for ITT-populationen skal angives hvis muligt, hvis komparative analyser ikke i udgangspunktet er baseret på denne population. Alle ekstraherede data skal krydstjekkes med de resultater, der beskrives i EPAR'en. Findes uoverensstemmelser, gives en mulig grund herfor.

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

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

For alle effektmål skal både absolut og relativ forskel angives. Den relative forskel vil 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 risiko reduktion (ARR) = 30 – 30*0,5 = 15 %-point).

Hvis der er mere end et sammenlignende studie, foretages en metaanalyse for de effektmål, hvor det er metodemæssigt forsvarligt. Herunder en vurdering af om studierne er homogene nok til at kunne sammenlignes i en metaanalyse. Hvis der ikke foreligger sammenlignende studier, kan data eventuelt syntetiseres indirekte (evt. i form af formelle netværksmetaanalyser eller ved brug af Buchers metode), hvis intervention og komparator er sammenlignet med samme alternative komparator i separate studier.

Medicinrådet forbeholder sig retten til at foretage sensitivitets- og subgruppeanalyser på baggrund af studiernes validitet og relevans.

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

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

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

6 Referencer

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7 Bilag: Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende svær astma

Navn	**Udpeget af**
Uffe Christian Heitmann Bødtger, formand *Overlæge, ph.d., forskningslektor*	Formand, Lægevidenskabelige selskaber (LVS)
Kirsten Sidenius *Praktiserende speciallæge, ph.d.*	Udpeget af formanden
Pernille Hauschildt *Ledende overlæge*	Region Midtjylland
Hanne Madsen *Ledende overlæge, ph.d.*	Region Syddanmark
Niels Maltbæk *Overlæge*	Region Sjælland
Lars Pedersen *Overlæge, ph.d., klinisk lektor*	Region Hovedstaden
Bo Chawes *Afdelingslæge, seniorforsker, dr.med., ph.d.*	Dansk Pædiatrisk Selskab
Helena Marjanovic *Farmaceut*	Dansk Selskab for Sygehusapoteksledelse (DSS)
Daniel Pilsgaard Henriksen *Læge, ph.d.*	Dansk Selskab for Klinisk Farmakologi (DSKF)
2 patienter eller patientrepræsentanter	Danske Patienter

Medicinrådets sekretariat

Projekt- og metodeansvarlig: Louise Klokker Madsen Mail: lkm@medicinraadet.dk Tlf.: 21 30 39 47	Medicinrådet Dampfærgevej 27-29 2100 København Ø
Fagudvalgskoordinator: Anette Pultera Nielsen Mail: apn@medicinraadet.dk Tlf.: 21 34 09 77	