Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende baricitinib til behandling af moderat til svær atopisk eksem hos voksne (≥ 18 år)

Vers. 1.0

Bilagsoversigt

1. Medicinrådets sundhedsøkonomiske afrapportering vedr. baricitinib til behandling af moderat til svær atopisk eksem hos voksne (≥ 18 år), version 1.0
2. Forhandlingsnotat fra Amgros vedr. baricitinib
3. Høringssvar fra ansøger
4. Medicinrådets vurdering vedrørende baricitinib til behandling af moderat til svær atopisk eksem hos voksne (≥ 18 år), version 1.1
5. Ansøgers endelige ansøgning
6. Ansøgers tekniske dokument til den sundhedsøkonomiske ansøgning
7. Medicinrådets protokol for vurdering vedr. baricitinib til behandling af moderat til svær atopisk eksem hos voksne (≥ 18 år), version 1.0

Medicinrådet

Medicinrådets sundhedsøkonomiske afrapportering

Baricitinib

Voksne med moderat til svær atopisk eksem

Version 1.0

Om Medicinrådet

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

Dokumentets formål

Den sundhedsøkonomiske analyse indeholder Medicinrådets vurdering af de inkrementelle omkostninger pr. patient og budgetkonsekvenserne ved anbefaling. Værdien for patienten og omkostningerne for samfundet danner grundlaget for Medicinrådets beslutning om, hvorvidt lægemidlet anbefales som mulig standardbehandling. Dette bliver sammenfattet i Medicinrådets anbefaling vedr. lægemidlet.

Den sundhedsøkonomiske analyse er udarbejdet efter Metodevejledning for omkostningsanalyse af nye lægemidler og indikationsudvidelser i hospitalssektoren.

Dokumentoplysninger	
Godkendelsesdato	26. maj 2021
Dokumentnummer	115933
Versionsnummer	1.0

Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 26. maj 2021

Indholdsfortegnelse

1. Begreber og forkortelser

AIP	Apotekernes indkøbspris
DKK	Danske kroner
DRG	Diagnose Relaterede Grupper
SAIP	Sygehusapotekernes indkøbspriser

2. Konklusion

Inkrementelle omkostninger og budgetkonsekvenser
I det scenarie, Medicinrådet mener er mest sandsynligt, er de inkrementelle omkostninger for baricitinib ca. [redacted] DKK pr. patient om året sammenlignet med dupilumab. Der vil således i gennemsnit være [redacted] DKK pr. patient, hvis de behandles med baricitinib sammenlignet med dupilumab. Når analysen er udført med apotekets indkøbspriser (AIP), er de inkrementelle omkostninger til sammenligning ca. -37.000 DKK pr. patient.

Analysen er en omkostningsminimeringsanalyse, da fagudvalget vurderer, at der ikke er grund til at tro, at effekten af baricitinib skulle være dårligere eller bedre end effekten af dupilumab. De inkrementelle omkostninger er næsten udelukkende drevet af lægemiddelomkostningerne, [redacted]. Følsomhedsanalyserne af de centrale parametre viser, at der ikke er store usikkerheder forbundet med analysens resultat.

Analysen har en tidshorisont på et år på trods af, at der potentielt kan være tale om livslang behandling. Det er valgt af ansøger og accepteret af Medicinrådet, [redacted]

Medicinrådet vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af baricitinib som mulig standardbehandling vil være ca. [redacted] DKK i år 5. Når analysen er udført med AIP, er budgetkonsekvenserne ca. -5,4 mio. DKK i år 5.

3. Introduktion

Formålet med analysen er at estimere de gennemsnitlige inkrementelle omkostninger pr. patient og de samlede budgetkonsekvenser for regionerne ved anbefaling af baricitinib som mulig standardbehandling på danske hospitaler til voksne patienter med moderat til svær atopisk eksem.

Medicinrådet modtog den 24. februar 2021 en endelig ansøgning fra Eli Lilly, der inkluderede en analyse af de gennemsnitlige inkrementelle omkostninger pr. patient og de samlede budgetkonsekvenser for regionerne ved anbefaling af baricitinib.

3.1 Patientpopulation

Atopisk eksem er en kronisk eller kronisk recidiverende eksemsygdom karakteriseret ved udslæt og kløe samt perioder med akut opblussen. Moderat til svær atopisk eksem er karakteriseret ved udtalt tørhed, rødme, afskalning, evt. papler/vesikler, ekskoriationer (forkradsninger) og lichenisering (fortykkelse af huden). Huden er ofte hævet med udslæt, revner og kroniske fortykkelser. Den defekte hudbarriere fører til en øget risiko for infektioner [1].

Den relevante population for denne analyse er voksne patienter med moderat til svær atopisk eksem, som er kandidater til systemisk behandling, som har haft utilstrækkelig effekt af optimeret lokalbehandling og én systemisk behandling eller ikke er kandidater til de øvrige systemiske behandlinger. Fagudvalget anslår, at der aktuelt er ca. 225 voksne patienter, som vil være kandidater til baricitinib. Fagudvalget anslår, at ca. 30 nye patienter om året vil være kandidater til enten dupilumab eller baricitinib [1].

3.1.1 Komparator

Medicinrådet har vurderet den kliniske værdi af baricitinib på baggrund af følgende kliniske spørgsmål:

Klinisk spørgsmål 1:

Hvad er værdien af baricitinib og optimeret lokalbehandling sammenlignet med dupilumab og optimeret lokalbehandling for patienter med moderat til svær atopisk eksem, som har haft utilstrækkelig effekt af optimeret lokalbehandling og mindst én systemisk behandling, eller som ikke er kandidater til de øvrige systemiske behandlinger?

4. Vurdering af den sundhedsøkonomiske analyse

I sin ansøgning har ansøger indsendt en sundhedsøkonomisk analyse, der består af en omkostningsanalyse og en budgetkonsekvensanalyse. I omkostningsanalysen estimeres de inkrementelle omkostninger pr. patient for baricitinib sammenlignet med dupilumab. Medicinrådet vurderer nedenfor den sundhedsøkonomiske analyse, som ansøger har indsendt.

4.1 Antagelser og forudsætninger for model

Den kliniske sammenligning af effekten mellem baricitinib og dupilumab er lavet på baggrund af data fra fire studier: BREEZE AD 7 [2], BREEZE AD 4 [3], CAFÉ [4] og CHRONOS [5]. Ansøger har udført følgende indirekte sammenligninger:

- BREEZE AD 7 vs. CAFÉ/CHRONOS (hvor data for dupilumab er samlet i metaanalyser)
- BREEZE AD 7 vs. CHRONOS

- BREEZE AD 4 vs. CAFÉ

Fagudvalget anvender kun den indirekte sammenligning mellem BREEZE AD 4 og CAFÉ i den kliniske vurdering. BREEZE AD 4 er et fase III, multicenter, dobbeltblindet, randomiseret, placebokontrolleret studie, hvor baricitinib doseres som enten 1 mg, 2 mg eller 4 mg én gang dagligt og i kombination med topikale steroider og sammenlignes med placebo i kombination med topikale steroider. CAFÉ er et randomiseret, placebo-kontrolleret fase III-studie. Her sammenlignes dupilumab (subkutan) 300 mg hver uge + topikale steroider og dupilumab (subkutan) 300 mg hver anden uge + topikale steroider med placebo + topikale steroider.

4.1.1 Modelbeskrivelse

Ansøger har indsendt en omkostningsminimeringsanalyse til at estimere omkostningerne forbundet med behandling med baricitinib og dupilumab.
Omkostningsminimeringsanalysen er valgt, da ansøger i den kliniske sammenligning argumenterer for, at der ikke er nogen effektmæssig forskel mellem baricitinib og dupilumab. Dermed indgår der ingen effektmål i den sundhedsøkonomiske analyse. Ansøger antager, at der ikke er forskel på behandlingslængden med baricitinib og dupilumab. Da effekten antages at være ens for baricitinib og dupilumab, har ansøger ikke inkluderet andel af patienter, der ophører behandling på grund af manglende effekt. Af den samlede patientpopulation, der kandiderer til behandling med baricitinib, antager ansøger, at 90 % af patienterne allerede vil være i behandling med dupilumab og derfor ikke har nogle omkostninger til opstart af behandling.

Medicinrådets vurdering af ansøgers valg af model
Fagudvalget vurderer på baggrund af det kliniske datagrundlag, at der ikke er grund til at tro, at der er forskel i effekten mellem baricitinib og dupilumab. Medicinrådet accepterer derfor ansøgers valg af model.

Medicinrådet accepterer ansøgers valg af model.

4.1.2 Analyseperspektiv

I overensstemmelse med Medicinrådets metoder har ansøger valgt et begrænset samfundsperspektiv til sin analyse. Analysen har en tidshorisont på 1 år. Selvom behandlingen potentielt er livslang, argumenterer ansøger for, at den valgte tidshorisont er tilstrækkelig lang til at kunne illustrere forskelle i omkostninger mellem baricitinib og komparator. På baggrund af den valgte tidshorisont er der ikke anvendt en diskonteringsrate.

Medicinrådets vurdering af ansøgers analyseperspektiv
[redacted]

Medicinrådet accepterer ansøgers analyseperspektiv.

4.2 Omkostninger

I det følgende præsenteres ansøgers antagelser for omkostningerne i den sundhedsøkonomiske analyse af baricitinib sammenlignet med dupilumab. Ansøger har inkluderet lægemiddelomkostninger, hospitalsomkostninger, bivirkningsomkostninger og patientomkostninger.

4.2.1 Lægemiddelomkostninger

Ansøger anvender de lægemiddeldoseringer, som er angivet i Medicinrådets protokol for baricitinib. Baricitinib administreres som tablet af 4 mg én gang dagligt. Ved behandling med dupilumab anvendes en initial dosis af 600 mg (2 x 300 mg) efterfulgt af vedligeholdelsesdosis på 300 mg hver anden uge. Uanset om patienterne behandles med baricitinib eller dupilumab, skal patienterne i tillæg behandles med optimeret lokalbehandling i form af fugtighedscreme, topikale steroider og topikal calcineurininhibitorer. Ansøger har inkluderet omkostninger til optimeret lokalebehandling ved behandling med baricitinib og dupilumab. Ansøger har jf. *Metodevejledning for omkostningsanalyser af nye lægemidler og indikationer i hospitalssektoren* estimeret lægemiddelomkostninger på baggrund af apotekets indkøbspris (AIP).

Medicinrådets vurdering af ansøgers antagelser vedr. lægemiddelomkostninger
Medicinrådet accepterer ansøgers antagelser vedr. lægemiddelomkostninger. Medicinrådet har udskiftet AIP med sygehusapotekets indkøbspris (SAIP), se Tabel 1.

Tabel 1. Anvendte lægemiddelpriser, SAIP, (marts 2021)

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Kilde
Baricitinib	4 mg	28 stk.	[redacted]	Amgros
Dupilumab	300 mg	2 stk.	[redacted]	Amgros

Medicinrådet ekskluderer omkostningerne til optimeret lokalbehandling fra Medicinrådets hovedanalyse, da omkostningerne er ens, uanset om patienterne behandles med baricitinib eller dupilumab.

Medicinrådet accepterer ansøgers antagelser vedr. lægemiddelomkostninger, men ekskluderer omkostninger til optimeret lokalbehandling i egen hovedanalyse.

4.2.2 Hospitalsomkostninger

Administrationsomkostninger

Baricitinib indtages peroralt i hjemmet, og ansøger har derfor ikke inkluderet administrationsomkostninger for baricitinib. Dupilumab administreres subkutant. På baggrund af kliniske eksperters vurdering antager ansøger, at 10 % af patienterne skal have hjælp til hver administration med dupilumab af en sygeplejerske. Ansøger antager, at en sygeplejerske bruger 10 min. pr. administration. Ansøger anvender Medicinrådets værdisætning af enhedsomkostninger, hvor en sygeplejerskes timeomkostning er 544 DKK.

Medicinrådets vurdering af ansøgers antagelser vedr. administrationsomkostninger
Fagudvalget vurderer, at ansøgers antagelse om, at 10 % af patienterne, der behandles med dupilumab, skal have hjælp til hver administration af en sygeplejerske, er overestimeret. Fagudvalget vurderer, at ca. 1-2 % af patienterne, der behandles med dupilumab, får hjælp af en sygeplejerske. Medicinrådet ændrer derfor andelen til 1,5 % i Medicinrådets hovedanalyse. Fagudvalget vurderer yderligere, at det tager en sygeplejerske 15 min. pr. administration af dupilumab, hvilket Medicinrådet tilpasser i sin hovedanalyse. Ændringerne har minimal betydning for analysens resultat.

Medicinrådet ændrer andelen af patienter, der skal have hjælp af en sygeplejerske til administration af dupilumab til 1,5 % og antager, at hver administration hos en sygeplejerske tager 15 min. i egen hovedanalyse.

Monitoreringsomkostning

Ansøger antager, at patienter i gennemsnit vil have to konsultationer hos en dermatolog i induktionsperioden (16 uger) og 2,5 konsultationer pr. år i vedligeholdelsesperioden, uanset om patienterne behandles med baricitinib eller dupilumab.

I induktionsperioden antager ansøger, at patienter, der behandles med baricitinib, vil have én konsultation med en sygeplejerske, mens patienter, der behandles med dupilumab, i gennemsnit vil have 2,7 konsultationer med en sygeplejerske. Hver konsultation antages at tage 20 min, og ansøger anvender timeomkostningen for en sygeplejerske på 544 DKK jf. *Medicinrådets værdisætning af enhedsomkostninger*.

Ansøger antager, at patienter, der behandles med baricitinib, skal have taget to blodprøver i induktionsperioden og fire årligt i vedligeholdelsesperioden. For patienter i behandling med dupilumab antager ansøger, at patienter får taget én blodprøve i opstart af behandlingen og én blodprøve årligt i vedligeholdelsesperiode. Ansøger anvender en enhedsomkostning på 256 DKK pr. blodprøve, som er baseret på priser fundet ved Rigshospitalets Labportal.

Medicinrådets vurdering af ansøgers antagelser vedr. monitoreringsomkostninger
Medicinrådet accepterer ansøgers tilgang vedr. monitoreringsomkostninger, men ekskluderer omkostningerne til konsultationer hos dermatolog, da omkostninger er de samme, uanset om patienten modtager baricitinib eller dupilumab i egen hovedanalyse.

Bivirkningsomkostninger

Ansøger har inkluderet omkostninger forbundet med bivirkninger ved behandling med baricitinib og dupilumab, og her anvendes de rapporterede bivirkningsrater fra de kliniske studier, BREEZE AD 4 og CAFÉ. Følgende bivirkninger er rapporteret: reaktion ved indstikssted, allergisk eller smitsom øjenbetændelse, oral herpes samt infektion i øvre luftveje.

Ansøger antager, at en reaktion ved indstikssted og oral herpes ikke medfører afledt behandling. For patienter med øjenbetændelse antager ansøger, at alle patienterne behandles med øjengel. Det antages, at 10 % af tilfældene kræver behandling med Ultracortenol. Ydermere vil 10 % af patienterne, der modtager Ultracortenol, også have behov for at se en øjenlæge. Ansøger anvender en timeomkostning for konsultation ved en

øjenlæge på 1.283 DKK fra Kommunernes og Regionernes Løndatakontor. For infektion i øvre luftvej antager ansøger, at 25 % af alle tilfælde vil kræve en konsultation på ca. 15 min. ved en praktiserende læge. Hertil anvender ansøger samme timeomkostning på 1.283 DKK for en praktiserende læge.

Medicinrådets vurdering af ansøgers antagelser vedr. bivirkningsomkostninger
Bivirkningsfrekvenser for baricitinib og dupilumab kan ses i Tabel 2.

Tabel 2. Bivirkningsfrekvenser ved behandling med baracitinib rapporteret i hhv. BREEZE AD 4 og CAFÉ

	Baricitinib [%]	Dupilumab [%]
Reaktion ved indstikssted	0,0	9,0
Allergisk øjenbetændelse	3,0	40,0
Smitsom øjenbetændelse	0,0	26,0
Oral herpes	17,0	6,0
Infektion i øvre luftvej	7,0	0,0

Fagudvalget vurderer, at 50 % af de patienter, der får Ultracortenol mod øjenbetændelse, også vil have behov for en lægekonsultation. Medicinrådet ændrer derfor andelen i sin hovedanalyse, men det har minimal betydning for analysens resultat. Fagudvalget vurderer, at patienter vil have omkostninger til behandling af oral herpes. Dette inkluderer Medicinrådet i hovedanalysen. Patienterne køber selv medicin til behandling af bivirkningerne på apoteket. Medicinrådet rykker derfor omkostninger til behandling af bivirkninger fra hospitalsomkostninger til patientomkostninger.

Medicinrådet accepterer ansøgers tilgang vedr. bivirkningsomkostninger, men hæver andelen af de patienter, der har behov for lægekonsultation ved øjenbetændelse og tilføjer omkostninger til behandling af oral herpes. Omkostninger til behandling, som købes på apoteket, rykkes til patientomkostninger.

4.2.3 Patientomkostninger

Patientomkostninger er estimeret på baggrund af administrations- og monitorerings-besøg på hospitalet og inkluderer patientens effektive tid på hospitalet og transporttid ved dermatologiske konsultationer. Ansøger anvender en enhedsomkostning for patienttid på 179 DKK pr. time og transportomkostninger på 100 DKK pr. besøg, jf. *Medicinrådets værdisætning af enhedsomkostninger*.

Medicinrådets vurdering af ansøgers antagelser vedr. patientomkostninger
Medicinrådet tilføjer omkostninger til behandling af bivirkninger under patientomkostninger og inkluderer patientomkostninger til kontrol ved en dermatologisk sygeplejerske. Yderligere tilpasses patientomkostningerne relateret til administration af dupilumab hos

en sygeplejerske, jf. fagudvalgets vurdering om, at 1,5 % af patienterne har behov for hjælp til administrationen.

Medicinrådet tilføjer omkostninger til Oftagel på 49,25 DKK for alle patienter, der oplever øjenbetændelse, og omkostninger til Ultracortenol på 137,90 DKK til 10 % af de patienter der har behov for yderligere behandling af øjenbetændelsen. Medicinrådet tilføjer også omkostninger til Acivir til behandling af oral herpes på 30,75 DKK (priser fundet hos medicinpriser.dk og webapoteket.dk).

Medicinrådet accepterer ansøgers tilgang vedr. patientomkostninger, men rykker omkostninger til behandling af bivirkninger til patientomkostningerne og inkluderer omkostninger til behandling af oral herpes. Medicinrådet inkluderer patientomkostninger til kontrol hos dermatologisk sygeplejerske og tilpasser andelen af patienter, der har behov for hjælp til administration af dupilumab.

4.3 Følsomhedsanalyser

Formålet med følsomhedsanalyserne er at undersøge usikkerhederne i analysen og de økonomiske konsekvenser af at justere de parametre, der er usikre. Ansøger har udført følsomhedsanalyserne listet i Tabel 3.

Tabel 3. Ansøger følsomhedsanalyser og beskrivelse

Følsomhedsanalyse af Omkostningsanalyse	Beskrivelse
Pris pr. pakning af baricitinib	+/- 20 %
Pris pr. pakning af dupilumab	+/- 20 %
Enhedsomkostning for konsultation ved dermatologisk speciallæge	+/- 20 %
Enhedsomkostning for konsultation ved dermatologisk sygeplejerske	+/- 20 %
Omkostning for blod- og urinprøve	+/- 20 %
Omkostning til blodtælling	+/- 20 %
Omkostninger ved bivirkninger	+/- 20 %
Andel af dupilumab administrationer foretaget af sygeplejerske	+/- 20 %
Fugtighedscremers enhedspris	+/- 20 %
Topikale steroider enhedspris	+/- 20 %
Calcineurininhibitor enhedspris	+/- 20 %
Patienttid brugt på administration af dupilumab	+/- 20 %

Medicinrådets vurdering af ansøgers valg af følsomhedsanalyser
Medicinrådet vælger ikke at præsentere ansøgers følsomhedsanalyser, da Medicinrådet ønsker at præsentere resultaterne ved ændring af værdien af specifikke parametre i stedet for resultatet af en arbitrær procentvis reduktion/øgning af bestemte omkostninger.

Medicinrådet præsenterer en følsomhedsanalyse, hvor det antages, at patienter har lige mange kontrolbesøg hos en dermatologisk sygeplejerske, uanset om de modtager baricitinib eller dupilumab. Yderligere præsenterer Medicinrådet en følsomhedsanalyse, hvor det antages, at ingen patienter har behov for hjælp af en sygeplejerske til administration af dupilumab.

4.4 Opsummering af basisantagelser

I Tabel 4 opsummeres basisantagelserne i henholdsvis ansøgers og Medicinrådets hovedanalyse.

Tabel 4. Basisantagelser for ansøgers og Medicinrådets hovedanalyse

Basisantagelser	Ansøger	Medicinrådet
Tidshorisont	1 år	1 år
Inkluderede omkostninger	Lægemiddelomkostninger Hospitalsomkostninger (inkl. bivirkningsomkostninger) Patientomkostninger	Lægemiddelomkostninger Hospitalsomkostninger (inkl. bivirkningsomkostninger) Patientomkostninger
Dosering af baricitinib	4 mg dagligt	4 mg dagligt
Behandlingslængde	Ens for baricitinib og dupilumab	Ens for baricitinib og dupilumab
Andel af patienter, der skal have hjælp til administration af dupilumab	10 %	1,5 %

5. Resultater

5.1 Resultatet af Medicinrådets hovedanalyse

Medicinrådets hovedanalyse bygger på samme antagelser som ansøgers hovedanalyse med undtagelse af mindre ændringer, der ikke påvirker resultatet væsentligt.

Den gennemsnitlige inkrementelle omkostning pr. patient bliver [redacted] DKK i Medicinrådets hovedanalyse.

[redacted]

Er analysen udført med AIP, bliver den inkrementelle omkostning pr. patient -37.000 DKK.

Resultaterne fra Medicinrådets hovedanalyse er præsenteret i Tabel 5.

Tabel 5. Resultatet af Medicinrådets hovedanalyse ved sammenligning med dupilumab, DKK

	Baricitinib	Dupilumab	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	1.326	958	368
Patientomkostninger	175	1.155	-981
Totale omkostninger	[redacted]	[redacted]	[redacted]

5.1.1 Resultatet af Medicinrådets følsomhedsanalyser

Ved samme antagelser som i Medicinrådets hovedanalyse for meromkostninger har Medicinrådet udført en følsomhedsanalyse ud fra scenarierne listet i Tabel 6.

Tabel 6. Resultatet af Medicinrådets følsomhedsanalyse sammenlignet med hovedanalysen, DKK

Scenarie	Inkrementelle omkostninger
Resultatet af hovedanalysen	[redacted]
Alle patienter har lige mange kontrolbesøg hos en sygeplejerske, uanset om de modtager baricitinib eller dupilumab	[redacted]
Ingen patienter har behov for hjælp til administration af dupilumab	[redacted]

6. Budgetkonsekvenser

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

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

- Baricitinib bliver ikke anbefalet som mulig standardbehandling.

Budgetkonsekvenserne udgør forskellen mellem de samlede omkostninger i de to scenarier.

6.1 Ansøgers estimat af patientantal og markedsandel

Ansøger antager, at der på nuværende tidspunkt er 250 patienter, der kandiderer til behandling med baricitinib, og at der årligt vil komme 30 nye patienter. Af den samlede patientpopulation antager ansøger, at 90 % af patienterne vil være i behandling med dupilumab og derfor ikke har nogle omkostninger til opstart af behandling. Såfremt baricitinib anbefales som standardbehandling, antager ansøger et markedsoptag på 21,5 % i år 1, stigende til 80 % i år 5.

Medicinrådets vurdering af ansøgers budgetkonsekvensanalyse
Fagudvalget vurderer, at 225 patienter på nuværende tidspunkt er kandidater til behandling med baricitinib, og Medicinrådet ændrer derfor antallet af patienter i sin hovedanalyse. Fagudvalget vurderer yderligere, at patienter, der aktuelt er i behandling med dupilumab, er velbehandlet, og at størstedelen vil fortsætte behandlingen. Det vurderes derfor, at ansøgers antagelser vedr. markedsoptaget for baricitinib er overestimeret. Fagudvalget anslår, at baricitinib vil have et markedsoptag på 25 % i år 1 stigende til 50 % i år 5, hvis baricitinib anbefales som standardbehandling. Tabel 7 viser fordelingen af patienter, der er/sættes i behandling med baricitinib eller dupilumab fra år 1 til år 5 ved og uden en anbefaling af baricitinib som standardbehandling.

Tabel 7. Medicinrådets estimat af antal patienter pr. år

	År 1	År 2	År 3	År 4	År 5
			Anbefales		
Baricitinib	56	77	100	126	173
Dupilumab	169	179	185	189	173
			Anbefales ikke		
Baricitinib	0	0	0	0	0
Dupilumab	225	255	285	315	345

Medicinrådet ændrer det initiale patientantal til 225, og justerer markedsoptaget jf. fagudvalgets vurdering.

6.2 Medicinrådets budgetkonsekvensanalyse

Medicinrådet har korrigeret følgende estimater i sin budgetkonsekvensanalyse i forhold til ansøgers budgetkonsekvensanalyse:

- Det initiale patientantal, der kandiderer til behandling med baricitinib, er ændret fra 250 patienter til 225 patienter.
- Markedsoptaget er justeret jf. fagudvalgets vurderinger.

Medicinrådet estimerer, at anvendelse af baricitinib vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Resultatet er præsenteret i Tabel 8.

Er analysen udført med AIP, bliver budgetkonsekvenserne ca. -5,4 mio. DKK i år 5.

Tabel 8. Medicinrådets analyse af totale budgetkonsekvenser, mio. DKK, ikkediskonterede tal

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

7. Diskussion

Behandling med baricitinib er forbundet med inkrementelle omkostninger på [redacted] DKK om året sammenlignet med behandling med dupilumab. De inkrementelle omkostninger er næsten udelukkende drevet af lægemiddelomkostningerne, [redacted]

Analysen er en omkostningsminimeringsanalyse, da fagudvalget vurderer, at der ikke er grund til at tro, at effekten af baricitinib skulle være dårligere end effekten af dupilumab. Baricitinib administreres oralt, og der er derfor færre hospitalsbesøg og patienttid forbundet med denne behandling sammenlignet med dupilumab. Analysen viser, at der ikke er store usikkerheder forbundet med de inkluderede parametre og dermed analysens resultat. Ved antagelsen om, at alle patienter har lige mange kontrolbesøg hos en sygeplejerske, ændres de inkrementelle omkostninger med [redacted] DKK. Det samme gør sig gældende, når det antages, at ingen patienter har behov for hjælp til administration af dupilumab.

[redacted]

8. Referencer

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5. Blauvelt A, de Bruin-Weller M, Gooderham M, Cather JC, Weisman J, Pariser D, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. Lancet. 2017;389(10086):2287–303.

9. Bilag

9.1 Resultatet af ansøgers hovedanalyse

I ansøgers hovedanalyse bliver den inkrementelle omkostning pr. patient ca. [redacted] DKK over en tidshorisont på 1 år. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 9.

Tabel 9. Resultatet af ansøgers hovedanalyse, DKK

	Baricitinib	Dupilumab	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	2.988	2.822	165
Patientomkostninger	373	1.541	-1.168
Totale omkostninger	[redacted]	[redacted]	[redacted]

9.2 Resultatet af ansøgers budgetkonsekvensanalyse

Ansøger har inkluderet de samme omkostninger i budgetkonsekvensanalysen, som der er inkluderet i omkostningsanalysen, dog uden patientomkostninger.

Med de ovenstående antagelser om patientantal og markedsandel estimerer ansøger, at anvendelse af baricitinib vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Ansøgers estimat af budgetkonsekvenserne fremgår af Tabel 10.

Tabel 10. Ansøgers hovedanalyse for totale budgetkonsekvenser, mio. DKK, ikkediskonterede tal

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

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Forhandlingsnotat

Dato for behandling i Medicinrådet	26.05.2021
Leverandør	Eli Lilly
Lægemiddel	Baricitinib (Olumiant)
Ansøgt indikation	Moderat til svær atopisk eksem hos voksne (> 18 år)

Forhandlingsresultat

Amgros har opnået følgende pris på baricitinib:

Lægemiddel	Styrke/dosis	Pakningsstørrelse	AIP	Udbudspris SAIP	Rabatprocent ift. AIP
Baricitnib (Olumiant)	2 mg	28 stk. (blister)	6.711,67	[redacted]	[redacted]
Baricitnib (Olumiant)	4 mg	28 stk. (blister)	6.711,67	[redacted]	[redacted]

Baricitinib er allerede i udbud sammen med andre biologiske lægemidler til dermatologi, gastroenterologi og reumatologi. Aftalen løber foreløbigt til 31. december 2021, men har mulighed for forlængelse 2x6 måneder.

Vurdering af forhandlingsresultatet

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

- Leverandøren har allerede givet en pris i udbuddet. Amgros har derfor ikke forhandlet i forbindelse med Medicinrådets vurdering til denne indikation.

Konklusion
Amgros vurderer, at vi har en udmærket pris på baricitinib sammenlignet med dupilumab.

Relation til markedet

Der findes ikke en behandlingsvejledning for atopisk eksem. Medicinrådet er dog i gang med at vurderer 3 yderligere lægemidler til indikationen; tralokinimab, upadacitinib og abrocitinib.

I Medicinrådets vurdering sammenlignes baricitinib med dupilumab til indikationen. I tabellen herunder ses lægemiddelomkostningerne for første år og andet års behandling.

Lægemiddel	Styrke	Pakningsstørrelse	Dosis ved sammenligning	SAIP	Årlig lægemiddelpris første år	Årlig lægemiddelpris andet år
Dupixent	200 mg	2 stk.	Startdosis på 400 mg SC, efterfulgt af 200 mg SC hver anden uge	[redacted]	[redacted]	[redacted]
Dupixent	300 mg	2 stk.	Startdosis på 600 mg SC efterfulgt af 300 mg SC hver anden uge	[redacted]	[redacted]	[redacted]
Olumiant	2 mg	28 stk. (blister)	2 mg/dagligt	[redacted]	[redacted]	[redacted]
Olumiant	4 mg	28 stk. (blister)	4 mg/dagligt	[redacted]	[redacted]	[redacted]

Baricitinib er desuden inkluderet i behandlingsvejledningen for kronisk leddegigt.

Fra: Jeppe Schultz Christensen
Til: Louise Klokker Madsen
Cc: Dorthea Elise Christiansen; Katrine Jürs; Camilla Nybo Holmberg
Emne: RE: Høring over godkendt vurdering af lægemidlets værdi for baricitinib til atopisk eksem
Dato: 5. maj 2021 08:58:12
Vedhæftede filer: image002.jpg
image003.png

Kære Louise,

Tak for den fremsendte rapport. Eli Lilly har ingen kommentarer til kategoriseringen af Olumiants værdi sammenlignet med Dupixent.

Mvh.

Jeppe S. Christensen
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From: Louise Klokker Madsen <LKM@medicinraadet.dk>
Sent: 28. april 2021 19:06
To: Jeppe Schultz Christensen <jeppe_sc@lilly.com>
Cc: Dorthea Elise Christiansen <DEC@medicinraadet.dk>; Katrine Jürs <KJU@medicinraadet.dk>; Camilla Nybo Holmberg <CNH@medicinraadet.dk>
Subject: [EXTERNAL] Høring over godkendt vurdering af lægemidlets værdi for baricitinib til atopisk eksem

Kære Jeppe

Sekretariatet fremsender hermed den endelige vurdering af lægemidlets værdi for baricitinib til atopisk eksem, som Medicinrådet godkendte på rådsmødet i dag den 28. april 2021. Medicinrådet var enigt med fagudvalgets konklusion om lægemidlets værdi, som derfor svarer til det resultat, I tidligere har haft i høring. De sundhedsøkonomiske modelantagelser blev ligeledes

godkendt.
Vi ser frem til at modtage jeres eventuelle høringssvar senest den 5. maj 2021.

Vh Louise

Fra: Louise Klokker Madsen
Sendt: 19. april 2021 13:48
Til: Jeppe Schultz Christensen <jeppe_sc@lilly.com>
Cc: Dorthea Elise Christiansen <DEC@medicinraadet.dk>; Katrine Jürs <KJU@medicinraadet.dk>; Camilla Nybo Holmberg <CNH@medicinraadet.dk>
Emne: Høring over udkast til vurdering af lægemidlets værdi og sundhedsøkonomisk afrapportering for baricitinib til atopisk eksem

Kære Jeppe

Sekretariatet fremsender hermed udkast til Medicinrådets vurdering af lægemidlets værdi og sundhedsøkonomisk afrapportering for baricitinib til atopisk eksem.

Medicinrådet drøfter vurderingen af lægemidlets værdi og modelantagelserne for den sundhedsøkonomiske afrapportering den 28. april. I får besked fra sekretariat, hvis Rådet har ændringer til vurderingen udarbejdet af fagudvalget.

I har i alt 20 dage til at sende eventuelle bemærkninger til kategoriseringen af lægemidlets værdi og den sundhedsøkonomiske afrapportering. **Jeres frist for at indgive høringssvar er derfor den 5. maj 2021.** I er selvfølgelig velkomne til at sende eventuelle bemærkninger inden denne dato. I må også gerne meddele, hvis I ikke har kommentarer til kategoriseringen.

Vurderer sekretariatet og fagudvalget, at jeres høringssvar giver anledning til at revurdere kategoriseringen af lægemidlets værdi, skal Rådet drøfte vurderingen igen. Det vil med overvejende sandsynlighed udskyde tidspunktet for Rådets drøftelse af anbefalingen.
Jeres eventuelle høringssvar indgår i det materiale, som bliver fremlagt for Medicinrådet i forbindelse med behandlingen af anbefalingen. Jeres eventuelle høringssvar bliver offentliggjort sammen med anbefalingen.

Vh
Louise

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Medicinrådets behandling af personoplysninger

Når du har kontakt med Medicinrådet (f.eks. når du sender en e-mail til os), indsamler og behandler vi dine personoplysninger (f.eks. kontaktoplysninger i form af navn, e-mailadresse, titel/stilling mv.) I Medicinrådets persondatapolitik finder du mere information om Medicinrådets behandling af personoplysninger, dine rettigheder og oplysninger om, hvordan du kan kontakte os.

Medicinrådet

Medicinrådets vurdering vedrørende baricitinib til behandling af moderat til svær atopisk eksem hos voksne (≥ 18 år)

Version 1.1

Om Medicinrådet

Medicinrådet er et uafhængigt råd etableret af Danske Regioner.

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

Om vurderingsrapporten

Vurderingsrapporten indeholder Medicinrådets vurdering af, hvilken værdi lægemidlet har for patienten i forhold til nuværende standardbehandling.

Værdien for patienten og omkostningerne for samfundet danner grundlaget for Medicinrådets beslutning om, hvorvidt lægemidlet anbefales som mulig standardbehandling. Dette bliver sammenfattet i Medicinrådets anbefaling vedr. lægemidlet.

Lægemidlet er vurderet efter *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*, som du kan finde på Medicinrådets hjemmeside under siden Metoder.

Dokumentoplysninger	
Godkendelsesdato	26. maj 2021
Dokumentnummer	116265
Versionsnummer	1.1

Indholdsfortegnelse

1. Medicinrådets konklusion

Medicinrådet vurderer, at den samlede værdi af baricitinib sammenlignet med dupilumab til patienter med moderat-svær atopisk eksem ikke kan kategoriseres efter Medicinrådets metoder.

Der er foretaget en indirekte sammenligning af lægemidlerne baseret på to kliniske studier. Resultaterne af analysen er usikre, men viser ingen statistisk signifikante forskelle og de mindste klinisk relevante forskelle er ikke opnået.

På det foreliggende datagrundlag konstaterer Rådet, at der er forskellige bivirkninger ved de to lægemidler, men at de er håndterbare. På grund af risikoen for øgning af blod-lipider ved behandling med baricitinib bør man dog være tilbageholdende med at give dette lægemiddel til patienter med forhøjet kolesterol.

Samlet set vurderer Rådet, at effekt og sikkerhed ved baricitinib er sammenlignelig med dupilumab. Evidensens kvalitet vurderes at være lav.

Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 26. maj 2021

MEDICINRÅDET KATEGORISERER LÆGEMIDLERS VÆRDI I EN AF FØLGENDE KATEGORIER:

- **Stor merværdi:** Der er påvist en stor forbedring i effektforhold i forhold til gældende standardbehandling, eksempelvis markant forbedret overlevelse, markant reduktion i forekomsten af alvorlige symptomer og/eller alvorlige bivirkninger.
- **Moderat merværdi:** Der er påvist en moderat forbedring i forhold til gældende standardbehandling, eksempelvis moderat forbedret overlevelse, moderat reduktion i forekomsten af symptomer og/eller bivirkninger.
- **Lille merværdi:** Der er påvist en lille forbedring i forhold til gældende standardbehandling, eksempelvis en dokumenteret forbedret overlevelse, en reduktion i forekomsten af symptomer og/eller bivirkninger.
- **Merværdi af ukendt størrelse:** Der er påvist en forbedring i forhold til gældende standardbehandling, men størrelsen af forbedring kan ikke bestemmes. Lægemidlets merværdi er som minimum lille, men kunne også være moderat eller stor.
- **Ingen dokumenteret merværdi:** Der er ikke påvist en merværdi i forhold til gældende standardbehandling. Omvendt tyder den tilgængelige evidens heller ikke på, at der er en negativ værdi.
- **Negativ værdi:** Der er påvist en negativ værdi i forhold til gældende standardbehandling.

I nogle situationer er det ikke muligt at kategorisere lægemidlets samlede værdi. De situationer opstår, når evidensgrundlaget for vurderingen er for usikkert til at kategorisere værdien jf. Medicinrådets metoder (f.eks. på grund af usikkerheder omkring effektforhold og spinkelt datagrundlag). Medicinrådet konkluderer da, at samlet værdi ikke kan kategoriseres. Medicinrådet vil i disse tilfælde argumentere for, om der er grund til at formode, at det nye lægemiddel er dårligere eller evt. bedre end gældende standardbehandling, eller der ikke er grund til at skelne mellem behandlingerne. Det sker på baggrund af det foreliggende datagrundlag og fagudvalgets kliniske erfaring. Vurderingen er forbundet med større usikkerhed end vurderinger, hvor lægemidlets værdi kan kategoriseres.

MEDICINRÅDET VURDERER KVALITETEN AF DE DATA, DER LIGGER TIL GRUND FOR VURDERINGEN AF LÆGEMIDLET (EVIDENSENS KVALITET) I EN AF FØLGENDE GRADE-KATEGORIER:

- **Høj:** Nye studier vil med meget lav sandsynlighed ændre konklusionen.
- **Moderat:** Nye studier vil med lav sandsynlighed ændre konklusionen.
- **Lav:** Nye studier vil med moderat sandsynlighed ændre konklusionen.
- **Meget lav:** Nye studier vil med høj sandsynlighed ændre konklusionen.

2. Begreber og forkortelser

CI:	Konfidensinterval
DLQI:	*Dermatology Life Quality Index*
EASI:	*Eczema Area and Severity Index*
EMA:	*European Medicines Agency*
GRADE:	*Grading of Recommendations Assessment, Development and Education System* (system til vurdering af evidens)
HR:	*Hazard ratio*
IL:	Interleukin
MKRF:	Mindste klinisk relevante forskel
NRS:	*Numerical Rating Scale*
OR:	*Odds ratio*
POEM:	*Patient-Oriented Eczema Measure*
RR:	Relativ risiko
SCORAD:	*SCORing Atopic Dermatitis*
TCI:	Topikale calcineurininhibitorer
TCS:	*Topical corticosteroids* (topikale glukokortikoider)

3. Introduktion

Formålet med Medicinrådets vurdering af baricitinib til moderat-svær atopisk eksem hos voksne er at vurdere den værdi, lægemidlet har sammenlignet med dansk standardbehandling.

Vurderingen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra Eli-Lilly. Medicinrådet modtog ansøgningen den 24. februar 2021.

Det kliniske spørgsmål er:

Hvad er værdien af baricitinib og optimeret lokalbehandling sammenlignet med dupilumab og optimeret lokalbehandling for patienter med moderat til svær atopisk eksem, som har haft utilstrækkelig effekt af optimeret lokalbehandling og mindst én systemisk behandling, eller som ikke er kandidater til de øvrige systemiske behandlinger?

3.1 Atopisk eksem

Atopisk eksem er en kronisk eller kronisk recidiverende eksemsygdom karakteriseret ved udslæt og kløe samt perioder med akut opblussen, hvor der vil være behov for hurtig indsættende behandling [1].

Moderat til svær atopisk eksem er karakteriseret ved udtalt tørhed, rødme, afskalning, evt. papler/vesikler, ekskoriationer (forkradsninger) og lichenisering (fortykkelse af huden). Huden er ofte hævet med udslæt, revner og kroniske fortykkelser. Den defekte hudbarriere fører til en øget risiko for infektioner [2].

Et centralt symptom for atopisk eksem er kløe, der ved moderat til svær sygdom kan lede til udtalt søvnmangel [3]. Sygdommen har ofte et fluktuerende forløb, hvor udbrud kan forekomme med forskellige hyppigheder [4]. Patienter, der lider af atopisk eksem, har generelt nedsat livskvalitet [3] og kan have øget forekomst af selvmordstanker [5]. Derudover kan sygdommen også have indflydelse på arbejdsevnen.

Fagudvalget anerkender to måder at definere sværhedsgraden af atopisk eksem:

1. **Vurdering foretaget af læge i samarbejde med patienten** ved hjælp af et eller begge af følgende to måleværktøjer: Eczema Area and Severity Index (EASI) eller SCORing Atopic Dermatitis (SCORAD), hvor udbredelse, graden af hudaffektion og hyppigheden af opblussen vurderes. SCORAD indeholder en mere subjektiv vurdering vedrørende kløe og deraf følgende søvnmangel, mens EASI kan vurderes objektivt. Graden af hudaffektion vurderes i EASI opdelt pr. kropsdel. Sværhedsgraden ifølge SCORAD kan være mild (< 25), moderat (25-50) eller svær (> 50) og ifølge EASI moderat (7,1-21), svær (21,1-50) og rigtig svær (50,1-72).
2. **Vurdering foretaget af patienten** ved hjælp af et eller begge af følgende to måleværktøjer: Patient-Oriented Eczema Measure (POEM) eller Dermatology Life Quality Index (DLQI). DLQI er rettet mod betydningen af dermatologiske sygdomme for patientens livskvalitet, mens POEM omhandler patientens oplevede sværhedsgrad af eksem (Patient-Oriented Eczema Measure, POEM). Begge er udtryk for sværheds-

graden af eksem, som det opleves af patienten. En lav score på disse to måleværktøjer er udtryk for mindre sværhedsgrad. Dette er især vigtigt hos patienter, hvor eksemet har en mindre udbredelse, men med svær grad af hudaffektion lokaliseret til mindre områder af huden. Dette kaldes svær lokaliseret eksem, selvom der ikke nødvendigvis er tale om svær eksem defineret ved EASI eller SCORAD. Fagudvalget mener derfor, at der også bør tages højde for patientperspektivet i vurderingen af eksemets sværhedsgrad.

Patofysiologien af atopisk eksem er kompleks, da den involverer både genetiske og miljømæssige faktorer såvel som immundysregulering, hvor det inflammatoriske respons er induceret af aktivering af type 2 T-hjælperceller [6]. De to cytokiner interleukin (IL) 4 og IL 13 er centrale i initieringen og vedligeholdelsen af det inflammatoriske respons [7]. Ligeledes spiller enzymer kaldet Janus-kinaser (JAK) en vigtig rolle i den inflammatoriske proces ved atopisk eksem ved at påvirke aktiviteten af cytokiner og vækstfaktorer involveret i den inflammatoriske respons. Hos unge forekommer atopisk eksem ofte sammen med en eller flere komorbiditeter så som astma, høfeber, kontakteksem og håndeksem [8].

Andelen af unge voksne med atopisk eksem (alle sværhedsgrader) i Danmark anslås at være 10 % [8]. Heraf vil langt størstedelen have effekt af lokalbehandling (fugtighedscremer eller steroidcremer). Andelen, som vil have behov for systemisk behandling, vil omfatte moderate til svære tilfælde. Baricitinib vil først være aktuel, efter man har afprøvet og oplevet utilstrækkelig effekt af mindst én systemisk behandling og er dermed relevant for de samme patienter, som nu får dupilumab, dog kun patienterne $\geq$ 18 år.

Fagudvalget anslår, at der er opstartet ca. 250 patienter i behandling med dupilumab siden Medicinrådets anbefaling af dette lægemiddel til patienter med moderat til svær atopisk eksem. Nogle af disse patienter er ophørt med, eller har pauseret behandlingen.

Fagudvalget anslår derfor, at der aktuelt er ca. 225 voksne patienter, som vil være kandidater til baricitinib eller dupilumab. En del af disse patienter vil dog være i behandling med dupilumab allerede. Fagudvalget anslår, at der kunne være behov for behandling med baricitinib for ca. 60 af de patienter, som aktuelt er eller har været i behandling med dupilumab. Enten som følge af at dupilumab er blevet seponeret, eller dette overvejes, på grund af bivirkninger eller manglende effekt. Fagudvalget anslår, at ca. 30 nye patienter om året vil være kandidater til enten dupilumab eller baricitinib.

3.2 Baricitinib

Baricitinib er et immunsupprimerende lægemiddel, som er godkendt af EMA til behandling af reumatoid artritis (leddegigt).

Denne protokol gælder indikationsudvidelsen til voksne patienter ≥ 18 år med moderat til svær atopisk eksem, som er kandidater til systemisk behandling. Ved kandidater til systemisk behandling forstås patienter, som har utilstrækkelig effekt af optimeret lokalbehandling.

Baricitinib inhiberer aktiviteten af enzymer kaldet Janus-kinaser (JAK). Der findes fire forskellige JAK-kinaser, JAK1, JAK2, JAK3 og TYK2, heraf hæmmer baricitinib JAK1 og JAK2.

Baricitinib er en tabletbehandling, som kan administreres af patienten selv. Tabletterne forekommer i doser på enten 2 eller 4 mg. Den anbefalede dosis er 4 mg én gang dagligt. En dosis på 2 mg én gang dagligt er passende til nogle patienter, f.eks. patienter over 75 år, eller til patienter med kroniske og tilbagevendende infektioner, nedsat nyrefunktion eller ved dosisreduktion hos patienter, som har vedvarende kontrol af sygdomsaktiviteten ved 4 mg.

Der anbefales blodprøver før opstart, efter 12 uger og rutinemæssigt efterfølgende, det vil sige i forbindelse med klinisk kontrol typisk hver 3. måned. Se afsnit 6 vedrørende ansøgers redegørelse for blodprøver.

Baricitinib bør seponeres ved manglende effekt, vurderet efter 16 uger. Desuden bør behandlingen seponeres efter langvarigt fravær af kliniske symptomer på atopisk eksem. Hos voksne vurderes, om behandlingen bør fortsætte efter 12 måneder [2]. Ved seponering og efterfølgende opblussen af symptomer, kan systemisk behandling genoptages med samme eller andet præparat.

Baricitinib kan anvendes som monoterapi, men vil i overensstemmelse med dansk praksis blive anvendt i kombination med optimeret lokalbehandling som beskrevet ovenfor. Fagudvalget bemærker, at baricitinib udgør en ny behandlingsmodalitet inden for sygdomsområdet atopisk eksem.

Fagudvalget mener, at baricitinib bør anvendes til patienter, som har haft utilstrækkelig effekt af optimeret lokalbehandling og én systemisk behandling eller ikke er kandidater til de øvrige systemiske behandlinger. Dermed er baricitinib et alternativ til behandling med dupilumab.

3.3 Nuværende behandling

Den nonfarmakologiske behandling af atopisk eksem består i at minimere eller undgå en række forværrende faktorer, herunder udtørring af huden, irritanter, infektioner og eventuelt komplicerende allergier. Desuden anvendes fugtighedscremer ved alle sværhedsgrader i tillæg til den øvrige behandling af atopisk eksem, da den hydrerer huden, forhindrer mikrofissurer, hudkløe og nedsætter behovet for topikalt glukokortikoid (TCS) [2].

Den farmakologiske behandling af atopisk eksem sigter mod at forebygge episoder med opblussen (flares) samt, når sådanne episoder opstår, at afkorte perioden, indtil sygdommen igen er stabiliseret [1]. Behandlingen afhænger af sværhedsgraden og kan være lokal, systemisk eller begge dele.

3.3.1 Lokalbehandling

Som lokalbehandling er topikale glukokortikoider (TCS, steroidcreme) førstevalg til moderat til svær atopisk eksem. Ved opblussen benyttes TCS som udgangspunkt dagligt i 1-2 uger, men i svære tilfælde kan den daglige smøring med TCS forlænges i op til 4 uger eller om nødvendigt længere. Derefter gives typisk vedligeholdelsesbehandling med TCS to gange om ugen. Som andetvalg, efter at behandling med TCS har vist utilstrækkelig effekt, eller hvor behandlingen med TCS vurderes uhensigtsmæssig grundet bivirkningsprofilen, kan lokalbehandling med topikale calcineurininhibitorer (TCI) benyttes [2]. Sidstnævnte benyttes også som vedligeholdelsesbehandling mellem episoder med opblussen i eksemet. Som tillægsbehandling til lokalbehandling kan lysterapi benyttes [2]. TCI er velegnet til proaktiv langtidsbehandling, det vil sige brug af TCI som forebyggende behandling i længere tid. Adherence er fortsat et stort problem ved lokalbehandling, specielt under vedligeholdelsesbehandlingen hvor eksemet er i ro, og det kan medføre, at patienten glemmer de daglige smøringer, og at lokalbehandlingen dermed mister effekt. Derfor anvendes begrebet 'optimeret lokalbehandling', hvilket forstås som konsekvent og daglig anvendelse af fugtighedscreme sammen med konsekvent anvendelse af TCS eller TCI.

3.3.2 Systemisk behandling

Det er en forudsætning for systemisk behandling, at lokalbehandlingen er optimeret og anvendes samtidig med den systemiske terapi.

Såfremt lokalbehandling, eventuelt kombineret med lysterapi, har utilstrækkelig effekt, kan følgende længerevarende systemiske behandlinger benyttes til patienter med moderat til svær atopisk eksem: methotrexat, azathioprin, mycophenolat mofetil, ciclosporin og dupilumab. Af disse lægemidler har kun ciclosporin og dupilumab indikation til atopisk eksem. Ingen af de øvrige lægemidler har indikation til atopisk eksem, men har i en længere årrække været anvendt uden for indikation (off-label) i Danmark som standardbehandling til patienter (både børn og voksne), der har utilstrækkelig effekt af optimeret lokalbehandling.

Ciclosporin er godkendt til behandling af patienter ≥ 16 år med svær atopisk eksem [9]. Dupilumab har indikation til atopisk eksem hos patienter ≥ 12 år, som er kandidater til systemisk behandling. Dupilumab er i Danmark anbefalet af Medicinrådet til patienter, som ikke tåler de øvrige systemiske behandlinger, eller efter brug af mindst én tidligere systemisk behandling hos 12-17-årige og mindst to tidligere systemiske behandlinger hos voksne ≥ 18 år. Dette er en indsnævring af indikationen godkendt i EMA, som fagudvalget valgte ud fra et forsigtighedsprincip, idet dupilumab på det tidspunkt var et nyt behandlingsprincip indenfor dermatologiske lidelser. I klinisk praksis er der nu erfaring med anvendelsen af dupilumab, og fagudvalget finder det hensigtsmæssigt, at dupilumab og baricitinib, såfremt det anbefales, begge kan anvendes efter mindst én tidligere systemisk behandling.

Af de systemiske behandlinger vil methotrexat eller azathioprin som regel være førstevalg, men ved akut, svær opblussen kan systemisk immunhæmmende terapi i form af orale glukokortikoider eller ciclosporin være et bedre behandlingsalternativ.

Ciclosporin er, ligesom for kronisk eksem, også effektivt ved akut svær opblussen, da det har en hurtigt indsættende effekt i forhold til anden systemisk behandling. Dette gælder også for området omkring hoved og hals, som ellers kan være svære at opnå respons på. Grundet bivirkninger kan orale glukokortikoider kun benyttes i kortere tid (mindre end 1 måned) og ciclosporin kun i samlet set 2 år pr. levetid.

Hvis der ikke opnås tilstrækkelig effekt ved afprøvning af én eller flere af de gængse systemiske behandlinger (methotrexat, azathioprin, mycophenolat mofetil, ciclosporin), kan behandling med dupilumab afprøves.

Hvorvidt effekten af den systemiske behandling er tilstrækkelig, vurderes efter de initiale 16 ugers behandling, ud fra EASI, DLQI og POEM samt en kvalitativ lægelig helhedsvurdering og efter samtale med patienten. Effekten måles herefter i klinikken hver 3. måned ved kontrol.

4. Metode

Medicinrådets protokol for vurdering vedrørende baricitinib til behandling af moderat til svær atopisk eksem hos voksne (≥ 18 år) beskriver sammen med *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*, hvordan Medicinrådet vil vurdere lægemidlets værdi for patienterne.

5. Resultater

5.1 Klinisk spørgsmål 1

Hvad er værdien af baricitinib og optimeret lokalbehandling sammenlignet med dupilumab og optimeret lokalbehandling for patienter med moderat til svær atopisk eksem, som har haft utilstrækkelig effekt af optimeret lokalbehandling og mindst én systemisk behandling, eller som ikke er kandidater til de øvrige systemiske behandlinger.

5.1.1 Litteratur

Nedenfor beskriver og vurderer Medicinrådet den litteratur, som ansøger har anvendt i sin endelige ansøgning.

Ansøgningen baserer sig på data fra de tre kliniske studier, der er angivet i protokollen; ét for baricitinib (BREEZE-AD 7) og to for dupilumab (CHRONOS, CAFÉ). Derudover indgår der også data fra endnu et baricitinibstudie (BREEZE AD-4), som ansøger har inkluderet for at gøre datagrundlaget mere fyldestgørende og sammenligneligt med populationen defineret i protokollen. Data fra BREEZE AD-4 er publiceret på clinicaltrials.gov.

I tabel 1 vises en oversigt over de kliniske studier, som indgår i ansøgningen. Alle fire studier er randomiserede, kontrollerede, dobbeltblindede fase III-studier.

De to baricitinibstudier samt CHRONOS inkluderer voksne patienter med moderat-svær atopisk eksem, mens CAFÉ kun inkluderer voksne patienter med svær atopisk eksem.

Tabel 1 Oversigt over kliniske studier, publikationer, populationer og behandlingsarme.

Publikationer	Klinisk studie NCT-nummer Opfølgningstid	Population	Behandlingsarme*
Reich 2020. Efficacy and Safety of Baricitinib Combined With Topical Corticosteroids for Treatment of Moderate to Severe Atopic Dermatitis: A Randomized Clinical Trial [10]	BREEZE-AD 7 NCT03733301 16 uger	Voksne med moderat-svær atopisk eksem og utilstrækkeligt respons på TCS	Placebo + TCS Baricitinib 2 mg, en gang dagligt + TCS **Baricitinib 4 mg, en gang dagligt + TCS**
Publiceret på ClinicalTrials.gov (2018): A Long-term Study of Baricitinib (LY3009104) With Topical Corticosteroids in Adults With Moderate to Severe Atopic Dermatitis That Are Not Controlled With Cyclosporine or for Those Who Cannot Take Oral Cyclosporine Because it is Not Medically Advisable (BREEZE-AD4)	BREEZE-AD 4 NCT03428100 16 uger (primære analyse) 52 uger i alt	Voksne med moderat-svær atopisk eksem og utilstrækkeligt respons, intolerabilitet eller kontraindikation for ciclosporin	Placebo + TCS Baricitinib 1 mg, en gang dagligt + TCS Baricitinib 2 mg, en gang dagligt + TCS **Baricitinib 4 mg, en gang dagligt + TCS**
de Bruin-Weller 2018. Dupilumab with concomitant topical corticosteroid treatment in adults with atopic dermatitis with an inadequate response or intolerance to ciclosporin A or when this treatment is medically inadvisable: a placebo-controlled, randomized phase III clinical trial (LIBERTY AD CAFÉ) [11]	LIBERTY AD CAFE NCT02755649 52 uger (behandling) + 12 uger (opfølgning)	Voksne med svær atopisk eksem og utilstrækkeligt respons, intolerabilitet eller kontraindikation for ciclosporin	Placebo + TCS Dupilumab s.c. 300 mg hver uge + TCS **Dupilumab s.c. 300 mg hver 2. uge + TCS**
Blauvelt 2017. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial [12]	LIBERTY AD CHRONOS NCT02260986 52 uger (behandling) + 12 uger (opfølgning)	Voksne med moderat-svær atopisk eksem og utilstrækkeligt respons på TCS	Placebo + TCS Dupilumab s.c. 300 mg hver uge + TCS **Dupilumab s.c. 300 mg hver 2. uge + TCS**

*Relevant dosering for det kliniske spørgsmål er markeret med fed skrift

Baselinekarakteristika for populationen i de relevante studiearme, der er inkluderet i ansøgers analyser, fremgår af tabel 2.

Tabel 2 Baselinekarakteristika.

	BREEZE-AD 7 Baricitinib 4 mg dagligt + TCS (n = 111)	BREEZE-AD 4 Baricitinib 4 mg dagligt + TCS (n = 92)	CAFÉ Dupilumab 300 mg hver 2. uge + TCS (n = 107)	CHRONOS Dupilumab 300 mg hver 2. uge + TCS (n = 106)
	Gennemsnit (SD)		Median (IQR)	
Alder	33,9 (11,4)	38,7 (13,3)	38 (25 - 47)	40,5 (28 - 49)
Køn, mænd, %	68 %	62 %	61 %	58 %
Etnicitet Kaukasisk Asiatisk Øvrige	 49 % 49 % 3 %	 77 % 20 % 3 %	 97 % 2 % 1 %	 70 % 27 % 3 %
Sygdomsvarighed, år	26 (13,2)	27,5 (16,2)	29 (19 - 43)	28 (20 - 44)
EASI	30,9 (12,6)	32,7 (13,7)	31,6 (25,2 - 39,2)	30,9 (22,3 - 41,6)
SCORAD	68,3 (13,2)	69 (13)	66,7 (61,1 – 76,2)	69,7 (60,4 - 79,8)
Påvirket kropsoverflade	52,1 % (23,3)	53,9 % (23,8)	55 % (44-66)	58,8 % (43,5 - 78,5)
Kløe, NRS	7,0 (2,0)	6,7 (2,3)	7 (5,4 – 8)	7,7 (6,6 - 8,5)
POEM	21,4 (6,0)	20,8 (6)	20 (15 – 24)	21 (16 - 25)
DLQI	14,7 (7,9)	14 (8,1)	14 (8 – 22)	13,5 (8 - 20)
HADS, angst	6,7 (4,4)	-	HADS total: 13 (6 – 19)	HADS total: 12,5 (7-18)
HADS, depression	5,5 (4,1)	-		

TCS: topikale korticosteroider. SD: standardafvigelse. IQR: interkvartilt interval. EASI: Eczema Area and Severity Index (0-72; 0 = ingen sygdom). SCORAD: SCORing Atopic Dermatitis (0-103; 0 = ingen sygdom). NRS: numerisk rangskala (0-10; 0 = ingen kløe). POEM: Patient Oriented Eczema Measures (0-28; 0 = ingen sygdom). DLQI: Dermatology Life Quality Index (0-30; 0 = ingen sygdom) HADS, Hospital Anxiety Depression Scale.

Fagudvalget har sammenlignet baselinekarakteristika med forbehold for, at der for baricitinib er angivet gennemsnit og for dupilumab medianer. Disse kan adskille sig væsentligt, men idet der også er angivet usikkerheder i form af standardafvigelser og interkvartile intervaller giver oplysningerne et tilstrækkeligt udgangspunkt for sammenligningen.

Fagudvalget bemærker, at der ikke er baselinedata for antal episoder med opblussen, hvilket er et væsentligt parameter. Dette kan dermed adskille sig mellem populationerne. Baseret på de øvrige parametre er sværhedsgraden af eksemet dog formentlig sammenligneligt, selvom CAFÉ kun inkluderer patienter med svær atopisk eksem. Der er en forholdsvis høj andel af asiatiske patienter i BREEZE-AD 7 (49 %), stort set ingen i CAFÉ (2 %) og nogenlunde samme andel i BREEZE-AD 4 og CHRONOS (henholdsvis 20 og 27 %). Det er uvist, hvilken betydning dette kan have, men det er fagudvalgets kliniske erfaring, at patienter med asiatisk oprindelse kan være sværere at behandle.

Fagudvalget vurderer, at populationerne i de fire studier overordnet set er tilstrækkeligt ens til at kunne foretage en indirekte sammenligning mellem dem og til at sammenligne med danske patienter med moderat-svær atopisk eksem, som får optimeret lokalbehandling og har afprøvet systemisk behandling. Dog bemærker fagudvalget, at der fortsat bør skelnes mellem populationer, der har eller ikke har fået en tidligere systemisk behandling. Det skyldes, at det kan være sværere at vise en effekt i de populationer, der tidligere har fået systemisk behandling, sammenlignet med populationer, som ikke tidligere har modtaget systemisk behandling.

5.1.2 Databehandling og analyse

I dette afsnit er ansøgers datagrundlag, databehandling og analyse for hvert effektmål beskrevet.

Ansøger har indsendt indirekte sammenlignende analyser baseret på data fra følgende studier:

- BREEZE AD 4 vs. CAFÉ
- BREEZE AD 7 vs. CHRONOS
- BREEZE AD 7 vs. CAFÉ/CHRONOS (hvor data for dupilumab er samlet i metaanalyser)

Ansøger argumenterer for, at det kliniske spørgsmål bedst besvares ved at lave en indirekte sammenligning mellem studierne BREEZE AD-4 og CAFÉ, da begge inkluderer patienter, som tidligere har modtaget en systemisk behandling (CsA), jævnfør populationen defineret i det kliniske spørgsmål. I CAFÉ er det dog kun patienter med svær atopisk eksem, som er inkluderet, mens det i BREEZE AD-4 er patienter med moderat-svær atopisk eksem. Baselinedata tyder dog på, at populationerne ikke adskiller sig væsentligt med hensyn til klinisk eksem samt selvrapporteret sværhedsgrad. Dermed kan det forventes at behandlingseffekten vil være sammenlignelig.

Fagudvalget er enig med ansøger i, at vurderingen bør baseres på sammenligningen mellem BREEZE-AD 4 og CAFÉ, da populationerne herfra stemmer bedst overens med det kliniske spørgsmål. Sammenligningen mellem BREEZE-AD 7 og CHRONOS inddrages derfor ikke i vurderingen, da populationen i disse studier ikke tidligere har modtaget systemisk behandling. Sammenligningen medtages dog som supplement til vurderingen og kan ses i bilag 3. Sammenligningen mellem BREEZE-AD 7 og CAFÉ/CHRONOS anvendes ikke, da fagudvalget ikke mener, at der bør foretages en metaanalyse af disse to studier da de adskiller sig i forhold til inklusionskriterier vedrørende sværhedsgrad af eksemet samt tidligere behandling.

Den indirekte sammenligning mellem BREEZE-AD 4 og CAFÉ er foretaget jf. Medicinrådets metoder til indirekte analyser. For at tage højde for forskelle i placebogrupperne er de absolutte forskelle beregnet ud fra eventraten i CAFÉ, som er det studie, der bedst ligner dansk klinisk praksis.

Tidshorisonten på 16 ugers behandling er acceptabel da den svarer til opfølgningstidspunkt for behandling i dansk praksis.

5.1.3 Evidensens kvalitet

Medicinrådet har anvendt GRADE til at foretage en systematisk og transparent vurdering af kvaliteten af evidensen. Nedenfor følger en beskrivelse af vurderingen af de væsentligste domæner. Vurdering af risikoen for bias ved de enkelte studier fremgår af bilag 1.Den fuldstændige GRADE-vurdering og begrundelserne er samlet i en GRADE-profil, som fremgår af bilag 2.

For **sammenligningen mellem BREEZE-AD 4 vs. CAFÉ** er der for samtlige effektmål nedgraderet et niveau for indirekthed, fordi der er anvendt indirekte analyser. For effektmålene *Eksem udbredelses- og sværhedsgrad* (EASI75 og SCORAD50) samt *Andel af patienter som oplever en eller flere alvorlige bivirkninger* er der nedgraderet et niveau for unøjagtighed, da konfidensintervallerne er brede og indeholder både positive og negative konklusioner. Kvaliteten af den samlede evidens for denne sammenligning er vurderet at være lav. Dette betyder, at nye studier med moderat sandsynlighed kan ændre konklusionen.

5.1.4 Effektestimater og kategorier

I tabellen herunder fremgår de absolutte og relative effektforskelle, de foreløbige og aggregerede kategorier, den samlede kategori og den samlede kvalitet af evidensen for klinisk spørgsmål 1.

Tabel 3 Resultater for klinisk spørgsmål 1: sammenligning ved 16 uger baseret på data fra BREEZE-AD 4 (baricitinib) og CAFÉ (dupilumab).

Effektmål	Målenhed (MKRF)	Vigtighed	Forskel i absolutte tal		Forskel i relative tal		Aggregeret værdi for effektmålet
			Forskel [95 % CI]	Foreløbig værdi	Forskel (95 % CI)	Foreløbig værdi	
Eksem udbredelses- og sværhedsgrad	EASI: andel, der opnår mindst 75 % reduktion (10 %-point)	Kritisk	-8,1 [-33,8; 39,5]	Kan ikke kategoriseres	0,87 [0,46; 1,63]	Kan ikke kategoriseres	Kan ikke kategoriseres
	SCORAD: andel, der opnår 50 % reduktion (10 %-point)		-19,2 [-40,5; 18,6]	Kan ikke kategoriseres	0,71 [0,39; 1,28]	Kan ikke kategoriseres	
Eksem udbredelses- og sværhedsgrad, patientrapporteret	POEM, gennemsnitlig ændring fra baseline (3 point)	Kritisk	2,51 [-0,46; 5,48]	Kan ikke kategoriseres			Kan ikke kategoriseres
Bivirkninger	Andel, som oplever mindst en alvorlig bivirkning (2 %-point)	Kritisk	3,7 [-1,4; 66,6]	Kan ikke kategoriseres	3 [0,25; 36,6]	Kan ikke kategoriseres	Kan ikke kategoriseres
	Opgørelse af langtids-bivirkninger, alle grader		Se tekst				
Livskvalitet	DLQI, gennemsnitlig ændring fra baseline (4 point)	Kritisk	2 [-0,41; 4,41]	Kan ikke kategoriseres			Kan ikke kategoriseres
Kløe	NRS, gennemsnitlig ændring fra baseline (3 point)	Vigtig	0,28 [-0,59; 1,15]	Ingen dokumenteret merværdi			Ingen dokumenteret merværdi
Episoder med opblussen	Andel, der oplever mindst en episode med opblussen i løbet af 16 uger (10 %-point)	Vigtig	IA		IA		
Konklusion							
Samlet kategori for lægemidlets værdi	Kan ikke kategoriseres						
Kvalitet af den samlede evidens	Lav						

MKRF: Mindste klinisk relevante forskel. CI: konfidensinterval. RR: relativ risiko. IA: ikke angivet. Grå felter betyder, at værdien ikke kan beregnes.

Eksem udbredelses- og sværhedsgrad
Som beskrevet i protokollen er effektmålet *Eksem udbredelses- og sværhedsgrad* kritisk for vurderingen af lægemidlets værdi for patienterne, fordi symptomerne er stærkt generende og har direkte betydning for livskvalitet og søvn for patienter med moderat til svær atopisk eksem.

Eksemudbredelses- og sværhedsgrad vurderes ved både EASI og SCORAD, da de tilsammen giver fyldestgørende information om effektmålet.

Eczema Area and Severity Index (EASI)

EASI er et måleredskab baseret på systematisk scoring for hver enkelt kropsregion af sværhedsgraden og kropsarealet påvirket af henholdsvis rødme, fortykkelse, forkradsninger og lichenisering. EASI anvendes i både kliniske forsøg og klinisk praksis. Den samlede score ligger i intervallet 0-72, hvor højere score indikerer en højere sværhedsgrad [11]. EASI er valideret og udpeget af ekspertgruppen fra Harmonising Outcome Measures for Eczema (HOME) som det foretrukne instrument til at vurdere objektive tegn på atopisk eksem [12,13]. EASI75 er andelen af patienter, der har en 75 % reduktion fra baseline på skalaen. En forskel på 10 procentpoint mellem grupperne vurderes at være mindste klinisk relevante forskel for EASI75.

SCORing Atopic Dermatitis (SCORAD)

SCORAD er et bredt valideret og anbefalet instrument, der anvendes i både kliniske forsøg og klinisk praksis [11,12]. SCORAD evaluerer sygdommens sværhedsgrad baseret på arealet og sværhedsgraden af objektivt vurderet rødme, ødem, skorpedannelse, forkradsninger, lichenisering og tørhed samt patientens subjektive vurdering af kløe og manglende søvn. Dette kan tilsammen højst give en score på 103, hvor en høj score indikerer en betydelig sværhedsgrad af sygdommen [14]. Fagudvalget vurderer, at SCORAD-instrumentet giver en bred karakterisering af sværhedsgraden af patientens eksem og patientens subjektive sygdomsopfattelse og dermed komplementerer den objektive EASI-skala. Der er ikke angivet faste retningslinjer for, hvor stor en reduktion skal være for at være klinisk relevant. Da SCORAD giver en mere helhedsorienteret bedømmelse af sygdomsbyrden end EASI, vurderer fagudvalget, at en reduktion på 50 % på skalaen (SCORAD50) vil være en betydelig forbedring for den enkelte patient, og at andelen af patienter, der opnår en sådan reduktion, giver information om effekten af en behandling på udbredelse og sværhedsgrad af eksemet. En forskel på 10 procentpoint mellem grupperne vurderes at være den mindste klinisk relevante forskel for SCORAD-50.

Tabel 4 viser resultater pr. studie for effektmålet *Eksem udbredelses- og sværhedsgrad*, opgjort ved EASI og SCORAD. Disse resultater er grundlaget for den indirekte sammenlignende analyse mellem baricitinib og dupilumab. For at tage højde for forskelle i placebogrupperne er de absolutte forskelle beregnet ud fra eventraten i CAFÉ. Forskellen bliver dermed markant anderledes end ved en mere uprækcis naiv sammenligning, det vil sige hvor man blot trækker andelene fra hinanden.

Tabel 4 Resultater pr. studie for effektmålet *Eksem udbredelses- og sværhedsgrad.*

	BREEZE-AD 4		CAFÉ	
	Baricitinib 4 mg dagligt + TCS (n = 92)	**Placebo + TCS (n = 93)**	**Dupilumab 300 mg hver 2. uge + TCS (n = 107)**	**Placebo + TCS (n = 108)**
EASI: andel, der opnår mindst 75 % reduktion, % [95 % CI]	**31,5 [22,9; 41,6]**	17,4 [11; 26,4]	**62,6 [53,2; 71,2]**	29,6 [21,8; 38,8]
SCORAD: andel, der opnår 50 % reduktion, % [95 % CI]	**37,0 [27,8; 47,2]**	20,4 [13,5; 29,7]	**66,4 [57; 74,6]**	25,9 [18,6; 34,9]

Fed skrift markerer de estimater, der er anvendt i den indirekte analyse. For at tage højde for forskelle i placebogrupperne er de absolutte forskelle beregnet ud fra eventraten i CAFÉ.

Eczema Area and Severity Index (EASI)

Den absolutte forskel i EASI75 er beregnet til -8,1 %-point [95 % CI -33,8; 39,5], det vil sige, at 8,1 % færre i behandling med baricitinib opnår EASI75 i forhold til dupilumab. Dermed er den mindste klinisk relevante forskel ikke opnået. Konfidensintervallet er meget bredt, hvilket betyder, at estimatet er usikkert. Derfor kan den foreløbige værdi af baricitinib vedr. EASI75 ikke kategoriseres efter Medicinrådets metoder.

Baseret på den relative effektforskel (RR 0,87 95 % CI [0,46; 1,63], som fremgår af tabel 3, kan værdien af baricitinib foreløbigt ikke kategoriseres vedr. EASI75, fordi estimatet er for usikkert.

SCORing Atopic Dermatitis (SCORAD)

Den absolutte forskel i SCORAD50 er beregnet til -19,2 [95 % CI -40,5; 18,6], det vil sige, at 19,2 % færre i behandling med baricitinib opnår SCORAD50 sammenlignet med dupilumab. Dette afspejler en negativ klinisk relevant forskel. Konfidensintervallet er dog meget bredt, hvilket betyder, at estimatet er usikkert. Derfor kan den foreløbige værdi af baricitinib vedr. SCORAD50 ikke kategoriseres efter Medicinrådets metoder.

Baseret på den relative effektforskel (RR 0,81 [0,48; 1,38], som fremgår af tabel 3, kan værdien af baricitinib foreløbigt ikke kategoriseres vedr. SCORAD50, fordi estimatet er for usikkert.

Delkonklusion, Eksem udbredelses- og sværhedsgrad

Fagudvalget vurderer, at værdien af baricitinib aggregeret ikke kan kategoriseres vedr. effektmålet *Eksem udbredelses- og sværhedsgrad*, da estimaterne er for usikre.

Fagudvalget bemærker, at andelen, der opnår EASI75 er en del lavere i BREEZE-AD 4 sammenlignet med CAFÉ. Dette gælder både de aktive behandlinger og placebo. Det samme ses for SCORAD50, hvor forskellen i placeboarmene dog ikke er så udtalt. Årsagen kan måske være, at BREEZE-AD 4 har en større andel af patienter med asiatisk baggrund, som erfaringsmæssigt kan være sværere at behandle. Der kan også potentielt være forskelle i andelen af inkluderede patienter, som ikke tidligere har fået en systemisk behandling grundet kontraindikationer, eller hvor potent den samtidige TCS-behandling var. Dette er der dog ikke oplysninger om. Endelig kan forskelle i

inklusionskriterier vedrørende tidligere behandling have en betydning. Dette forekommer dog mindre sandsynligt da baselinekarakteristika ikke tydede på en forskel.

Eksem udbredelses- og sværhedsgrad, patientrapporteret

Som beskrevet i protokollen er effektmålet *Eksem udbredelses- og sværhedsgrad, patientrapporteret* kritisk for vurderingen af lægemidlets værdi for patienterne, fordi man på denne måde får belyst, hvilken betydning symptomerne ved atopisk eksem har for patienterne. Aspekter af dette kan tolkes som livskvalitet, specifikt opgjort i forhold til atopisk eksem. Effektmålet måles ved Patient-Oriented Eczema Measure (POEM). POEM er et vigtigt instrument til brug i kombination med de objektive scoringssystemer (særligt til patienter med svær lokaliseret eksem), da det giver en omfattende vurdering af symptomer ud fra patientens perspektiv [13]. Den mindste klinisk relevante forskel for POEM er 3 [14] i gennemsnitlig ændring fra baseline. En negativ ændring fra baseline angiver en forbedring. Tabel 5 viser resultater pr. studie.

Tabel 5 Resultater pr. studie for effektmålet *Eksem udbredelses- og sværhedsgrad, patientrapporteret.*

	BREEZE-AD 4		CAFÉ	
	Baricitinib 4 mg dagligt + TCS (n = 92)	**Placebo + TCS (n = 93)**	**Dupilumab 300 mg hver 2. uge + TCS (n = 107)**	**Placebo + TCS (n = 108)**
POEM, gennemsnitlig ændring fra baseline, point [95 % CI]	**-9,27 [-10,9; -7,59]**	-4,18 [-5,96; -2,4]	**-11,9 [-13,1; -10,7]**	-4,3 [-5,51; -3,09]

Fed skrift markerer de estimater, der er anvendt i den indirekte analyse.

De absolutte forskelle på de gennemsnitlige ændringer i POEM var 2,51 point [95 % CI -0,46; 5,48]. Det vil sige, at der var et større fald i POEM for dupilumab, hvilket reflekterer en større forbedring af patientrapporteret eksem udbredelses- og sværhedsgrad med dupilumab sammenlignet med baricitinib. Forskellen er dog ikke klinisk relevant. Den foreløbige værdi af baricitinib vedr. POEM ikke kategoriseres efter Medicinrådets metoder, da konfidensintervallets grænser indeholder værdier, som både kan indikere, at der ingen forskel er og at dupilumab har en bedre effekt end baricitinib.

Fagudvalget vurderer, at værdien af baricitinib aggregeret ikke kan kategoriseres vedr. effektmålet *Eksem udbredelses- og sværhedsgrad, patientrapporteret*.

Fagudvalget vurderer, at resultaterne kan indikere en bedre effekt af dupilumab. Det er dog ikke statistisk signifikant. Derfor kan det ikke ud fra de foreliggende data konkluderes, at der er en effektforskel mellem behandlingerne.

Bivirkninger

Som beskrevet i protokollen er effektmålet *Bivirkninger* kritisk for vurderingen af lægemidlets værdi for patienterne, fordi det har betydning for den enkelte patients livskvalitet og for kompliance. Der bør være lav tolerance for alvorlige bivirkninger, idet sygdommen ikke er livstruende, og der er et forventet behov for langtidsbehandling.

Bivirkninger opgøres som både *Andel, som oplever mindst én alvorlig bivirkning* og *Opgørelse af langtidsbivirkninger, alle grader*.

Andel, som oplever mindst én alvorlig bivirkning

Den mindste klinisk relevante forskel blev i protokollen fastsat til 2 procentpoint. Tabel 6 viser resultater pr. studie.

Tabel 6 Resultater pr. studie for effektmålet *Andel, som oplever mindst en alvorlig bivirkning.*

	BREEZE-AD 4		CAFÉ	
	Baricitinib 4 mg dagligt + TCS (n = 92)	**Placebo + TCS (n = 93)**	**Dupilumab 300 mg hver 2. uge + TCS (n = 107)**	**Placebo + TCS (n = 108)**
Andel, som oplever mindst én alvorlig bivirkning, % [95 % CI]	**6,5 [3; 7,5]**	2,2 [0,6; 7,5]	**1,9 [0,5; 6,6]**	1,9 [0,5; 6,5]

Fed skrift markerer de estimater, der er anvendt i den indirekte analyse.

Punktestimatet for den absolutte effektforskel (3,7 %-point [95 % CI -1,4; 66,6]) afspejler en klinisk relevant effektforskel, som indikerer, at baricitinib medfører flere alvorlige bivirkninger sammenlignet med dupilumab. Konfidensintervallet er imidlertid så bredt, at den foreløbige værdi af baricitinib vedr. andel, som oplever mindst én alvorlig bivirkning ikke kategoriseres efter Medicinrådets metoder.

Baseret på den relative effektforskel (RR 3 [95 % CI 0,25; 36,6], som fremgår af tabel 3, kan værdien af baricitinib foreløbigt ikke kategoriseres vedr. *Andel, som oplever mindst én alvorlig bivirkning.*

Opgørelse af langtidsbivirkninger, alle grader

Herunder følger en gennemgang af bivirkningstyperne med henblik på at vurdere alvorlighed, håndterbarhed og tyngde af bivirkningerne. Tabel 7 viser en opgørelse over uønskede hændelser ved baricitinib og dupilumab.

Tabel 7 Uønskede hændelser observeret hos patienter med atopisk eksem, behandlet med baricitinib [15] **eller dupilumab** [16] **i kliniske studier, angivet i EMAs EPAR.**

System organ class	Baricitinib			Dupilumab		
	Meget almindelig ≥ 1/10	**Almindelig ≥ 1/100 to < 1/10**	**Sjælden ≥ 1/1,000 to < 1/100**	**Meget almindelig ≥ 1/10**	**Almindelig ≥ 1/100 to < 1/10**	**Sjælden ≥ 1/1,000 to < 1/100**
Infektioner og parastisygdomme	Infektion i øvre luftveje (forkølelse, bihulebetændelse)	Herpes simplex Maveinfluenza Urinvejsinfektion	Lungeinfektion		Øjenbetændelse Oral herpes	
Blod og lymfesystem		Trombocytose > 600 x 10^9 celler/L	Neutropeni < 1 x 10^9 celler/L		Eosinofili	
Metabolisme- og ernæring	Forhøjet kolesterol		Forhøjet triglycerid			
Nervesystem			Hovedpine		Hovedpine	
Øjne					Allergisk øjenbetændelse Øjenkløe Øjenlågsbetændelse	Hornhindebetændelse (m/u sårdannelse)
Gastrointestinelt	Kvalme	Mavesmerter	Diverticulitis			
Lever- og galdevejssygdomme			ALT øget ≥3 x ULN AST øget ≥3 x ULN			
Generelle lidelser				Injektionsreaktioner		
Hud og underhud			Udslæt Akne			
Immunsystemet			Hævelse i ansigtet Nældefeber			
Respiratorisk, brystkasse, mediastrium			Lungeemboli			
Vaskulært			Dyb venetrombose			
Undersøgelser		Øget kreatinin fosfokinase > 5 x ULN				

ALT, blood alanine transaminase; AST, aspartate transaminase; ULN, upper limit of normal.
For dupilumab er der I EPARen desuden nævnt serumsygdom som meget sjælden og anafylaktisk reaktion, angioødem samt ledsmerter som ikke kendt forekomst.

Baricitinib
I alt er 2.531 patienter med atopisk eksem behandlet med baricitinib i de kliniske studier, svarende til 2.247 patient-års eksponering. Af disse patienter var 1.106 i behandling i mindst et år. Data fra fem placebokontrollerede studier (589 patienter fik 4 mg baricitinib en gang dagligt, og 743 patienter fik tilsvarende placebo) blev anvendt til at evaluere sikkerheden ved baricitinib sammenlignet med placebo i op til 16 uger efter behandlingsstart.

Infektioner er den primære risiko ved behandling med baricitinib. Derfor anbefales en lavere dosis (2 mg) til patienter som tidligere har haft kroniske eller tilbagevendende infektioner. Blodlipider er forhøjede hos patienter behandlet med baricitinib. I de kliniske studier, der er foretaget i en population med atopisk eksem, var der følgende observationer af forhøjet kolesterol for henholdsvis baricitinib og placebo, som vist ved andelene herunder:

- Total kolesterol ≥ 5,17 mmol/L: 20,7 % vs. 10 %
- LDL kolesterol ≥ 3,36 mmol/L: 13,2 % vs. 6,3 %
- HDL kolesterol ≥ 1,55 mmol/L: 25,3 % vs. 14,7 %
- Triglycerider ≥ 5,65 mmol/L: 0,7 % vs. 0,8 %

Derfor bør blodlipider måles ca. 12 uger efter behandlingsstart og herefter ifølge retningslinjerne for hyperlipidæmi.

Dupilumab
Sikkerheden ved dupilumab er evalueret i fire placebokontrollerede studier og et dosisrangeringsstudie vedr. patienter med moderat-svær atopisk eksem. I alt blev 1.689 patienter behandlet med subkutan dupilumab, med eller uden samtidig TCS. I alt 305 patienter blev behandlet i mindst et år.

De hyppigste uønskede hændelser ved dupilumab sammenlignet med placebo var reaktioner på injektionsstedet (som stod for størstedelen af alle rapporterede hændelser), hovedpine, oral herpes, øjenbetændelse og eosinofili. Nogle infektioner var mere hyppige ved dupilumab sammenlignet med placebo, herunder øjenbetændelse og oral herpes. Allergisk øjenbetændelse og andre øjenproblemer forekom også hyppigere ved dupilumab. Hovedparten var af mild til moderat sværhedsgrad og kunne behandles.

Konklusion vedr. bivirkninger
Fagudvalget bemærker, at der forekommer flere almindelige bivirkninger ved baricitinib sammenlignet med dupilumab. De fleste bivirkninger er dog sjældne. Hyperkolesterolæmi er en almindelig bivirkning ved baricitinib og er potentielt behandlingskrævende. Derfor bør man være tilbageholdende med at give baricitinib til patienter med forhøjet kolesterol. Desuden kræver baricitinib rutineblodprøver på grund af denne risiko. Ved dupilumab foretages kun blodprøver ved behov. Det er dog ikke fagudvalgets erfaring, at der er øget forekomst af forhøjet kolesterol hos patienter med atopisk eksem generelt.

Ved dupilumab ses injektionsrelaterede bivirkninger, hvilket undgås ved baricitinib, da det er en tabletbehandling.

Fagudvalget vurderer, at værdien af baricitinib aggregeret ikke kan kategoriseres vedr. effektmålet *Bivirkninger*. Der er endnu ikke klinisk erfaring med baricitinib til behandling af atopisk eksem og de tilgængelige data er baseret på relativt få patienter og med kort opfølgningstid.

Livskvalitet

Som beskrevet i protokollen er effektmålet livskvalitet kritisk for vurderingen af lægemidlets værdi for patienterne, fordi det drejer sig om en kronisk og for de svære tilfælde invaliderende sygdom. Livskvalitet ønskes opgjort med spørgeskemaet Dermatology Life Quality Index (DLQI). DLQI er er udviklet til at vurdere den helbredsrelaterede livskvalitet i forbindelse med dermatologiske sygdomme og deres behandling. DLQI indeholder 10 spørgsmål relateret til symptomer, følelser, daglige aktiviteter, tøj, arbejde eller skole, fritidsaktiviteter, relationer og gener af behandlingen [15]. Den maksimale score er 30, hvor højere score indikerer dårligere helbredsrelateret livskvalitet [15,16]. Den mindste klinisk relevante forskel er i litteraturen rapporteret at være 4 point for DLQI [17] i gennemsnitlig ændring fra baseline. Tabel 8 viser resultater pr. studie.

Tabel 8 Resultater pr. studie for effektmålet *Livskvalitet.*

	BREEZE-AD 4		CAFÉ	
	Baricitinib 4 mg dagligt + TCS (n = 92)	**Placebo + TCS (n = 93)**	**Dupilumab 300 mg hver 2. uge + TCS (n = 107)**	**Placebo + TCS (n = 108)**
DLQI, gennemsnitlig ændring fra baseline, point [95 % CI]	**-7,95 [-9,33; -6,57]**	-1,64 [-2,27; -1,01]	**-9,5 [-10,4; -8,6]**	-4,5 [-5,46; -3,54]

Fed skrift markerer de estimater, der er anvendt i den indirekte analyse.

Både baricitinib og dupilumab viste en forbedring i livskvalitet, sammenlignet med placebo. Den absolutte forskel på de gennemsnitlige ændringer i DLQI er 2 point [-0,41; 4,41], det vil sige at patienter i behandling med dupilumab i gennemsnit forbedrede deres livskvalitet med 2 point mere end patienter i behandling med baricitinib. Dette afspejler ikke en klinisk relevant forskel.

Den øvre grænse af konfidensintervallet er lidt højere end den mindste klinisk relevante forskel. Men da den nedre grænse indikerer, at der ikke er nogen effektforskel, kan den foreløbige værdi af baricitinib vedr. livskvalitet ikke kategoriseres efter Medicinrådets metoder.

Det er ikke muligt at beregne den relative effektforskel for dette effektmål.

Fagudvalget vurderer, at værdien af baricitinib aggregeret ikke kan kategoriseres vedr. effektmålet *Livskvalitet* i henhold til Medicinrådets metoder.

Kløe

Som beskrevet i protokollen er effektmålet kløe vigtigt for vurderingen af lægemidlets værdi for patienterne, fordi kløe typisk er det mest generende symptom. Peak pruritus numeric rating scale (NRS) er et valideret instrument, som patienterne bruger til at rapportere maksimal intensitet af kløe i løbet af de foregående 24 timer [17]. Score ligger mellem 0-10, hvor en høj score indikerer en højere sværhedsgrad. Mindste klinisk relevante forskel er rapporteret i litteraturen til at være 2-3 point for voksne [18]. Fagudvalget vurderer, at en reduktion på 3 point vil være en stor forbedring i kløen for den enkelte patient. Fagudvalget vurderer derfor, at mindste klinisk relevante forskel er 3 point i gennemsnitlig ændring fra baseline. Tabel 9 viser resultater pr. studie.

Tabel 9 Resultater pr. studie for effektmålet *Kløe.*

	BREEZE-AD 4		CAFÉ	
	Baricitinib 4 mg dagligt + TCS (n = 92)	**Placebo + TCS (n = 93)**	**Dupilumab 300 mg hver 2. uge + TCS (n = 107)**	**Placebo + TCS (n = 108)**
Kløe NRS, gennemsnitlig ændring fra baseline, point [95 % CI]	**-3,16 [-3,73; -2,59]**	-1,64 [-2,27; -1.01]	**-3,5 [-3,88; -3,12]**	-1,7 [-2,08; -1,32]

Fed skrift markerer de estimater, der er anvendt i den indirekte analyse.

Den absolutte forskel på de gennemsnitlige ændringer i Kløe NRS er 0,28 point [95 % CI -0,59; 1,15], hvilket ikke afspejler en klinisk relevant forskel.

Det er ikke muligt at beregne den relative effektforskel for dette effektmål.

Fagudvalget vurderer, at baricitinib har ingen dokumenteret merværdi vedrørende kløe sammenlignet med dupilumab.

Episoder med opblussen

Som beskrevet i protokollen er effektmålet *Episoder med opblussen* vigtigt for vurderingen af lægemidlets værdi for patienterne, fordi episoder med opblussen er generende for patienterne og kan kræve optrapning eller intensivering af behandling. Episoder med opblussen måles over en tidsperiode på f.eks. 3 måneder, hvorimod tilsvarende information om symptomforværring i spørgeskemaerne gælder en kortere tidsperiode. Fagudvalget ønsker information om behandlingseffekten over en længere periode og mener derfor, at dette bør vurderes selvstændigt som et vigtigt effektmål. Den mindste klinisk relevante forskel vurderes at være 10 procentpoints forskel i andel patienter, der oplever en eller flere episoder med opblussen.

Der er ikke rapporteret data for dette effektmål, hvorfor værdien ikke kan kategoriseres.

5.1.5 Fagudvalgets konklusion

Fagudvalget vurderer, at den samlede værdi af baricitinib sammenlignet med dupilumab til patienter med moderat-svær atopisk eksem ikke kan kategoriseres.

Fagudvalget bemærker, at de tilgængelige data kan indikere, at dupilumab har en bedre effekt end baricitinib, herunder for eksemudbredelse- og sværhedsgrad vurderet ved SCORAD og EASI. Forskellene er dog ikke statistisk signifikante og opnår ikke den mindste klinisk relevante forskel. Desuden er der usikkerheder ved estimaterne idet de er baserede på indirekte sammenligninger. Bivirkningsprofilerne for baricitinib og dupilumab er forskellige. Der er efterhånden opbygget klinisk erfaring med behandling af atopisk eksem med dupilumab og dermed også håndtering af bivirkningerne. Baricitinib er et nyt lægemiddel på området, og datagrundlaget for bivirkninger er sparsomt. Baricitinib har flere almindelige bivirkninger end dupilumab, men fagudvalget vurderer, at de bivirkninger, der vil opstå ved baricitinib, også vil være håndterbare. Derfor vurderer fagudvalget, at baricitinib samlet set ikke har dårligere effekt eller sikkerhedsprofil end dupilumab. På grund af påvirkningen af blodlipider vil man dog være tilbageholdende med at give baricitinib til patienter med forhøjet kolesterol.

6. Andre overvejelser

Ansøger blev i protokollen bedt om at redegøre for, hvilke blodprøver der skal tages ved opstart og monitorering. Ansøgers svar er opsummeret i nedenstående. Fagudvalget bemærker, at proceduren ligner standard ved biologisk behandling.

Ansøgers svar

Den anbefalede monitorering ifølge EMAs EPAR er angivet i tabel 10 [15].

Tabel 10 Den anbefalede monitorering ved behandling med baricitinib [15].

Laboratorie-undersøgelser	Handling	Monitorering
Lipid parametre	Patienter bør behandles jævnfør internationale kliniske retningslinjer for hyperlipidæmi	12 uger efter behandlingsstart og derefter jævnfør internationale kliniske retningslinjer for hyperlipidæmi
Neutrofile (ANC)	Behandlingen bør afbrydes hvis ANC < 1 x 109 celler/L og kan genoptages hvis ANC stiger til over dette niveau	Før behandlingsopstart og derefter jævnfør standard behandlings- og kontrolbesøg
Lymfocytter (ALC)	Behandlingen bør afbrydes hvis ALC < 0,5 x 109 celler/L og kan genoptages, hvis ALC stiger til over dette niveau	
Hæmoglobin (Hb)	Behandlingen bør afbrydes hvis Hb < 8 g/dL og kan genoptages, hvis Hb stiger til over dette niveau	
Lever transaminase	Behandlingen bør midlertidigt afbrydes ved mistanke om behandlingsinduceret leverskade	

ALC: Absolute Lymphocyte Count. ANC: Absolute Neutrophil Count. Hb: Hemoglobin

Patienter bør screenes for tuberkulose (TB) før opstart, da baricitinib ikke bør gives ved aktiv TB. Derfor bør TB-behandling overvejes hos patienter med tidligere ubehandlet latent TB [15].

Ligeledes bør der screenes for viral leverbetændelse i overensstemmelse med kliniske retningslinjer. Patienter med påvist aktiv hepatitis B eller C blev ekskluderet fra de kliniske studier, hvorimod patienter med positiv hepatitis C antistof, men negativ virus RNA kunne deltage. Ligeledes var hepatitis B overflade- og kerneantistof uden overfladeantigen tilladt, dog under monitorering for virus (HBV) DNA. Ved påvisning af HBV DNA var tilsyn ved leverspecialist påkrævet [15].

I kliniske studier er observeret hæmatologiske abnormaliteter ved behandling med baricitinib (hos mindre en 1 %). Derfor bør hæmatologiske parametre monitoreres, som angivet i tabel 11 [15].

Baricitinib er vist at give en dosisafhængig forøgelse af blodlipider, levertal (alanine transaminase (ALT) og aspartate transaminase (AST)), sammenlignet med placebo. Dette bør derfor monitoreres, som angivet i tabel 11 [15].

7. Relation til behandlingsvejledning

Der findes ikke en relevant behandlingsvejledning fra Medicinrådet.

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9. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende atopisk eksem	
Formand	**Indstillet af**
Gabrielle Randskov Vinding *Afdelingslæge*	Lægevidenskabelige Selskaber og udpeget af Region Sjælland og Dansk Dermatologisk Selskab
Medlemmer	**Udpeget af**
Har ikke specialet	Region Nordjylland
Kan ikke udpege	Region Midtjylland
Evy Paulsen *Overlæge*	Region Syddanmark
Kati Hennele Kainu *Overlæge*	Region Hovedstaden
Britt Nilausen *Sygeplejerske*	Danske Sygepleje Selskab
Anne Holm Hansen *Patient/patientrepræsentant*	Danske Patienter
Rasmus Huan Olsen *Afdelingslæge*	Dansk Selskab for Klinisk Farmakologi
Marianne Hald Clemmensen *Farmaceut*	Dansk Selskab for Sygehusapoteksledelse
Charlotte Gotthard Mørtz *Professor, overlæge*	Inviteret af formanden
Tidligere medlemmer, som har bidraget til arbejdet	**Udpeget af**
Emma Johanna Svedborg *Klinisk farmaceut*	Dansk Selskab for Sygehusapoteksledelse

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10. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.1	26. maj 2021	Bivirkningsprofilen i tabel 7 for dupilumab er blevet opdateret således den stemmer overens med EPAR for dupilumab
1.0	28. april 2021	Godkendt af Medicinrådet

11. Bilag

Bilag 1: Cochrane – risiko for bias

Vurdering af risiko for bias ved Cochrane risk of bias tool 2.0.

Tabel 11 Vurdering af risiko for bias BREEZE-AD 4 NCT03428100 (vurderet på baggrund af studieprotokollen og clinicaltrials.gov).

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiserings-processen	Lav	*Assignment to treatment groups will be determined by a computer-generated random sequence*
Effekt af tildeling til intervention	Lav	*Double-blind study*
Manglende data for effektmål		Ikke muligt at vurdere pr. effektmål, men overordnet acceptabelt niveau af behandlingsophør (20 % i placebogruppen, 8 % i 4 mg baricitinib)
Risiko for bias ved indsamlingen af data	Lav	*Double-blind study. All study assessments will be performed by study personnel who are blinded to the patient's treatment group. Double-blind investigational product tablets. Except in clinical circumstances where unblinding is required, the patients, investigators, Lilly study team, and any personnel interacting directly with patients or investigative sites will remain blinded to baricitinib and placebo assignment until after completion of the double-blinded treatment periods.*
Risiko for bias ved udvælgelse af resultater, der rapporteres	Lav	Ikke noget der tyder på selektionsbias (Clinicaltrials.gov)
Overordnet risiko for bias	Lav	

Tabel 12 Vurdering af risiko for bias: De Bruin-Weller 2018 LIBERTY AD CAFÉ NCT02755649 [11].

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiserings-processen	Lav	*patients were randomized (1 : 1 : 1) to receive 16 weeks of subcutaneous dupilumab 300 mg weekly (qw) or subcutaneous dupilumab 300 mg every 2 weeks (q2w) or placebo, using a central interactive voice-/web-response randomization system*
Effekt af tildeling til intervention	Lav	*Randomized, double-blind, placebo-controlled, parallel-group, phase III clinical study. Efficacy assessments were based on the full-analysis set, which included all randomized patients, based on the treatment allocated as randomized (intention-to-treat).*
Manglende data for effektmål	Lav	*Patients were specified as being 'nonresponders' at rescue medication initiation. Continuous end points were analysed using multiple imputation with ANCOVA;* *data after rescue medication usage was set to missing and imputed by multiple imputation.* *Rescue medication use: placebo 18 %, dupilumab q2w 4 %*
Risiko for bias ved indsamlingen af data	Lav	Dobbeltblindet studie. *An independent data monitoring committee (IDMC) monitored patient safety*
Risiko for bias ved udvælgelse af resultater, der rapporteres	Lav	Sammenhold af artikel med information på clinicaltrials.gov viser ingen selektiv rapportering
Overordnet risiko for bias	Lav	Der er en mindre andel af patienterne, der får rescue treatment og dermed har manglende data. Der er anvendt imputation, hvilket i sig selv giver en risiko for bias. Da det imidlertid er placebogruppen, hvori der er flest, der får rescue treament, vurderes det, at den potentielle bias vil give et mere konservativt estimat af effekten af dupilumab. Derfor vurderes det, at der overordnet set er lav risiko for bias

Bilag 2: GRADE

Tabel 13 GRADE evidensprofil: baricitinib vs. dupilumab til voksne med moderat-svær atopisk eksem (indirekte sammenligning BREEZE-AD 4 vs. CAFÉ).

Sikkerhedsvurdering							Antal patienter		Effekt		Sikkerhed	Vigtighed
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	Baricitinib	dupilumab	Relativ [95 % CI]	Absolut [95 % CI]		
Eksem udbredelses- og sværhedsgrad, EASI75												
2	RCT	Ikke alvorlig	Ikke alvorlig	Alvorlig [a]	Alvorlig [b]	Ingen	92	107	0,87 [0,46; 1,63]	-8,1 [-33,8; 39,5]	⨁⨁◯◯ LAV	KRITISK
Eksem udbredelses- og sværhedsgrad, SCORAD50												
2	RCT	Ikke alvorlig	Ikke alvorlig	Alvorlig [a]	Alvorlig [b]	Ingen	92	107	0,71 [0,39; 1,28]	-19,2 [-40,5; 18,6]	⨁⨁◯◯ LAV	KRITISK
Eksem udbredelses- og sværhedsgrad, patientrapporteret. POEM												
2	RCT	Ikke alvorlig	Ikke alvorlig	Alvorlig [a]	Ikke alvorlig	Ingen	92	107	-	2,51 [-0,46; 5,48]	⨁⨁⨁◯ MODERAT	KRITISK
Andel af patienter som oplever en eller flere alvorlige bivirkninger												
2	RCT	Ikke alvorlig	Ikke alvorlig	Alvorlig [a]	Alvorlig [b]	Ingen	92	107	3 [0,25; 36,6]	3,7 [-1,4; 66,6]	⨁⨁◯◯ LAV	KRITISK
Livskvalitet												
2	RCT	Ikke alvorlig	Ikke alvorlig	Alvorlig [a]	Ikke alvorlig	Ingen	67	107	-	2 [-0,41; 4,41]	⨁⨁⨁◯ MODERAT	KRITISK
Kløe												
2	RCT	Ikke alvorlig	Ikke alvorlig	Alvorlig [a]	Ikke alvorlig	Ingen	66	107	-	0,28 [-0,59; 1,15]	⨁⨁⨁◯ MODERAT	VIGTIG
Episoder med opblussen												
0											⨁◯◯◯ MEGET LAV	VIGTIG
Kvalitet af den samlede evidens			Lav [c]									

[a] Sammenligningerne er foretaget med indirekte analyser. Derfor er der nedgraderet et niveau for indirekthed.

[b] Der er nedgraderet er niveau for unøjagtighed, da konfidensintervallet er bredt og indeholder både positive og negative konklusioner.

[c] Den samlede evidenskvalitet er vurderet ud fra den laveste kvalitet af de kritiske effektmål.

Bilag 3: resultater for sammenligningen BREEZE-AD 7 vs. CHRONOS

Tabel 14 Resultater for sammenligning v. 16 uger baseret på data fra BREEZE-AD 7 vs. CHRONOS samt kategorisering hvis denne havde dannet grundlag for vurderingen.

Effektmål	Målenhed (MKRF)	Vigtighed	Forskel i absolutte tal		Forskel i relative tal		Aggregeret værdi for effektmålet
			Forskel [95 % CI]	Foreløbig værdi	Forskel (95 % CI)	Foreløbig værdi	
Eksem udbredelses- og sværhedsgrad	EASI: andel, der opnår mindst 75 % reduktion (10 %-point)	Kritisk	-18,4 [-33,9; 6,5]	Kan ikke kategoriseres	0,69 [0,43; 1,11]	Kan ikke kategoriseres	Kan ikke kategoriseres
	SCORAD: andel, der opnår 50 % reduktion (10 %-point)			Kan ikke kategoriseres		Kan ikke kategoriseres	
Eksem udbredelses- og sværhedsgrad, patientrapporteret	POEM, gennemsnitlig ændring fra baseline (3 point)	Kritisk	2,47 [-0,05; 4,99]	Kan ikke kategoriseres	IA		Kan ikke kategoriseres
Bivirkninger	Andel, som oplever mindst en alvorlig bivirkning (2 %-point)	Kritisk		Kan ikke kategoriseres	**A:** 3 [0,25; 36,6]	Kan ikke kategoriseres	Kan ikke kategoriseres
	Opgørelse af langtidsbivirkninger, alle grader						
Livskvalitet	DLQI, gennemsnitlig ændring fra baseline (4 point)	Kritisk	1,09 [-0,93; 3,11]	Kan ikke kategoriseres	Kan ikke beregnes		Kan ikke kategoriseres
Kløe	NRS, gennemsnitlig ændring fra baseline (3 point)	Vigtig	0,31 [-0,47; 1,09]	Ingen dokumenteret merværdi	Kan ikke beregnes		Ingen dokumenteret merværdi
Episoder med opblussen	Andel, der oplever mindst en episode med opblussen i løbet af 16 uger (10 %-point)	Vigtig	IA		IA		Kan ikke kategoriseres
Konklusion							
Samlet kategori for lægemidlets værdi	Kan ikke kategoriseres						
Kvalitet af den samlede evidens	Meget lav						

MKRF: Mindste klinisk relevante forskel. CI: konfidensinterval. RR: relativ risiko. IA: ikke angivet.

Tabel 15 Resultater fra studierne BREEZE-AD 7 og CHRONOS.

	BREEZE-AD 7		CHRONOS	
	Baricitinib 4 mg dagligt + TCS (n = 99)*	**Placebo + TCS (n = 89)***	**Dupilumab 300 mg hver 2. uge + TCS (n = 106)**	**Placebo + TCS (n = 315)**
EASI: andel, der opnår mindst 75 % reduktion, % [95 % CI]	47,7 [38,7; 57]	22,9 [16; 31,7]	59,4 [49,9; 68,3]	19,7 [15,7; 24,4]
POEM, gennemsnitlig ændring fra baseline, point [95 % CI]	-10,8 [-12,2; -9,37]	-5,6 [-7,1; -4,1]	-12,4 [-13,6; -11,2]	-4,7 [-5,44; -3,96]
DLQI, gennemsnitlig ændring fra baseline, point [95 % CI]	-8,89 [-10; -7,75]	-5,58 [-6,77; -4,39]	-9,7 [-10,7;-8,7]	-5,3 [-5,91; -4,69]
Kløe NRS, gennemsnitlig ændring fra baseline, point [95 % CI]	-3,68 [-4,1; -3,26]	-1,99 [-2,42; -1,56]	-4,1 [-4,51; -3,69]	-2,1 [-2,35; -1,85]

*n for EASI = 111 og 109.

Application for the assessment of Olumiant (baricitinib) for atopic dermatitis

Contents

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1. Basic information

Kontaktoplysninger	
Navn	**Jeppe Schultz Christensen**
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Overview of the pharmaceutical	
Proprietary name	Olumiant
Generic name	Baricitinib
Marketing authorization holder in Denmark	Eli Lilly Nederland B.V.
ATC code	L04AA37
Pharmacotherapeutic group	JAK/STAT inhibitor with JAK-1/JAK-2 selectivity
Active substance(s)	baricitinib
Pharmaceutical form(s)	Oral tablet
Mechanism of action	Baricitinib is a selective and reversible inhibitor of Janus kinase (JAK) -1 and JAK2

Overview of the pharmaceutical	
Dosage regimen	The recommended dose of Olumiant is 4 mg once daily. A dose of 2 mg once daily is appropriate for patients such as those aged ≥ 75 years and may be appropriate for patients with a history of chronic or recurrent infections. A dose of 2 mg once daily should be considered for patients who have achieved sustained control of disease activity with 4 mg once daily and are eligible for dose tapering
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Olumiant is indicated for the treatment of moderate to severe atopic dermatitis in adult patients who are candidates for systemic therapy
Other approved therapeutic indications	Olumiant is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs.
Will dispensing be restricted to hospitals?	No
Combination therapy and/or co-medication	Olumiant can be used with or without topical corticosteroids. Olumiant's effectiveness may be increased when given with topical corticosteroids. Topical calcineurin inhibitors may be used, but should be reserved for sensitive areas only, such as the face, neck, intertriginous and genital areas.
Packaging – types, sizes/number of units, and concentrations	Olumiant of 2 or 4 mg film-coated tablets, in the following packaging: 28 x 1 film-coated tablets 98 x 1 film-coated tablets
Orphan drug designation	No

Abbreviations: JAK, Janus kinase; STAT, signal transducer and activator of transcription.

2. Abbreviations

AD	Atopic dermatitis
ADHD	Attention deficit hypertension disorder
ADSS	Atopic Dermatitis Sleep Scale
AE	Adverse events
ANCOVA	Analysis of covariance
BMI	Body mass index
BSA	Body surface area
CI	Confidence interval
CSA	Cyclosporine-A
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index

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EMA	European Medical Association
EQ-5D	EuroQol 5D
ETV	Early termination visit
GISS	Global Individual Sign Score
HADS	Hospital Anxiety and Depression Scale
HBV	Hepatitis B virus
HIV	Human immunodeficiency virus
HRQoL	Health related quality of life
IGA	Investigator's Global Assessment
IL	Interleukin
IQR	Interquartile range
ITT	Intent-to-treat
JAK	Janus kinase
LS	Least squares
NA	Not available
NRI	Non-responder imputation
NRS	Numeric Rating Scale
PGI-S-AD	Patient Global Impression of Severity for Atopic Dermatitis
POEM	Patient Oriented Eczema Measures
PTFU	Post Treatment Follow Up
QD	Twice daily
SAE	Serious adverse events
SCORAD	Scoring Atopic Dermatitis
SD	Standard deviation
SPC	Summary of Product Characteristics
STAT	Signal transducer and activator of transcription
TB	Tuberculosis
TCS	Topical corticosteroids
TESAE	Treatment-emergent serious adverse events
TSL	Thymus stromal lymphopoietin
VAS	Visual analogue scale
VTE	Venous thromboembolic even
WPAI	Work productivity scores

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3. Summary

Atopic dermatitis

Atopic dermatitis (AD) is the most common medical skin disease in Denmark and in the world. Prevalence estimates are subject to great uncertainty, but among children it is estimated in Denmark to be approx. 20% and in adults 5-10% (Calov 2020, Thyssen 2020). These figures cover large variations in the clinical presentation of the disease and its significance for patients' quality of life.

The etiology of the disease is only partially identified but is known to be multifactorial with both genetic and environmental factors (Calov 2020, Chee 2020). The pathophysiology is also complex. Overall, it consists of two components: a reduced barrier function of the skin as well as an immunological overactivity in the skin. The immunological overactivity is primarily characterized by a so-called Th2 response corresponding to the presence of certain signaling molecules (cytokines), such as: IL-1, IL-4, IL-13, IL-17, IL-22, IL31, IL-33 and thymus stromal lymphopoietin (TSL) in the inflamed skin. The signaling molecules act as messengers between the different types of cells of the immune system, and the different types of immune response in the skin are directed in a complex interplay between skin cells and immune cells, all secreting cytokines of different types in a still only partially understood system of effector mechanisms and feed-back loops (Calov 2020, Chee 2020, Thyssen 2020, Thyssen 2020, Pescitelli 2021).

The disease presents clinically with itching as the primary symptom. In addition, dry skin and eczema are often seen in the form of redness, swelling, scratching, peeling, cracks, and chronic thickening of the skin (Chee 2020). In addition to the itching, the skin changes can, to some extent, be characterized by pain, particularly if the crack formation in the skin has led to direct access to the subcutaneous tissue where nerves (and vessels) are located (Huet 2020, Silverberg 2020). Often the patient is generally affected with fatigue and malaise, especially during major and persistent outbreaks. Atopic dermatitis is often complicated by allergies, including hay fever and allergic asthma. Another common complication is skin infection with yellow staphylococci, and less frequently, with herpes virus or yeast. Asthma and hay fever are considered atopic comorbidities and are often associated with a high IgE level in addition to specific IgE mediated allergies (Chee 2020, Thyssen 2020, Thyssen 2020, Bakker 2021). Among the non-atopic comorbidities for AD are depression and ADHD (Hale 2019, Gilaberte 2020).

One can generally, and to some extent arbitrarily, divide the disease according to severity into mild, moderate, and severe. In this context, it is important to emphasize that in the vast majority of patients, the disease has a fluctuating course, while in some patients (10-15%) a difficult and chronic course is seen. AD is a disease that significantly affects the quality of life and ability to work in patients with moderate to severe AD, and the treatments are often time-consuming and thus further reduce the patients' capacity to work and also take time from their leisure activities (Chee 2020, Thyssen 2020, Thyssen 2020, Pescitelli 2021). Different scales have been developed for numerically scoring AD at a given time, i.e., to "measure" the severity of the disease. However, these are all to some extent “snapshots” that measure the degree of eczema now and then or the degree of symptoms and effects of quality of life through a week. There are scales of the doctor's assessment of the skin affections, such as EASI, and more complex scales that also involve the patient's indication of, for example, itching and sleep disturbance or quality of life in general. However, AD is a disease in which the true picture is more made of the span between minimum and maximum symptoms, frequency, and severity of outbreaks, frequency of complications, patient's impact on work function during flare-ups, etc. It is thus greatly simplified when severe AD is described as e.g., EASI> 21 (Leshem 2020).

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The standard treatment in Denmark, and in the rest of the world, consists of a treatment ladder, where the treatment for all patients starts at the first stage and further treatment is added in stages as needed (Wollenberg 2018, Thyssen 2020). The first step consists of moisture care and patient awareness about their own illness, including the importance of allergies and various triggering factors such as cold, hand washing, sweating, wool, and more. In the subsequent steps, topical steroids with increasing strengths, topical calcineurin inhibitors, and light therapy are added. Comorbidity and complications are treated in parallel. If topical treatments and light cannot satisfactorily reduce the symptoms, systemic treatments in the form of oral corticosteroids (usually only for a short time) or immunosuppressants in the form of methotrexate, azathioprine, mycophenolate mofetil or cyclosporine are used. Use of these drugs is primarily off label and borne by clinical experience. Cyclosporine in particular, despite having a market authorization for AD, is not routinely used in Denmark due to the risk of kidney side effects (Thyssen 2020). In addition, conventional systemic treatments have relatively poor drug survival and approximately 50% of patients discontinue treatment with methotrexate, azathioprine, mycophenolate, or cyclosporine during the first year of treatment either due to unsatisfactory treatment results or unacceptable side effects (Garritsen 2015, Politiek 2016, van der Schaft 2016).

Since 2017, patients with moderate to severe atopic dermatitis have been able to be treated with the dupilumab, which is a fully human antibody to IL-4 receptor alpha subunit, and which blocks both IL-4 and IL-13 signaling and thereby effectively the Th 2 pathway. The clinical experience with dupilumab is good and the effect of the treatment seems to be lasting. However, in some surveys, over 20% of patients develop a clinically significant conjunctivitis, the mechanism of which is still unknown (Bakker 2019, Waldman 2019). In addition, up to 10% of patients on dupilumab treatment develop a pronounced redness of the face (Waldman 2020).

Baricitinib for treating atopic dermatitis

Baricitinib is a new treatment offering a new mechanism of action, for patients with moderate to severe atopic dermatitis. The Danish patient group, which is expected to be candidates for treatment, consists of adult patients with moderate to severe atopic dermatitis who have had insufficient effect of optimized local treatment and at least one systemic treatment, or who are not candidates for other systemic treatments. It is difficult to estimate the size of this patient group with any certainty. It is estimated that there are approximately 5,000 – 10,000 patients in Denmark with moderate to severe atopic dermatitis. Of these, many will have sufficient effect from topical treatment, and of those that are eligible for systemic treatment, a significant proportion will have sufficient effect from conventional systemic treatment, e.g. cyclosporin or methotrexate. The Medicines Council have estimated that approximately 250 patients are currently treated with dupilumab in Denmark, and that there are an additional 225 patients that are candidates for baricitinib or dupilumab. This group is expected to grow by approximately 30 new patients per year (DMC 2020).

No head-to-head studies have been performed between dupilumab and baricitinib, but indirect comparative studies show that the effect is comparable (Eli Lilly 2020). Both drugs have favorable safety data, with very few side effects. The published clinical data for baricitinib have a follow-up to 16 weeks. The final effect or plateau effect is seen in all studies to have been reached before week 16, and a relevant timepoint for clinical follow-up after starting treatment with AD with baricitinib appears be at week 8-12. The published data show a rapid onset of treatment, which in indirect comparative studies is comparable to the rate of efficacy seen with dupilumab. For example, a significant effect on itching is seen after two weeks (Simpson 2020). Regarding the long-term treatment, the EMA has stated that the benefits in patients that respond well to baricitinib, appear to continue with sustained longer-term response (EMA 2020). Beyond 16 weeks, it can be emphasized that baricitinib is a sustained and safe treatment for rheumatoid arthritis, and that baricitinib is a non-biological "small molecule" and with all the experience available for such molecules, there is no risk of anti -drug antibody formation with baricitinib and thereby treatment failure or reduced effect at several consecutive starts of treatment or pause / discontinuation. Many patients will be more confident with a tablet treatment than an injection treatment as with biological treatment. Baricitinib treatment can be easily initiated in

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specialist practice, and blood test monitoring is recommended according to normal routine and can easily be adapted to practice for other systemic treatments.

4. Literature search

The clinical question posed by the Medicines Council is the following:

What is the value of baricitinib and optimized topical treatment compared to dupilumab and optimized topical treatment for patients with moderate to severe atopic eczema, who have had insufficient effect of optimized local treatment and at least one systemic treatment, or who are not candidates for the other systemic treatments.

The Medicines Council has not requested a literature search, and specified that the indirect comparison between baricitinib and dupilumab should be based on the following studies:

- BREEZE-AD 7, NCT03733301 (baricitinib + TCS vs placebo + TCS)
- LIBERTY AD CHRONOS, NCT02260986 (dupilumab + TCS vs placebo + TCS)
- LIBERTY AD CAFÉ, NCT02755649 (dupilumab + TCS vs placebo + TCS)

However, whereas these studies all measure the effect of baricitinib or dupilumab vs placebo with topical corticosteroids as background treatment, they have different, non-heterogeneous study populations which complicates comparison (Table 1).

Table 1: Study populations of BREEZE-AD 7, CHRONOS, and CAFÉ

Study name	Study population
BREEZE-AD 7	Adults with moderate-to-severe AD and inadequate response to topical corticosteroids
CHRONOS	Adults with moderate-to-severe AD and inadequate response to topical corticosteroids
CAFÉ	Adults with severe AD who are not adequately controlled with, or are intolerant to, oral cyclosporine, or when this treatment is currently not medically advisable

Abbreviation: AD, atopic dermatitis

BREEZE-AD 7 and CHRONOS both included patients with no prior exposure to systemic treatments and are therefore not aligned with the clinical question posed by the Medicines Council. Only CAFÉ consists exclusively of patients who have experienced failure to cyclosporine or are intolerant to, or have contraindication to, cyclosporine.

Comparing studies with heterogeneous populations in an indirect comparison is not advisable as it is likely to result in biased results.

In order to reduce the risk of bias in the comparison and provide results specific for the population of interest – patients with prior exposure to systemic treatments – Eli Lilly suggest including the BREEZE-AD 4 trial in an indirect comparison with the CAFÉ study. BREEZE-AD 4 evaluates baricitinib in combination with topical corticosteroids in adult patients with moderate to severe AD who have experienced failure to cyclosporine or are intolerant to, or have contraindication to, cyclosporine.

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4.1 Main characteristics of included studies

4.1.1 BREEZE-AD 4

For further insight into the BREEZE-AD 4 study (NCT03428100), please see Table A1b in the **Appendices** section.

Study objective and population

BREEZE-AD 4 is a multicenter, randomized, double-blind, placebo-controlled phase III study evaluating the efficacy and safety of three baricitinib dosing regimens (oral 4-mg QD, 2-mg QD and 1-mg QD) in combination with TCS as compared to oral placebo+TCS in adult patients with moderate to severe AD who have experienced failure to cyclosporine or are intolerant to, or have contraindication to, cyclosporine. Patients were randomized in a 1:1:2:1 ratio (placebo, baricitinib 1-mg; baricitinib 2-mg; baricitinib 4-mg) at Week 0. The BREEZE-AD4 trial was conducted at 105 sites across Austria, Belgium, Brazil, Finland, France, Germany, Italy, Japan, Netherlands, Poland, Russian Federation, Spain, Switzerland and UK (ClinicalTrials.gov 2018).

BREEZE-AD 4 trial evaluated the efficacy and safety of baricitinib (1-mg QD, 2-mg QD, and 4-mg QD) in combination with TCS compared to placebo+TCS in adult patients with moderate to severe AD who have experienced failure to cyclosporine or are intolerant to, or have contraindication to, cyclosporine.

Study design

The four study periods of BREEZE-AD 4 trial are (Figure 38) (ClinicalTrials.gov 2018):

- Period 1: Screening Period, between 8 and 35 days prior to Period 2 (Week 0), determined patient eligibility.
- Period 2: Double Blinded Treatment Dosing Period, from Week 0 (baseline) to Week 52, evaluated the efficacy and safety of two baricitinib dosing regimens (oral 4-mg QD and 2-mg QD) compared to placebo. Patients applied TCS therapy on active lesions and on areas where application of TCS was considered inappropriate, TCIs and/or crisaborole was used.
- Period 3: Double Blind, Long Term Extension Period, from Week 52 through Week 104.
- Period 4: Post Treatment Follow Up (PTFU) Period, only patients who completed the study through Week 104 were eligible for the PTFU approximately 28 days after the dose of investigational product.

During the screening period, a washout of systemic and topical treatments for AD was incorporated following which all the eligible patients in the baricitinib treatment group were randomized at a 1:1:2:1 ratio to 1 of 4 treatment groups (placebo QD, baricitinib 1-mg QD, baricitinib 2-mg QD, or baricitinib 4-mg QD). All the patients received 3 tablets per day (one investigational 1-mg or 2-mg or 4-mg baricitinib tablet and two placebos to match either 1-mg or 2-mg or 4-mg) during the double-blind treatment period. The last patient visit was at Week 52 and patients' completing the study through Week 52 progressed into the double-blind long-term extension phase through Week 104. Patients completing the study through Week 104 had a post-treatment follow-up visit approximately 28 days after the last dose of investigational product. In case of any patient withdrawing the consent, continued to the ETV. Patients returned for the post-treatment safety follow-up visit approximately 28 days after the last dose of baricitinib (ClinicalTrials.gov 2018, Eli Lilly 2018).

Endpoints

The primary objective of the BREEZE-AD 4 clinical trial was to test the hypothesis that baricitinib 4-mg + TCS or baricitinib 2-mg + TCS is superior to placebo + TCS in the treatment of moderate–to-severe AD (ClinicalTrials.gov 2018). The endpoints assessed in the BREEZE-AD 4 trial included:

Primary endpoint:

- Proportion of patients achieving EASI75 at Week 16 (for baricitinib 4-mg+TCS or baricitinib 2-mg+TCS)

Key secondary endpoints:

- Proportion of patients achieving IGA of 0 or 1 with a ≥2-point improvement at Week 16 (baricitinib 1-mg+TCS)
- Proportion of patients achieving EASI90 at 16 weeks
- Percent change from baseline in EASI score at 16 weeks
- Proportion of patients achieving SCORAD75 at 16 weeks
- Proportion of patients achieving a 4-point improvement in Itch NRS at 16, 4, 2, and 1 weeks
- Mean change from baseline in the score of Item 2 of the ADSS at 16 weeks and 1 week
- Mean change from baseline in Skin Pain NRS at 16 weeks
- Proportion of patients achieving IGA of 0 or 1 with a ≥2-point improvement from baseline at Week 52
- Proportion of patients achieving EASI75 at 52 weeks

Rescue medications:

In the BREEZE-AD 4 study, the symptoms of AD were controlled by avoiding exacerbating factors, intensifying emollient applications, and using only the permitted study treatments, including background TCS therapy (e.g., triamcinolone 0.1% cream and/or hydrocortisone 2.5% ointment).

In patients whose lesions persisted or worsened despite the use of emollients and background TCS therapy (e.g., triamcinolone 0.1% cream and/or hydrocortisone 2.5% ointment) and/or patients who required prolonged applications of triamcinolone 0.1% cream (moderate-potency TCS) on large surfaces were rescued using the high- or ultra-high-potency TCS for up to 14 consecutive days or less based on prescription. High- or ultra-high-potency TCS were stopped when patient reached “clear” to “almost clear” skin. Patients were also rescued by phototherapy (investigator’s decision). In patients failing on TCS and phototherapy, systemic therapies (conventional systemics or biologics) were used as the rescue medications (Eli Lilly 2018).

4.1.2 BREEZE-AD 7

For further insight into the BREEZE- AD 7 study (NCT03733301), please see Table A1a in the **Appendices** section.

Study objective and population

BREEZE AD-7 is a multicenter, randomized, double-blind, placebo-controlled phase III study evaluating the efficacy and safety of two baricitinib dosing regimens (oral 4-mg QD and 2-mg QD) in combination with TCS as compared to oral placebo+TCS in adult patients with moderate to severe AD. Patients were randomized in a 1:1:1 ratio (placebo, baricitinib 2-mg; baricitinib 4-mg) at Week 0. The BREEZE-AD 7 trial was conducted at 68 sites across Argentina, Australia, Austria, Germany, Italy, Japan, Republic of Korea, Poland, Spain and Taiwan (ClinicalTrials.gov 2018, Reich 2020).

Study design

The three study periods of BREEZE-AD7 trial are (ClinicalTrials.gov 2018, Reich 2020) :

- Period 1: Screening Period, between 8 and 35 days prior to Visit 2 (Week 0), determined patient eligibility and required washout of systemic and topical AD therapies.
- Period 2: Double-Blind Placebo-Controlled Treatment, 16 weeks: patients who met all eligibility criteria at Visit 2 (Week 0) were randomized at a 1:1:1 ratio into: placebo QD + TCS; baricitinib 2–mg QD + TCS, or baricitinib 4–mg QD + TCS.
- Period 3: Post Treatment Follow Up (PTFU) Period, only patients who completed the study through Week 16 were eligible for the PTFU approximately 28 days after the dose of investigational product.

During the screening period, a washout of systemic and topical treatments for AD was incorporated following which all the eligible patients in the baricitinib treatment group were randomized at a 1:1:1 ratio to 1 of 3 treatment groups (placebo QD, baricitinib 2-mg QD, or baricitinib 4-mg QD). All the patients received 2 tablets per day (one investigational 2-mg or 4-mg baricitinib tablet and two placebos to match either 2-mg or 4-mg) during the double-blind treatment period. The last patient visit was at Week 16 and patients' completing the study through Week 16 progressed into the double-blind long-term extension phase through Week 104. In case of any patient withdrawing the consent, continued to the ETV. Patients returned for the post-treatment safety follow-up visit approximately 28 days after the last dose of baricitinib (ClinicalTrials.gov 2018, Reich 2020).

Endpoints

The primary objective of the BREEZE-AD7 clinical trial was to test the hypothesis that baricitinib 4-mg QD + TCS or baricitinib 2-mg QD + TCS is superior to placebo + TCS in the treatment of patients with moderate to severe AD (ClinicalTrials.gov 2018, Reich 2020) .

The endpoints assessed in the BREEZE-AD7 trial included:

Primary endpoint:

- Proportion of patients achieving IGA of 0 or 1 with a ≥2-point improvement at Week 16 (for baricitinib 4-mg QD+TCS or baricitinib 2-mg QD+TCS)

Key secondary endpoints:

- Proportion of patients achieving EASI75 at 16 weeks
- Proportion of patients achieving EASI90 at 16 weeks
- Percent change from baseline in EASI score at 16 weeks
- Proportion of patients achieving SCORAD75 at 16 weeks
- Proportions of patients achieving a 4-point improvement in Itch NRS at 2 days, 1 week, 2 weeks, 4 weeks, and 16 weeks
- Mean change from baseline in the score of Item 2 of the ADSS at 1 week and 16 weeks
- Mean change from baseline in Skin Pain NRS at 16 weeks

Rescue medications:

Patients experiencing unacceptable or worsening symptoms of AD in the BREEZE-AD7 trial were eligible for rescue with topical and systemic therapies. The use of rescue medications was limited to patients where control of symptoms could not be achieved with increased emollient and background TCS use (low potency and moderate potency (e.g., triamcinolone 0.1% cream and/or hydrocortisone 2.5% ointment)). Patients whose lesions persisted or worsened despite the use of emollients and background TCS therapy and/or patients who required prolonged applications of triamcinolone 0.1% cream (moderate-potency TCS) on large surfaces were considered for rescue to high- or ultra-high-potency TCS for up to 14 consecutive days or less based on prescription. In case of patients failing on topical rescue therapy, systemic medications (e.g., corticosteroids, cyclosporine, methotrexate) was used while baricitinib was permanently discontinued for the remaining study duration (ClinicalTrials.gov 2018, Reich 2020).

4.1.3 CAFÉ

For further insight into the CAFÉ study (NCT02755649), please see Table A1d in the **Appendices** section.

Study objective and population

This was a randomized, placebo-controlled, double-blind, parallel-group phase 3 study. The study evaluated efficacy and safety of dupilumab with concomitant topical corticosteroids (TCS) in adults with atopic dermatitis with inadequate response to/intolerance of CsA, or for whom CsA treatment was medically inadvisable.

Study design

The screening period ran from day −28 to baseline, and included a TCS standardization period, which ran from day −14 to baseline. Enrolled patients were randomly assigned (3:1:3) to receive subcutaneous dupilumab 300 mg once weekly, 300 mg every 2 weeks, or placebo. Randomization was stratified by baseline disease severity (moderate [IGA=3] vs severe [IGA= 4]) and geographical region. During Weeks 17–28, patients were followed for safety or could enter an open-label extension study (R668-AD-1225; ClinicalTrials.gov: NCT01949311; EudraCT: 2013-001449-15)(DMC 2018, ClinicalTrials.gov 2020).

During the initial 2 weeks of the screening period, patients could use TCS at investigator discretion. Starting at day −14, and during the study treatment period, all eligible patients applied medium-potency TCS once daily to active lesion areas, or low-potency TCS on areas of thin skin (e.g. face, neck, intertriginous and genital areas) or where continued treatment with medium-potency TCS was considered unsafe. Patients could stop TCS upon adverse reaction to the TCS. Patients achieving an IGA of 0 by Weeks 4, 8 or 12 could taper TCS to every other day. After Week 4, patients who continued to have an IGA of 0 for 4 weeks could switch TCS to twice per week; if they did not continue to have an IGA of 0 they would revert to daily dosing. Patients with clear skin continued to apply TCS to lesion-prone areas at intervals of every other day (if prior to day 57) or twice weekly (after day 57), as described above. During the safety follow-up, patients could remain on TCS at investigator discretion. Patients recorded TCS use in a medication diary; tubes were weighed at each visit through Week 16. Patients were instructed to apply emollients twice daily for the 7 days prior to randomization and throughout the study; stable doses of prescription moisturizers or moisturizers containing additives were permitted if initiated before screening (DMC 2018, ClinicalTrials.gov 2020).

Endpoint

The primary end point was the proportion of patients with ≥ 75% improvement from baseline in EASI score (EASI-75) at Week 16. Secondary end points were the following (all at Week 16, unless otherwise indicated): per cent change from baseline in EASI, SCORAD, weekly average of peak daily pruritus NRS (Weeks 2 and 16) and Global Individual Sign Score (GISS); change from baseline in percent BSA affected by atopic dermatitis, DLQI, POEM, and Hospital Anxiety and Depression Scale (HADS); mean weekly dose of TCS during the treatment period; and proportions of patients with ≥ 50% or ≥ 90% improvement from baseline in EASI score (EASI-50 or EASI-90), EASI-75 (among patients with prior CsA exposure), ≥ 4-point reduction in weekly average of peak daily pruritus NRS score (among patients with baseline pruritus NRS score ≥ 4), ≥ 50% improvement from baseline in SCORAD (SCORAD-50) and both IGA 0 or 1 (clear or almost clear) and a 2-point reduction in IGA from baseline (DMC 2018, ClinicalTrials.gov 2020).

Rescue medication

Patients could receive rescue medication, including potent or very potent TCS, topical calcineurin inhibitors or systemic medication, if medically necessary (e.g. to control intractable atopic dermatitis symptoms), at investigator discretion. Patients who received rescue medication were considered treatment failures, but continued study visits and assessments; those on topical rescue medication could continue study treatment, whereas those on systemic rescue medication discontinued study treatment (DMC 2018, ClinicalTrials.gov 2020).

4.1.4 CHRONOS

For further insight into the CHRONOS study (NCT02260986), please see Table A1c in the **Appendices** section.

Study objective and population
CHRONOS was a randomized, placebo-controlled, double-blind, parallel-group phase 3 study. The primary objective of the study was to demonstrate the efficacy of Dupilumab administered concomitantly with topical corticosteroid (TCS) through Week 16 in adult participants with moderate-to-severe atopic dermatitis (AD) compared to placebo administered concomitantly with TCS (ClinicalTrials.gov 2017, DMC 2018).

Study design
Enrolled patients were randomly assigned (3:1:3) to receive subcutaneous dupilumab 300 mg once weekly, 300 mg every 2 weeks, or placebo. Randomization was stratified by baseline disease severity (moderate [IGA=3] vs severe [IGA= 4]) and geographical region. Randomization was performed centrally by use of an interactive voice/web response system. Drug kits were coded, and to ensure double blinding, patients who were assigned to dupilumab every 2 weeks were given matching placebo every week when dupilumab was not given. The patients underwent weekly clinical and safety assessments weekly from baseline to week 4 and every 4 weeks until week 64. The study was blinded to patients, investigators and study personnel until the time of prespecified unblinding (ClinicalTrials.gov 2017, DMC 2018).

Endpoints
The primary endpoint was proportion of patients with both an Investigator's Global Assessment (IGA) 0 to 1 (clear or almost clear) at week 16 and a reduction from baseline of ≥2 points at week 16. Proportion of patients with EASI-75 response (reduction of EASI score by ≥75% from baseline) at week 16 was a co-primary endpoint in the EU. Key secondary outcomes included proportion of patients with improvement (reduction) in weekly average of peak daily pruritus NRS ≥4 (baseline to week 16), improvement (reduction) in weekly average of peak daily pruritus NRS ≥3 (baseline to week 16), IGA 0 or 1 and a reduction from baseline of ≥2 points (week 52), EASI-75 response at week 52, improvement (reduction) in weekly average of peak daily pruritus numerical rating scale (NRS) ≥4 (baseline to week 52), improvement (reduction) in weekly average of peak daily pruritus NRS ≥3 (baseline to week 52), improvement (reduction) in weekly average of peak daily pruritus numerical rating scale (NRS) ≥4 (baseline to week 24), improvement (reduction) in weekly average of peak daily pruritus NRS ≥4 (baseline to week 4), improvement (reduction) in weekly average of peak daily pruritus NRS ≥4 (baseline to week 2), and percent change from baseline to week 16 in weekly average of peak daily pruritus NRS (ClinicalTrials.gov 2017, DMC 2018).

Rescue medication
Rescue treatment, consisting of any locally approved treatments for atopic dermatitis, including topical or systemic medications or phototherapy, could be used after week 2. If the rescue medication was topical, the patient could continue the assigned regimen; however, if the rescue medication was systemic medication or phototherapy, the study drug was temporarily discontinued but could be restarted after discontinuation (allowing for appropriate wash-out) of systemic treatment or phototherapy (ClinicalTrials.gov 2017, DMC 2018).

5. Clinical questions

5.1 Clinical question 1: What is the value of baricitinib and optimized topical treatment compared to dupilumab and optimized local treatment for patients with moderate to severe atopic eczema, which has had insufficient effect of optimized local treatment and at least one systemic treatment, or who are not candidates for the other systemic treatments?

5.1.1 Presentation of relevant studies

The following studies are used in the assessment of clinical question #1:
For baricitinib

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- BREEZE-AD 7
- BREEZE-AD 4

For dupilumab

- LIBERTY AD CHRONOS
- LIBERTY AD CAFÉ

5.1.2 Results per study

Results by study are presented in Tables A2a-d in the **Appendices** section.

5.1.3 Comparative analyses

As described in section 4, the trials that are most relevant for the clinical question are BREEZE-AD 4 and CAFÉ. They both evaluate the study drug (baricitinib or dupilumab) in combination with local treatment in the relevant population, i.e., patients that had insufficient effect of one systemic treatment (cyclosporine) or are ineligible for such treatment. BREEZE-AD 7 and CHRONOS do evaluate the study drug in combination with local treatment, but in mix of naïve to systemic and previous systemic users. As treatment response to baricitinib or dupilumab may differ between patients with prior exposure to cyclosporine or not, the following comparisons are made:

1. BREEZE-AD 4 & CAFÉ (prior exposure to cyclosporine)
2. BREEZE-AD 7 & CHRONOS (few patients had prior exposure to cyclosporine)
3. BREEZE-AD 7 & CHRONOS & CAFÉ (comparison requested by the Medicines council; mixed populations for dupilumab, only cyclosporine naïve patients for baricitinib)

Also note that the availability of data for the outcomes requested by the Medicines Council varied between trials (table 2).

Table 2 Availability of outcome data for the comparative analyses

Outcome	BREEZE-AD 4	CAFÉ	BREEZE-AD 7	CHRONOS
EASI75	Y	Y	Y	Y
SCORAD50	Y	Y	N	N
POEM	Y	Y	Y	Y
SAEs	Y	Y	Y	N
DLQI	Y	Y	Y	Y
Itch NRS	Y	Y[1]	Y	Y[1]
Flares	N	N	N	Y

Abbreviations: DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; NRS, Numeric Rating Scale; POEM, Patient Oriented Eczema Measures; SAE, serious adverse events; SCORAD, SCORing Atopic Dermatitis; SD, standard deviation.
Notes: [1]Different censoring rules were reported for the CAFÉ (secondary censoring rule) and CHRONOS (primary censoring rule) trials.

The Bucher method (Bucher 1997) was used for indirect treatment comparison between baricitinib 4 mg and dupilumab via a common comparator (placebo), for relative risk based on log scale, for continuous outcomes based on actual scale. For continuous outcomes (POEM, DLQI and Itch NRS), the results are presented as mean difference. For dichotomous outcomes, results are presented as relative risk, relative risk difference and absolute risk difference. The absolute risk difference was calculated using the formula (#4) presented in the Medicines Council guidelines v2.6 (DMC 2018), based on an assumed event rate (ACR) drawn from the observed event rate in the comparator arm of the

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CAFÈ and CHRONOS trials. In the case of two comparator trials (CHRONOS & CAFÉ), the data was meta-analyzed before applying Bucher, and the median rate was used for determining the ACR.

For the ITC, the analyses were conducted with two sets of results, the primary and secondary censoring rules. For primary censoring, data was included only up to the time of rescue therapy or study drug discontinuation. For secondary censoring all data up to permanent study drug discontinuation was used as recorded, even if the patient had received moderate potency TCS rescue. Non-responder imputation was applied for binary outcomes. Presented below are results with the primary censoring rule, with the exception of Itch NRS, where availability of data only allowed for the secondary censoring rule for the BREEZE-AD 4 – CAFÉ comparison.

5.1.3.1 Eczema distribution and severity

Proportion of patients who achieve a minimum of 75% reduction on the EASI scale (EASI75)

The Eczema Area and Severity Index (EASI; described in detail in appendix, section 7.5) is a validated scoring system that measures the severity of clinical signs in atopic dermatitis. The results over all indirect comparisons indicate a similar effect of baricitinib compared to dupilumab in the proportion of patients who achieved at least a 75% reduction in symptom cores on the EASI scale (EASI75). The absolute risk difference between the drugs was 8.1 percent in the main comparison (BREEZE-AD 4 vs CAFÉ) and this difference was not statistically significant. Numerically, this risk difference is lower than the difference stipulated by the Medicines Council as clinically relevant (10 percent). In the other comparisons (BREEZE-AD 7 vs CHRONOS and BREEZE-AD 7 vs CHRONOS & CAFÉ), the differences were numerically larger (-18.4 and -11.6 percent), but not statistically significant either. Evidence from the indirect comparisons does not support a clinically meaningful difference in the efficacy of baricitinib and dupilumab on response on the EASI scale in patients with moderate-to-severe atopic dermatitis experienced to systemic treatment and co-treated with optimized topical treatment.

Table 3 Proportion of patients who achieve a minimum of 75% reduction on the EASI scale

EASI75	Relative risk (95% CI)	Absolute risk difference (percent; 95% CI)
BREEZE-AD 4 vs CAFÉ	0.87 (0.46 – 1.63)	-8.1 (-33.8 – 39.5)
BREEZE-AD 7 vs CHRONOS	0.69 (0.43 – 1.11)	-18.4 (-33.9 – 6.5)
BREEZE-AD 7 vs CHRONOS & CAFÉ	0.81 (0.48 – 1.38)	-11.6 (-29.3 – 16.5)

Abbreviation: CI, confidence interval
Note: Primary censoring rule. Relative risk and relative risk difference derived from indirect comparison using the Bucher method using data from baricitinib 4 mg and dupilumab via placebo. The absolute risk differences were calculated using the formula (#4) provided in the Medicines Council guidelines v2.6 using an assumed control rate (ACR) based on the observed event rates in the comparator group of each respective study. In the comparison vs CHRONOS & CAFÉ, the median (=mean) was used for ACR. CHRONOS & CAFÉ were meta-analyzed before applying Bucher.

SCORAD50

Proportion of patients achieving 50% reduction of SCORAD scale (SCORAD50)

SCORing Atopic Dermatitis (SCORAD; described in detail in appendix, section 7.5) is another validated symptom scale for the measurement of atopic dermatitis severity and response to treatment. For the proportion of patients achieving a 50 percent reduction on the SCORAD scale, SCORAD50, the Medicines Council protocol states that a difference between the groups of 10% is to be considered of clinical relevance. Data for the comparator was only available from CAFÉ. For that reason, the only comparison possible to perform was BREEZE-AD4 vs CAFÉ. The indirect comparison

showed an absolute risk reduction of -19.2 percent in favor of dupilumab. However, this difference was not statistically significant, with a confidence interval spanning -40 to 18.6 percent. The clinical evidence thus does not support a clinically meaningful difference between baricitinib and dupilumab in the proportion of patients achieving a 50 percent reduction on the SCORAD scale.

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Table 4 Proportion of patients achieving 50% reduction of SCORAD scale

SCORAD50	Relative risk (95% CI)	Absolute risk difference (percent; 95% CI)
BREEZE-AD 4 vs CAFÉ	0.71 (0.39 – 1.28)	-19.2 (-40.5 – 18.6)

Abbreviation: CI, confidence interval
Note: Primary censoring rule. Relative risk and relative risk difference derived from indirect comparison using the Bucher method using data from baricitinib 4 mg and dupilumab via placebo. The absolute risk differences were calculated using the formula (#4) provided in the Medicines Council guidelines v2.6 using an assumed control rate (ACR) based on the observed event rates in the comparator group of each respective study.

5.1.3.2 Eczema distribution and severity, patient reported

POEM, change from baseline

Change from baseline data in Patient-Oriented Eczema Measure (POEM; described in detail in appendix, section 7.5) was available in all included trials. Outcomes of the indirect comparisons were consistent, with differences between the drugs between 2.43 (BREEZE-AD 7 vs CHRONOS & CAFÉ) and 2.51 (BREEZE-AD 4 vs CAFÉ) in favor of dupilumab. In the case of the BREEZE-AD 7 vs CHRONOS & CAFÉ comparison, the difference was statistically significant. However, in the Medicines Council protocol, an absolute difference of 3 points is to be considered of clinical relevance. The point estimates of all comparisons lie below the threshold of clinical relevance. The evidence available does not support a clinically meaningful difference between baricitinib and dupilumab on the POEM score in patients with atopic dermatitis.

Table 5 Change from baseline in Patient-Oriented Eczema Measure

POEM	Mean difference (95% CI)
BREEZE-AD 4 vs CAFÉ	2.51 (-0.46 – 5.48)
BREEZE-AD 7 vs CHRONOS	2.47 (-0.05 – 4.99)
BREEZE-AD 7 vs CHRONOS & CAFÉ	2.43 (0.08 – 4.77)

Abbreviation: CI, confidence interval; POEM patient-oriented eczema measure
Note: Primary censoring rule. Mean differences derived from indirect comparison using the Bucher method using data from baricitinib 4 mg and dupilumab via placebo. CHRONOS & CAFÉ were meta-analyzed before applying Bucher.

5.1.3.3 Side effects

Serious adverse events

Proportion of patients who experiences one or more serious adverse events

Treatment emergent serious adverse event (TESAE) data could be retrieved from CAFÉ, but not for CHRONOS. Thus, the only comparison included here is the BREEZE-AD 4 vs CAFÉ comparison. The threshold stated in the protocol for a minimal clinically relevant difference was 2 percent. The comparison indicates a non-statistically significant difference in the proportion of patients experiencing serious adverse events, with an absolute risk difference of 3.7 percent. There were very few serious adverse events in both trials, resulting in a wide confidence interval. The clinical evidence does not support there being a clinically meaningful difference between baricitinib and dupilumab on the proportion of patients who experiences one or more serious adverse events.

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Table 6 Proportion of patients who experiences one or more serious adverse event

TESAEs	Relative risk (95% CI)	Absolute risk difference (percent; 95% CI)
BREEZE-AD 4 vs CAFÉ	3 (0.25 – 36.6)	3.7 (-1.4 – 66.6)

Abbreviation: CI, confidence interval; TESAEs, Treatment emergent serious adverse events
Note: Primary censoring rule. Relative risk and relative risk difference derived from indirect comparison using the Bucher method using data from baricitinib 4 mg and dupilumab via placebo. The absolute risk differences were calculated using the formula (#4) provided in the Medicines Council guidelines v2.6 using an assumed control rate (ACR) based on the observed event rates in the comparator group of each respective study.

Summary of long-term side effects, all degrees

A total of 2,531 patients were treated with baricitinib in clinical studies in atopic dermatitis, representing 2,247 patient-years of exposure. Of these, 1,106 atopic dermatitis patients were exposed to baricitinib for at least one year. Five placebo-controlled studies were integrated (589 patients on 4 mg once daily and 743 patients on placebo) to evaluate the safety of baricitinib in comparison to placebo for up to 16 weeks after treatment initiation. Infections are the key identified risks for baricitinib, and for that reason the posology section of the SmPC indicates that a lower dose (2 mg) may be appropriate for patients with a history of chronic or recurrent infections. Blood lipids, including total cholesterol, LDL and HDL were elevated for baricitinib treated patients. It is included in the warnings in the SmPC that lipid parameters should be assessed approximately 12 weeks following initiation of baricitinib and then followed according to clinical guidelines for hyperlipidemia.

Listed in table 7 adverse reactions observed in atopic dermatitis clinical trials presented by system organ class and frequency. More information is available in the Olumiant SmPC (EMA 2020) and EPAR (EMA 2020).

Table 7 list of adverse reactions of baricitinib in atopic dermatitis

System organ class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)
Infections and infestations	Upper respiratory tract infections	Herpes simplex Gastroenteritis Urinary tract infections	Pneumonia
Blood and lymphatic system disorders			Thrombocytosis >600 x 10^9 cells/L Neutropenia <1 x 10^9 cells/L
Metabolism and nutrition disorders	Hypercholesterolemia		Hypertriglyceridemia
Nervous system disorders		Headache	
Gastrointestinal disorders		Nausea Abdominal pain	Diverticulitis
Hepatobiliary disorders			ALT increased ≥3 x ULN AST increased ≥3 x ULN
Skin and subcutaneous tissue disorders		Rash Acne	
Immune disorders			Swelling of the face Urticaria
Respiratory, thoracic, mediastinal disorders			Pulmonary embolism

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Vascular disorders			Deep vein thrombosis
Investigations		Creatine phosphokinase increased > 5 x ULN	

Abbreviations: ULN, upper limit of normal

The safety of dupilumab was evaluated in four placebo-controlled studies and one dose-ranging study in patients with moderate-to-severe atopic dermatitis. In these trials, 1,689 subjects were treated with subcutaneous injections of dupilumab, with or without concomitant topical corticosteroids. A total of 305 patients were treated with dupilumab for at least 1 year. The most common treatment-related adverse events that occurred with a higher frequency with dupilumab than placebo were injection site reaction (which accounted for the majority of all reported adverse events), headache, conjunctivitis, and eosinophilia. Some infections were more frequent in the dupilumab group compared to placebo, including conjunctivitis and oral herpes. Allergic conjunctivitis and other eye disorders were also more prevalent with dupilumab. The majority were mild to moderate in severity and resolved with treatment.

Listed in table 8 are adverse reactions observed for dupilumab in atopic dermatitis clinical trials by system organ class and frequency. More information can be found in the SmPC for Dupixent (EMA 2021) and EPAR (EMA 2020).

Table 8 list of adverse reactions of dupilumab in atopic dermatitis

System organ class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)
Infections and infestations		Conjunctivitis Oral herpes	
Blood and lymphatic system disorders		Eosinophilia	
Metabolism and nutrition disorders			
Nervous system disorders		Headache	
Eye disorders		Conjunctivitis allergic Eye pruritus Blepharitis	Keratitis Ulcerative keratitis
Hepatobiliary disorders			
General disorders and administration site conditions	Injection site reactions		
Immune disorders			
Respiratory, thoracic, mediastinal disorders			Pulmonary embolism
Vascular disorders			Deep vein thrombosis
Investigations		Creatine phosphokinase increased > 5 x ULN	

Abbreviations: ULN, upper limit of normal

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5.1.3.4 Quality of life

DLQI, change from baseline

Quality of life was measured with the Dermatology Life Quality Index (DLQI; described in detail in appendix, section 7.5), in all the included trials. The comparison indicates a non-statistically significant difference between the compared drugs, with point estimates between 1.09 (BREEZE-AD 7 vs CHRONOS) and 2 (BREEZE-AD 4 vs CAFÉ) points in favor of dupilumab. This is below the threshold for clinical relevance of 4 points as determined by the Medicines Council. The clinical evidence thus does not support a clinically meaningful difference between baricitinib and dupilumab on quality of life measured by DLQI.

Table 9 Change from baseline in DLQI

DLQI	Mean difference (95% CI)
BREEZE-AD 4 vs CAFÉ	2 (-0.41 – 4.41)
BREEZE-AD 7 vs CHRONOS	1.09 (-0.93 – 3.11)
BREEZE-AD 7 vs CHRONOS & CAFÉ	1.35 (-0.51 – 3.22)

Abbreviation: CI, confidence interval; DLQI, Dermatology life Quality Index
Note: Primary censoring rule. Mean differences derived from indirect comparison using the Bucher method using data from baricitinib 4 mg and dupilumab via placebo. CAFÈ & CHRONOS were meta-analyzed before applying Bucher.

5.1.3.5 Itch

Itch NRS, change from baseline

Itch was measured by Peak Pruritus Numeric Rating Scale (Itch NRS; described in detail in appendix, section 7.5). In CAFÉ and CHRONOS, different censoring rules were applied on itch NRS scores, thus making the combined comparison of BREEZE-AD7 vs CHRONOS & CAFÉ impossible to perform. For that reason, only the BREEZE-AD 7 vs CHRONOS and the BREEZE-AD 4 vs CAFÉ comparisons are presented here. In both indirect comparisons, the difference between the drugs was small and not statistically significant with point estimates well below the threshold of clinical relevance of 3 points suggested in the protocol. Thus, the evidence available does not suggest a clinically meaningful difference between baricitinib and dupilumab on itch measured with NRS in patients with atopic dermatitis.

Table 10 Change from baseline in Itch NRS

Itch NRS	Mean difference (95% CI)
BREEZE-AD 4 vs CAFÉ[1]	0.28 (-0.59 – 1.15)
BREEZE-AD 7 vs CHRONOS[2]	0.31 (-0.47 – 1.09)

Abbreviation: CI, confidence interval; NRS, numerical rating scale
Note: Mean differences derived from indirect comparison using the Bucher method using data from baricitinib 4 mg and dupilumab via placebo. As different censoring rules were applied in CAFÈ (secondary) and CHRONOS (primary), the BREEZE-AD 7 vs CHRONOS & CAFÉ comparison was not feasible.[1]Secondary censoring rule, [2]Primary censoring rule.

5.1.3.6 Episodes with flares

Number of flares, defined as worsening of the disease that required escalation/intensification of AD treatment, was measured in the CHRONOS trial. Episodes with flares were however not captured in the baricitinib trials, hence no indirect comparison could be made between the treatments.

5.1.3.7 Other considerations

Treatment with baricitinib is associated with a need for laboratory testing.

Patients should be screened for tuberculosis (TB) before starting baricitinib therapy. Baricitinib should not be given to patients with active TB. Anti-TB therapy should be considered prior to initiation of baricitinib in patients with previously untreated latent TB (EMA 2020).

Screening for viral hepatitis should be performed in accordance with clinical guidelines before starting therapy with baricitinib. Patients with evidence of active hepatitis B or C infection were excluded from clinical trials. Patients, who were positive for hepatitis C antibody but negative for hepatitis C virus RNA, were allowed to participate. Patients with hepatitis B surface antibody and hepatitis B core antibody, without hepatitis B surface antigen, were also allowed to participate; such patients should be monitored for expression of hepatitis B virus (HBV) DNA. If HBV DNA is detected, a liver specialist should be consulted to determine if treatment interruption is warranted (EMA 2020).

It was observed in the clinical trials of baricitinib in atopic dermatitis as well as in rheumatoid arthritis that some patients (less than 1 percent) develop hematological abnormalities. For that reason, treatment should not be initiated, or should be temporarily interrupted, in patients with an Absolute Neutrophil Count (ANC) < 1 x 10^9 cells/L, Absolute Lymphocyte Count (ALC) < 0.5 x 10^9 cells/L or hemoglobin < 8 g/dL observed during routine patient management (EMA 2020).

Dose dependent increases in blood lipid parameters were reported in patients treated with baricitinib compared to placebo. Lipid parameters should therefore be assessed approximately 12 weeks following initiation of baricitinib therapy and thereafter patients should be managed according to guidelines for hyperlipidemia (EMA 2020).

Dose dependent increases in blood alanine transaminase (ALT) and aspartate transaminase (AST) activity were reported in patients treated with baricitinib compared to placebo. Increases in ALT and AST to ≥5 and ≥10 x upper limit of normal (ULN) were reported in less than 1 percent of patients in clinical trials. If increases in ALT or AST are observed during routine patient management and drug-induced liver injury is suspected, baricitinib should be temporarily interrupted until this diagnosis is excluded (EMA 2020).

Recommended laboratory monitoring in the SmPC for patients treated with baricitinib, is described in table 11.

Table 11: Laboratory measures and monitoring guidance

Laboratory Measure	Action	Monitoring Guidance
Lipid parameters	Patients should be managed according to international clinical guidelines for hyperlipidemia	12 weeks after initiation of treatment and thereafter according to international clinical guidelines for hyperlipidemia
Absolute Neutrophil Count (ANC)	Treatment should be interrupted if ANC < 1 x 109 cells/L and may be restarted once ANC return above this value	Before treatment initiation and thereafter according to routine patient management
Absolute Lymphocyte Count (ALC)	Treatment should be interrupted if ALC < 0.5 x 109 cells/L and may be restarted once ALC return above this value	

Hemoglobin (Hb)	Treatment should be interrupted if Hb < 8 g/dL and may be restarted once Hb return above this value
Hepatic transaminases	Treatment should be temporarily interrupted if drug-induced liver injury is suspected

Abbreviations: ALC, Absolute Lymphocyte Count; ANC, Absolute Neutrophil Count; Hb, Hemoglobin
Source: (EMA 2020)

5.2 Overall conclusions

The efficacy of baricitinib for the treatment of moderate to severe atopic dermatitis in adult patients who are candidates for systemic therapy, when used as a monotherapy or in combination with TCS, has been confirmed in several randomized, double-blind, placebo-controlled 16 week trials. Of interest here is the combination with TCS in patients with moderate to severe AD which has had insufficient effect of optimized local treatment and at least one systemic treatment, or who are not candidates for the other systemic treatments. The effectiveness of baricitinib in this particular population has to date only been investigated in one clinical trial, the ongoing BREEZE-AD4 trial. Currently, 16-week data is available, but the study is planned to continue for 52 weeks. The BREEZE-AD4 trial was not requested by the Medicines Council for the comparative analyses but was added as it best reflects the intended population. As of January 2021, results at 16 weeks are available in ClinicalTrials.gov (ClinicalTrials.gov 2018).

Clinically meaningful efficacy

Baricitinib 4-mg, when used in combination with TCS, demonstrates rapid, consistent, sustained and clinically meaningful efficacy compared to placebo across multiple different signs and symptoms of AD. Importantly for patients, this included improvements in the key debilitating signs and symptoms of AD:

- skin inflammation (EASI75 and SCORAD50)
- Patient-Oriented Eczema Measure (POEM)
- Itch (Itch NRS)
- Quality of life (DLQI)

These data emphasize that patients treated with baricitinib 4-mg benefit from this therapy beyond skin clearance. This was confirmed by the results of the patient benefit index in Study BREEZE-AD7, with a majority of patients in the baricitinib 4-mg group achieving clinically relevant patient-defined treatment goals.

Subgroup analyses did not identify any demographic or baseline variables with important effects on the efficacy of baricitinib. The treatment effect across patient subgroups by gender, age, weight, renal function, region, and prior use of AD therapy was consistent with the results in the overall study population.

Speed of onset is important to AD patients, and baricitinib 4-mg demonstrated a rapid onset of action in all Phase 3 studies, reaching maximal or near-maximal response by Week 4 for most endpoints including EASI75 and Itch NRS (Reich 2020).

The current comparison is made on 16-week data. Continued response was followed in the long-term extension study BREEZE-AD3. Data is available up to 32 weeks of cumulative treatment for patients from BREEZE-AD7. Continued response was observed in patients with at least some response (IGA 0, 1 or 2) after initiating baricitinib (EMA 2020).

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Indirect comparison with dupilumab

It is the view of Eli Lilly that the most relevant comparison for the clinical question stated by the Medicines Council is the BREEZE-AD 4 vs CAFÉ comparison, as the included patient populations best corresponded to the target population; patients with moderate to severe atopic dermatitis with insufficient response to prior systemic treatment or not eligible for conventional systemic treatment. The outcomes of the indirect comparisons performed suggest a numerically similar effect of baricitinib compared to dupilumab for most outcomes stated by the Medicines Council. For EASI75, POEM, serious adverse events, DLQI and Itch NRS, the absolute risk differences point estimates were below the threshold for clinically meaningful differences. For SCORAD50, the point estimate of the risk difference exceeded the threshold, but the CI was wide and the difference was not statistically significant.

In summary, the results from the indirect comparisons does not support there being a meaningful clinically relevant difference in efficacy between baricitinib and dupilumab combined with optimized topical treatment in patients with moderate to severe AD who have failed on or are not eligible for treatment with other systemic treatments.

Conclusion

In the Phase 3 clinical program, baricitinib demonstrated therapeutic efficacy in moderate to severe AD as assessed by improvements in skin inflammation, itch, sleep disturbances due to itch, and skin pain. Moreover, as demonstrated by indirect comparisons, the clinical efficacy and safety of baricitinib is similar to that of dupilumab. Taken together, these results support the therapeutic and clinical benefit of baricitinib for the treatment of moderate to severe AD.

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7. Appendices

7.1 Main characteristics of included studies

Table A1a Main study characteristics: BREEZE-AD 7	
Trial name	BREEZE-AD 7
NCT number	NCT03733301
Objective	To investigate the efficacy and safety / safety of baricitinib in combination with topical corticosteroid in the treatment of adult patients with moderate-to-severe atopic dermatitis, over a 16-week course of treatment
Publications – title, author, journal, year	Efficacy and Safety of Baricitinib in Combination with Topical Corticosteroids in Moderate to Severe Atopic Dermatitis (BREEZE-AD7): A Phase 3 Randomized Clinical Trial Kristian Reich, Kenji Kabashima, Ketty Peris, Jonathan I. Silverberg, Lawrence F. Eichenfield, Thomas Bieber, Aleksandra Kaszuba, Jill Kolodsick, Fan E. Yang, Margaret Gamalo, Dennis R. Brinker, Amy M. DeLozier, Jonathan M. Janes, Fabio P. Nunes, Jacob P. Thyssen, Eric L. Simpson JAMA Dermatology, 2020
Study type and design	BREEZE-AD 7 is a randomized, controlled, parallel-group, double-blind phase 3 study. Baricitinib was administered in doses of 2 mg and 4 mg, once daily, in combination with topical corticosteroid. Comparator was placebo in combination with topical corticosteroid. The study has been completed and some of the patients will continue with patients from BREEZE-AD 1 and 2 in the long-term study BREEZE-AD 3.
Follow-up time	16 weeks
Population (inclusion and exclusion criteria)	Ages Eligible for Study: 18 Years and older Sexes Eligible for Study: All **Inclusion Criteria:** • Have been diagnosed with moderate to severe atopic dermatitis for at least 12 months. • Have had inadequate response to existing topical (applied to the skin) medications within 6 months preceding screening. • Are willing to discontinue certain treatments for eczema (such as systemic and topical treatments during a washout period). • Agree to use emollients daily. **Exclusion Criteria:** • Are currently experiencing or have a history of other concomitant skin conditions (e.g., psoriasis or lupus erythematosus), or a history of erythrodermic, refractory, or unstable skin disease that requires frequent hospitalizations and/or intravenous treatment for skin infections. • A history of eczema herpeticum within 12 months, and/or a history of 2 or more episodes of eczema herpeticum in the past.

Table A1a Main study characteristics: BREEZE-AD 7

	• Participants who are currently experiencing a skin infection that requires treatment, or is currently being treated, with topical or systemic antibiotics. • Have any serious illness that is anticipated to require the use of systemic corticosteroids or otherwise interfere with study participation or require active frequent monitoring (e.g., unstable chronic asthma). • Have been treated with the following therapies: • Monoclonal antibody for less than 5 half-lives prior to randomization. • Received prior treatment with any oral Janus kinase (JAK) inhibitor less than 4 weeks prior to randomization. • Received any parenteral corticosteroids administered by intramuscular or intravenous (IV) injection within 6 weeks prior to planned randomization or are anticipated to require parenteral injection of corticosteroids during the study. • Have had an intra-articular corticosteroid injection within 6 weeks prior to planned randomization. • Have high blood pressure characterized by a repeated systolic blood pressure >160 mm Hg or diastolic blood pressure >100 mm Hg. • Have had major surgery within the past eight weeks or are planning major surgery during the study. • Have experienced any of the following within 12 weeks of screening: venous thromboembolic event (VTE), myocardial infarction, unstable ischemic heart disease, stroke, or New York Heart Association Stage III/IV heart failure. • Have a history of recurrent (≥2) VTE or are considered at high risk of VTE as deemed by the investigator. • Have a history or presence of cardiovascular, respiratory, hepatic, chronic liver disease gastrointestinal, endocrine, hematological, neurological, lymphoproliferative disease, or neuropsychiatric disorders or any other serious and/or unstable illness. • Have a current or recent clinically serious viral, bacterial, fungal, or parasitic infection including herpes zoster, tuberculosis. • Have specific laboratory abnormalities. • Have received certain treatments that are contraindicated. • Pregnant or breastfeeding.
Intervention	Patients were randomized 1: 1: 1 to placebo, baricitinib 2 mg or 4 mg, once daily, in combination with topical corticosteroid. Intervention: baricinib 2 mg: 109 patients; baricitinib 4 mg: 111 patients. Comparator: placebo: 109 patients.
Baseline characteristics	**Summary of Selected Baseline Characteristics**

Attribute	**Placebo +TCS** N=109	**BARI 2-mg +TCS** N=109	**BARI 4-mg +TCS** N=111
Age (years), mean (SD)	33.7 (13.2)	33.8 (12.8)	33.9 (11.4)
Female, %	35%	36%	32%
Race			
Caucasian, %	42%	46%	49%
Asian, %	52%	52%	49%
Other, %	6%	2%	3%
Duration since AD diagnosis (years), mean (SD)	22 (12.2)	25 (14.8)	26 (13.2)
Weight (kg), mean (SD)	73.0 (15.8)	72.4(15.5)	73.3 (17.8)

Table A1a Main study characteristics: BREEZE-AD 7

Body mass index, mean (SD)	25.5 (4.62)	25.2 (4.7)	25.1 (5.1)
Geographic region			
Europe, %	35%	35%	35%
Japan, %	19%	18%	20%
Rest of world, %	46%	47%	45%
EASI score, mean (SD)	28.5 (12.3)	29.3 (11.9)	30.9 (12.6)
SCORAD score, mean (SD)	66.6 (13.8)	66.8 (14.0)	68.3 (13.2)
Body surface area affected, mean (SD)	48.1 (24.4)	50.6 (21.6)	52.1 (23.3)
Itch NRS score, mean (SD)	7.4 (1.7)	7.0 (2.1)	7.0 (2.0)
Skin Pain NRS score, mean (SD)	6.8 (2.3)	6.3 (2.5)	6.0 (2.5)
ADSS Item 2 score, mean (SD)	1.8 (2.0)	1.9 (2.3)	1.8 (2.3)
POEM score, mean (SD)	20.9 (6.7)	21.0 (6.3)	21.4 (6.0)
DLQI score, mean (SD)	15.0 (7.9)	15.0 (7.7)	14.7 (7.9)
PGI-S-AD score, mean (SD)	4.2 (0.8)	3.9 (0.8)	4.0 (0.8)
HADS score, mean (SD)			
Anxiety	6.8 (4.3)	6.4 (4.0)	6.7 (4.4)
Depression	5.8 (4.3)	5.3 (3.7)	5.5 (4.1)
WPAI-AD score, mean (SD			
Absenteeism	10.9 (25.5)	9.1 (20.3)	8.8 (21.6)
Presenteeism	43.0 (26.5)	49.4 (24.6)	45.1 (26.7)
Overall impairment (work productivity loss)	45.8 (28.5)	51.7 (25.5)	47.0 (27.6)
Activity impairment	52.9 (28.0)	57.1 (25.3)	52.2 (26.0)
EQ-5D-5L score, mean (SD)			
VAS	57.2 (23.1)	58.0 (22.3)	57.4 (22.6)
Health State Index			
UK	0.7 (0.2)	0.7 (0.2)	0.7 (0.2)
US	0.6 (0.2)	0.6 (0.3)	0.6 (0.3)

Abbreviations: AD, atopic dermatitis; ADSS, Atopic Dermatitis Sleep Scale; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EQ-5D-5L, European Quality of Life-5 Dimensions–5 Levels; HADS, Hospital Anxiety Depression Scale; NRS, Numeric Rating Scale; PGI-S-AD, Patient Global Impression of Severity for Atopic Dermatitis; POEM, Patient Oriented Eczema Measures; SCORAD, SCORing Atopic Dermatitis; TCS, topical corticosteroid; VAS, visual analogue scale; vIGA-AD, validated Investigator Global Assessment for Atopic Dermatitis; WPAI-AD, Work Productivity and Activity Impairment for Atopic Dermatitis.

Note: for full list of baseline characteristics, please see Reich et al. (2020)

Primary and secondary endpoints

Primary endpoint:

The proportion of patients who achieve a vIGA-AD score of 0 or 1 at week 16 with a baseline improvement of at least 2 points is compared.

Significant secondary endpoints:

- Proportion of patients treated with baricitinib who achieved 50%, 75% or 90% improvement in EASI score at week 1, 2, 4, 8, 12, 16
- % improvement from baseline of total EASI score at week 16
- 75% and 90% improvement of the SCORing Atopic Dermatitis Index at week 16

Table A1a Main study characteristics: **BREEZE-AD 7**	
	• Proportion of patients who achieved ≥ 4-point improvement measured with Itch NRS (11-point scale 0-10, worst itching within the last 24 hours indicated) as well as% improvement of Itch NRS. Weekly until week 16. • Mean change from baseline on item-2 in the Atopic Dermatitis Sleep Scale (ADSS). Weekly until week 16. • Mean change in Skin Pain Numeric Rating Scale from baseline to week 16 (11-point scale 0-10, worst pain within the last 24 hours indicated). Weekly until week 16. • Proportion of patients who achieved vIGA-AD 0 at week 16 • Change from baseline in SCORAD to week 16 • Change from baseline of Patient-Oriented Eczema Measure (POEM) at weeks 1, 2, 4, 8, 12, and 16 • Change from baseline of Dermatology Life Quality Index (DLQI) at weeks 1, 2, 4, 8 and 16 • Change from baseline of body surface area (BSA) affected by AD • Change from baseline of Patient Global Impression of Severity — Atopic Dermatitis (PGI-S-AD) Score to week 16 • Change from baseline of Hospital Anxiety Depression Scale (HADS) to week 16 • Change from baseline of Work Productivity and Activity Impairment - Atopic Dermatitis (WPAI-AD) Questionnaire for week 16 • Change from baseline of European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L) to week 16 • Proportion of patients who developed antibiotic-requiring skin infection • Average consumption of TCS (weight of tube) • Number of days without using TCS • Adverse events
Method of analysis	Efficacy and health outcomes data were analyzed with the intention-to-treat population, defined as all randomized patients. For categorical end points, a logistic regression model was used for comparisons with region, baseline disease severity (vIGA-AD), baseline value, and treatment group in the model except for the analysis on vIGA-AD, which included region, baseline severity (vIGA-AD), and treatment group in the model. For continuous end points, a restricted maximum likelihood–based mixed-effects model of repeated measures was used for comparisons with treatment, region, baseline disease severity (vIGA-AD), visit, and treatment × visit interaction as fixed categorical effects and baseline and baseline × visit interaction as fixed continuous effects. For daily diary assessments, the model for analyses up to week 16 included all weekly assessments. Safety analyses included all randomized patients who received 1 dose or more of study drug and who did not discontinue participation in the study for the reason of lost to follow-up at the first postbaseline visit. Adverse events were inclusive of the treatment period. Comparisons for AEs, discontinuation, and other categorical safety data were assessed with the Fisher exact test. Continuous safety variables were analyzed using analysis of covariance with baseline value and treatment group in the model.
Subgroup analyses	Not at this time

Table A1b Main study characteristics: BREEZE-AD 4	
Trial name	BREEZE-AD 4
NCT number	NCT03428100
Objective	The aim is to investigate the efficacy and side effects / safety of baricitinib in combination with topical corticosteroid in the treatment of moderate-to-severe atopic dermatitis in adult patients who have had insufficient effect of cyclosporine, do not tolerate or have contraindications to cyclosporine
Publications – title, author, journal, year	The study is underway. Partial week 16 results are now available on clinicaltrials.gov Publication of data up to week 52 (primary endpoint) is expected in Q3 of 2021.
Study type and design	BREEZE-AD 4 is a randomized, controlled, parallel-group, double-blind phase 3 study. Baricitinib is included in doses of 4 mg, 2 mg, and 1 mg, once daily, in combination with topical corticosteroid. Comparator is placebo in combination with topical corticosteroid. The study is ongoing.
Follow-up time	The primary endpoint is at week 16. The study has a 52-week follow-up period for the individual patient. In the SPC for Olumiant (baricitinib), information on EASI-75 response rate and IGA 0 or 1 response rate is expected at week 16 as well as mean change in EASI score, mean change in Itch NRS and mean change in DLQI from baseline to week 16.
Population (inclusion and exclusion criteria)	Ages Eligible for Study: 18 Years and older Sexes Eligible for Study: All **Inclusion criteria:** • Have been diagnosed with moderate to severe Atopic Eczema (Atopic Dermatitis) for at least 12 months. • Have had inadequate response to existing topical (applied to the skin) medications within 6 months preceding screening. • Are willing to discontinue certain treatments for eczema (such as systemic and topical treatments during a washout period). • Agree to use emollients daily. • Have a medical contraindication to cyclosporine or had intolerance and/or unacceptable toxicity or inadequate response to cyclosporine in the past. **Exclusion Criteria:** • Are currently experiencing or have a history of other concomitant skin conditions (e.g., psoriasis or lupus erythematosus), or a history of erythrodermic, refractory, or unstable skin disease that requires frequent hospitalizations and/or intravenous treatment for skin infections. • A history of eczema herpeticum within 12 months, and/or a history of 2 or more episodes of eczema herpeticum in the past. • Participants who are currently experiencing a skin infection that requires treatment, or are currently being treated, with topical or systemic antibiotics. • Have any serious illness that is anticipated to require the use of systemic corticosteroids or otherwise interfere with study participation or require active frequent monitoring (e.g., unstable chronic asthma). • Have been treated with the following therapies: Monoclonal antibody for less than 5 half-lives prior to randomization.

Table A1b Main study characteristics: BREEZE-AD 4

- Received prior treatment with any oral Janus kinase (JAK) inhibitor less than 4 weeks prior to randomization.
- Received oral corticosteroids within 4 weeks prior to randomization or parenteral corticosteroids administered by intramuscular or intravenous (IV) injection within 2 weeks prior to study entry or within 6 weeks prior to planned randomization or are anticipated to require parenteral injection of corticosteroids during the study.
- Have had an intra-articular corticosteroid injection within 2 weeks prior to study entry or within 6 weeks prior to planned randomization.
- Have high blood pressure characterized by a repeated systolic blood pressure >160 mm Hg or diastolic blood pressure >100 mm Hg.
- Have had major surgery within the past eight weeks or are planning major surgery during the study.
- Have experienced any of the following within 12 weeks of screening: venous thromboembolic event (VTE), myocardial infarction (MI), unstable ischemic heart disease, stroke, or New York Heart Association Stage III/IV heart failure.
- Have a history of recurrent (≥ 2) VTE or are considered at high risk of VTE as deemed by the investigator.
- Have a history or presence of cardiovascular, respiratory, hepatic, chronic liver disease gastrointestinal, endocrine, hematological, neurological, lymphoproliferative disease, or neuropsychiatric disorders or any other serious and/or unstable illness.
- Have a current or recent and/or clinically serious viral, bacterial, fungal, or parasitic infection including herpes zoster, tuberculosis.
- Have specific laboratory abnormalities.
- Have received certain treatments that are contraindicated.
- Pregnant or breastfeeding

Intervention

Baricitinib 4 mg, 2 mg, or 1 mg once daily in combination with TCS as needed. The total number of patients in BREEZE-AD 4 is 462

Comparator: Placebo once daily in combination with TCS as needed.

Baseline characteristics

Summary of Selected Baseline Characteristics

BREEZE-AD4	PBO+TCS (N=93)	BARI 1 MG+TCS (N=93)	BARI 2 MG+TCS (N=185)	BARI 4 MG+TCS (N=92)
Age (years), mean (SD)	38.7 (13.6)	38.9 (14.0)	37.3 (13.6)	38.7 (13.3)
Female, %	47.3	37.6	28.1	38
Race				
Caucasian, %	79.6	75.5	78.4	77.2
Asian, %	17.2	20.4	19.5	19.6
Black, %	3.2	3.2	1.1	3.3
Duration since AD diagnosis (years), mean (SD)	27.2 (15.6)	25.1 (15.9)	25.3 (13.7)	27.5 (16.2)
Weight (kg), mean (SD)	74.8 (17.3)	72.2 (15.7)	76.6 (17.4)	77.3 (20.4)
Body Mass Index, mean (SD)	25.9 (5.4)	25.0 (4.7)	26.0 (5.5)	26.3 (5.7)
Geographic Region				
Europe, %	69.9	69.9	69.2	69.6
Japan, %	16.1	17.2	17.3	17.4
Rest of World*, %	14	12.9	13.5	13
IGA of 3, %	46.2	49.5	49.5	48.9
IGA of 4, %	53.8	50.5	50.5	51.1
EASI, mean (SD)	30.9 (11.6)	34.3 (13.5)	30.6 (12.4)	32.7 (13.7)
SCORAD, mean (SD)	69.1 (13.0)	70.9 (14.1)	67.8 (13.4)	69 (13.0)
BSA affected, mean (SD)	48.4 (21.3)	56.6 (23.8)	50.1 (22.2)	53.9 (23.8)

Table A1b Main study characteristics: BREEZE-AD 4

POEM, mean (SD)	21.3 (5.7)	21.4 (6.0)	21.3 (5.9)	20.8 (6.0)
Itch NRS, mean (SD)	7.1 (1.9)	6.7 (2.3)	6.7 (1.9)	6.7 (2.3)
Skin Pain, mean (SD)	6.5 (2.3)	6.3 (2.7)	6.1 (2.4)	6.1 (2.6)
ADSS item 2, mean (SD)	1.6 (1.6)	2.2 (2.7)	1.9 (3.1)	2.1 (1.8)
DLQI, mean (SD)	14.5 (6.9)	14.3 (8.3)	13.6 (7.4)	14.0 (8.1)
PGI-AD, mean (SD)	4,1 (0,7)	4,0 (0,8)	3,9 (0,7)	4,0 (0,9)

Abbreviations: SD, standard deviation

Primary and secondary endpoints	**Primary endpoint:** Proportion of patients achieving Eczema Area and Severity Index 75 (EASI75) at week 16 (baricitinib 4 mg and 2 mg daily). **Secondary endpoints:** • Proportion of patients achieving Eczema Area and Severity Index 75 (EASI75) at week 16 (baricitinib 1 mg daily). • The proportion of patients who achieve a vIGA-AD score of 0 or 1 at week 16 with a baseline improvement of at least 2 points. • Proportion of patients achieving Eczema Area and Severity Index 90 (EASI90) at week 16 • % improvement from baseline of total EASI score at week 16 • 75% improvement of SCORing Atopic Dermatitis Index at week 16 • The proportion of patients who achieved ≥ 4-point improvement measured with Itch NRS (11-point scale 0-10, worst itching within the last 24 hours indicated) to week 16. • Mean change from baseline at item-2 in the Atopic Dermatitis Sleep Scale (ADSS) to week 16. • Average change in the Skin Pain Numeric Rating Scale from baseline to week 16. • Proportion of patients achieving Eczema Area and Severity Index 50 (EASI50) at week 16 • The proportion of patients who achieve a vIGA-AD score of 0 at week 16 with a baseline improvement of at least 2 points. • Change from baseline in SCORAD to week 16 • 90% improvement in SCORing Atopic Dermatitis Index at week 16 • Change from baseline of body surface area (BSA) affected by AD • Proportion of patients who developed antibiotic-requiring skin infection • Average consumption of TCS (weight of tube) • Number of days without using TCS • % improvement of Itch NRS from baseline to week 16. • Change from baseline to week 16 in Patient-Oriented Eczema Measure (POEM) score. • Change from baseline of Patient Global Impression of Severity — Atopic Dermatitis (PGI-S-AD) Score to week 16 • Change from baseline of Hospital Anxiety Depression Scale (HADS) to week 16 • Change from baseline of Dermatology Life Quality Index (DLQI) to week 16 • Change from baseline of Work Productivity and Activity Impairment - Atopic Dermatitis (WPAI-AD) Questionnaire for week 16 • Change from baseline of European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L) to week 16
Method of analysis	The analyses for efficacy were based on the ITT population. Non-responder imputation was applied to missing values of the primary outcome and other categorical outcomes. A graphical multiple testing approach was employed for testing the primary outcome (EASI75) of the three dose groups against placebo at an α of 5%.
Subgroup analyses	Not at this time

Abbreviations: AD, atopic dermatitis; ADSS, Atopic Dermatitis Sleep Scale; BSA, body surface area; Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EQ-5D-5L, European Quality of Life-5 Dimensions–5 Levels; HADS, Hospital Anxiety Depression Scale; IV, intervenes; JAK, Janus kinase; NRS, Numeric Rating Scale; PGI-S-

AD, Patient Global Impression of Severity for Atopic Dermatitis; POEM, Patient Oriented Eczema Measures; SCORAD, SCORing Atopic Dermatitis; TCS, topical corticosteroid; VAS, visual analogue scale; vIGA-AD, validated Investigator Global Assessment for Atopic Dermatitis; VTE, venous thromboembolic event; WPAI-AD, Work Productivity and Activity Impairment for Atopic Dermatitis.
Source: (ClinicalTrials.gov 2018, Eli Lilly 2018)

Table A1c Main study characteristics: CHRONOS	
Trial name	CHRONOS
NCT number	NCT02260986
Objective	The primary objective of the study was to demonstrate the efficacy of Dupilumab administered concomitantly with topical corticosteroid (TCS) through Week 16 in adult participants with moderate-to-severe atopic dermatitis (AD) compared to placebo administered concomitantly with TCS.
Publications – title, author, journal, year	Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (CHRONOS): a 1-year, randomized, double blinded, placebo-controlled, phase 3 trial. Blauvelt A et al. Lancet. 2017; 389: 2287-2303.
Study type and design	This was a randomized, placebo-controlled, double-blind, parallel-group phase 3 study. Enrolled patients were randomly assigned (3:1:3) to receive subcutaneous dupilumab 300 mg once weekly, 300 mg every 2 weeks, or placebo. Randomization was stratified by baseline disease severity (moderate [IGA=3] vs severe [IGA= 4]) and geographical region. Randomization was performed centrally by use of an interactive voice/web response system. Drug kits were coded, and to ensure double blinding, patients who were assigned to dupilumab every 2 weeks were given matching placebo every week when dupilumab was not given. Rescue treatment, consisting of any locally approved treatments for atopic dermatitis, including topical or systemic medications or phytotherapy, could be used after week 2. If the rescue medication was topical, the patient could continue the assigned regimen; however, if the rescue medication was systemic medication or phototherapy, the study drug was temporarily discontinued but could be restarted after discontinuation (allowing for appropriate wash-out) of systemic treatment or phototherapy. The patients underwent weekly clinical and safety assessments weekly from baseline to week 4 and every 4 weeks until week 64. The study was blinded to patients, investigators, and study personnel until the time of prespecified unblinding. The study is completed.
Follow-up time	After the 52-week treatment period, patients entered a follow-up period of 12 weeks.
Population (inclusion and exclusion criteria)	**Key inclusion criteria:** • Chronic atopic dermatitis for at least 3 years before the screening visit • Documented recent history (within 6 months before the screening visit) of inadequate response to a sufficient course of outpatient treatment with topical AD medication(s).

Table A1c Main study characteristics: CHRONOS

Key exclusion criteria:

- Participation in a prior dupilumab clinical trial
- Important side effects of topical medication (e.g., intolerance to treatment, hypersensitivity reactions, significant skin atrophy, systemic effects), as assessed by the investigator or treating physician
- Having used immunosuppressive/immunomodulating drugs or phototherapy for AD within 4 weeks before the baseline visit, or any condition that, in the opinion of the investigator, is likely to require such treatment(s) during the first 2 weeks of study treatment
- Treatment with a live (attenuated) vaccine within 12 weeks before the baseline visit
- History of human immunodeficiency virus (HIV) infection or positive HIV serology at screening
- Positive hepatitis B surface antigen, hepatitis B core antibody or hepatitis C antibody at the screening visit
- Active or acute infection requiring systemic treatment within 2 weeks before baseline visit
- Known or suspected history of immunosuppression
- Pregnant or breastfeeding women, or planning to become pregnant or breastfeed during participation in this study

Intervention

Subcutaneous injections of dupilumab once weekly plus topical corticosteroids (n=319) or every 2 weeks plus topical corticosteroids (n=106).

Patients receiving dupilumab every other week received matched placebo every week when dupilumab was not given to maintain blinding.

Comparator: Subcutaneous injections of placebo plus topical corticosteroids (n=315).

Baseline characteristics

Selected baseline characteristics CHRONOS

	Placebo + TCS (n=315)	Dupilumab 300 m every 2 weeks + T (n=106)
Age, median years (IQR)	34.0 (25.0–45.0)	40.5 (28.0–49.0
Sex, n (%) male	193 (61%)	62 (58%)
Race, n (%)		
White	208 (66%)	74 (70%)
Black or African American	19 (6%)	2 (2%)
Asian	83 (26%)	29 (27%)
other	5 (2%)	1 (1%)
Disease duration, median years (IQR)	26.0 (17.0–38.0)	28.0 (20.0–44.0
Affected BSA, median % (IQR)	55.0 (40.0–75.0)	58.8 (43.5–78.5
EASI score, median (IQR)	29.6 (22.2–40.8)	30.9 (22.3–41.6
Patients with IGA score 4, n (%)	147 (47%)	53 (50%)
Patients with IGA score 3, n (%)	168 (53%)	53 (50%)
Peak score on pruritus NRS, median (IQR)	7.6 (6.3–8.6)	7.7 (6.6–8.5)
Total SCORAD score, median (IQR)	64.1 (55.9–76.1)	69.7 (60.4–79.8
DLQI score, median (IQR)	14.0 (9.0–20.0)	13.5 (8.0–20.0)
Comorbid type 2 immune diseases, %		
Allergies (other than food allergy)	63	62
Allergic rhinitis	43	48
Asthma	41	41
Food allergy	30	35
Allergic conjunctivitis (keratoconjunctivitis)	22	28
Hives	11	13
Chronic rhinosinusitis	8	6
Nasal polyps	2	2
Eosinophilic esophagitis	0	1

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Table A1c Main study characteristics: CHRONOS

Abbreviations: DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, investigator global assessment; IQR, interquartile range; NRS, Numeric Rating Scale; SCORAD, SCORing Atopic Dermatitis; TCS, topical corticosteroid

Primary and secondary endpoints	**Primary efficacy endpoints:** • Proportion of patients with both an Investigator's Global Assessment (IGA) 0 to 1 (clear or almost clear) at week 16 and a reduction from baseline of ≥2 points at week 16 • Proportion of patients with EASI-75 response (reduction of EASI score by ≥75% from baseline) at week 16 (this was a co-primary endpoint in the EU) **Key secondary efficacy endpoints:** • Proportion of patients with improvement (reduction) in weekly average of peak daily pruritus numerical rating scale (NRS) ≥4 from baseline to week 16 • Proportion of patients with improvement (reduction) in weekly average of peak daily pruritus NRS ≥3 from baseline to week 16 • Proportion of patients with IGA 0 or 1 and a reduction from baseline of ≥2 points at week 52 • Proportion of patients with EASI-75 response at week 52 • Percent change from baseline to week 16 in weekly average of peak daily pruritus NRS • Proportion of patients with improvement (reduction) in weekly average of peak daily pruritus numerical rating scale (NRS) ≥4 from baseline to week 52 • Proportion of patients with improvement (reduction) in weekly average of peak daily pruritus NRS ≥3 from baseline to week 52 • Proportion of patients with improvement (reduction) in weekly average of peak daily pruritus numerical rating scale (NRS) ≥4 from baseline to week 24 • Proportion of patients with improvement (reduction) in weekly average of peak daily pruritus NRS ≥4 from baseline to week 4 • Proportion of patients with improvement (reduction) in weekly average of peak daily pruritus NRS ≥4 from baseline to week 2 **Other secondary endpoints included but was not limited to:** • Percent change in SCORing Atopic Dermatitis (SCORAD) from baseline to week 16 • Change from baseline to week 16 in Dermatology Life Quality Index (DLQI) • Percent change in SCORAD from baseline to week 52 • Change from baseline to week 52 in DLQI • Number of flares through week 52 ○ Incidence of treatment-emergent serious adverse events (SAEs) through week 56
Method of analysis	For binary endpoints, a Cochran-Mantel-Haenszel test was used with adjustment for baseline disease severity and region for comparison of dupilumab to placebo. Binary data were categorized at time points after the use of rescue medication (either topical or systemic), withdrawal from the trial, or other missing data as indicating no response at all subsequent time points. The confidence intervals for the observed proportion by treatment group as well as for the absolute difference in proportions were calculated using a normal approximation with a continuity correction. The relative risk was calculated based on the observed number of events and the sample size by treatment group in such a way that relative risks below 1 corresponds to dupilumab being better than placebo. For continuous endpoints, data collected after the use of rescue medication were treated as missing. Subsequently, multiple imputation of missing data was performed using the Markov-chain Monte Carlo algorithm and a regression model to generate

Table A1c Main study characteristics: CHRONOS	
	multiple complete datasets at each time point. An analysis of covariance (ANCOVA) with adjustment for assigned treatment, region, baseline disease severity, and corresponding baseline value of the endpoint were used to evaluate datasets, and the results were combined to generate statistical inferences. When the standard error of the LS means for the treatment effect was not available, this was calculated as the square root of the sum of the squared standard errors for the LS means for the individual treatment groups. The standard error of the LS means for the treatment effect as well as for the LS means for the individual treatment groups were subsequently used to calculate the confidence intervals using a normal approximation. Statistical analyses of efficacy endpoints were based on the full analysis set whereas analysis of safety endpoints was based on the safety analysis set.
Subgroup analyses	A subset was defined as those patients for whom cyclosporine treatment was medically inadvisable (CsA subset 3): Patients who showed an inadequate efficacy response or were intolerant to oral cyclosporine, plus patients who did not receive prior oral cyclosporine treatment because cyclosporine was contraindicated according to the product prescribing information, or because treatment with oral cyclosporine was otherwise medically inadvisable. For the subgroup the same statistical methodology as described above was applied.

Abbreviations: AD, atopic dermatitis; ADSS, Atopic Dermatitis Sleep Scale; ANCOVA, analysis of covariance; BSA, body surface area; : CsA, cyclosporine-A; Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EQ-5D-5L, European Quality of Life-5 Dimensions–5 Levels; EU, European Union; HADS, Hospital Anxiety Depression Scale; IGA, investigator global assessment; IQR, interquartile range; NRS, Numeric Rating Scale; PGI-S-AD, Patient Global Impression of Severity for Atopic Dermatitis; POEM, Patient Oriented Eczema Measures; SCORAD, SCORing Atopic Dermatitis; TCS, topical corticosteroid; VAS, visual analogue scale; vIGA-AD, validated Investigator Global Assessment for Atopic Dermatitis; VTE, venous thromboembolic event; WPAI-AD, Work Productivity and Activity Impairment for Atopic Dermatitis.
Source: (ClinicalTrials.gov 2017, DMC 2018)

Table A1d Main study characteristics: CAFÉ	
Trial name	CAFÉ
NCT number	NCT02755649
Objective	The main objective of the trial is to evaluate the efficacy of 2 dose regimens of dupilumab compared to placebo, administered with concomitant topical corticosteroids (TCS), in adult patients with severe AD who are not adequately controlled with, or are intolerant to, oral Cyclosporine A (CSA), or when this treatment is currently not medically advisable. The secondary objective is to assess the safety and tolerability of 2 dose regimens of dupilumab compared to placebo, administered with concomitant TCS, in adult patients with severe AD who are not adequately controlled with, or are intolerant to, oral CSA, or when this treatment is currently not medically advisable.
Publications – title, author, journal, year	Dupilumab with concomitant topical corticosteroids in adult patients with atopic dermatitis who are not adequately controlled with or are intolerant to cyclosporine A, or when this treatment is medically inadvisable: a placebo-controlled, randomized phase 3 clinical trial (CAFÉ) de Bruin-Weller et al. British Journal of dermatology, 2018
Study type and design	This was a randomized, placebo-controlled, double-blind, parallel-group phase 3 study.

Table A1d Main study characteristics: CAFÉ	
	Enrolled patients were randomly assigned (3:1:3) to receive subcutaneous dupilumab 300 mg once weekly, 300 mg every 2 weeks, or placebo. Randomization was stratified by baseline disease severity (moderate [IGA=3] vs severe [IGA= 4]) and geographical region. Randomization was performed centrally by use of an interactive voice/web response system. Drug kits were coded, and to ensure double blinding, patients who were assigned to dupilumab every 2 weeks were given matching placebo every week when dupilumab was not given. Rescue treatment, consisting of any locally approved treatments for atopic dermatitis, including topical or systemic medications or phytotherapy, could be used after week 2. If the rescue medication was topical, the patient could continue the assigned regimen; however, if the rescue medication was systemic medication or phototherapy, the study drug was temporarily discontinued but could be restarted after discontinuation (allowing for appropriate wash-out) of systemic treatment or phototherapy. The patients underwent weekly clinical and safety assessments weekly from baseline to week 4 and every 4 weeks until week 64. The study was blinded to patients, investigators, and study personnel until the time of prespecified unblinding. The study is completed.
Follow-up time	After the 52-week treatment period, patients entered a follow-up period of 12 weeks.
Population (inclusion and exclusion criteria)	**Key inclusion criteria:** • Chronic atopic dermatitis for at least 3 years before the screening visit • Documented recent history (within 6 months before the screening visit) of inadequate response to a sufficient course of outpatient treatment with topical AD medication(s). **Key exclusion criteria:** • Participation in a prior dupilumab clinical trial • Important side effects of topical medication (e.g., intolerance to treatment, • hypersensitivity reactions, significant skin atrophy, systemic effects), as assessed by the investigator or treating physician • Having used immunosuppressive/immunomodulating drugs or phototherapy for AD within 4 weeks before the baseline visit, or any condition that, in the opinion of the investigator, is likely to require such treatment(s) during the first 2 weeks of study treatment • Treatment with a live (attenuated) vaccine within 12 weeks before the baseline visit • History of human immunodeficiency virus (HIV) infection or positive HIV serology at screening • Positive hepatitis B surface antigen, hepatitis B core antibody or hepatitis C antibody at the screening visit • Active or acute infection requiring systemic treatment within 2 weeks before baseline visit • Known or suspected history of immunosuppression • Pregnant or breastfeeding women, or planning to become pregnant or breastfeed during participation in this study
Intervention	Subcutaneous injections of dupilumab once weekly plus topical corticosteroids (n=319) or every 2 weeks plus topical corticosteroids (n=106). Patients receiving dupilumab every other week received matched placebo every week when dupilumab was not given to maintain blinding.

Table A1d Main study characteristics: CAFÉ

Comparator: Subcutaneous injections of placebo plus topical corticosteroids (n=315).

Baseline characteristics

Selected baseline characteristics CAFÉ

	Placebo + TCS (n=108)	Dupilumab 300 m every 2 weeks + T (n=107)
Age, median years (IQR)	37.5 (29.0–49.0)	38.0 (25.0–47.0
Sex, n (%) male	68 (63.0%)	65 (60.7%)
Race, n (%)		
White	104 (96.3%)	104 (97.2%)
Black or African American	0	0
Asian	2 (1.9%)	2 (1.9%)
Other	2 (1.9%)	0
Not reported/missing	0	1 (0.9%)
Disease duration, median years (IQR)	28.5 (19.5–40.0)	29.0 (19.0–43.0
Affected BSA, median % (IQR)	53.0 (38.3–69.3)	55.0 (44.0–66.0
EASI score, median (IQR)	31.7 (24.2–40.7)	31.6 (25.2–39.2
Patients with IGA score 4, n (%)	52 (48.1%)	50 (46.7%)
IGA score, median (IQR)	3.0 (3.0–4.0)	3.0 (3.0–4.0)
Peak weekly pruritus NRS, median (IQR)	6.9 (4.9–8.1)	7.0 (5.4–8.0)
Total SCORAD score, median (IQR)	67.5 (58.5–76.6)	66.7 (61.1–76.2
DLQI score, median (IQR)	13.0 (7.0–19.5)	14.0 (8.0–22.0)
Comorbid type 2 immune diseases, n (%)		
Allergic rhinitis	61 (56.5)	60 (56.1)
Asthma	50 (46.3)	41 (38.3)
Food allergy	41 (38.0)	51 (47.7)
Allergic conjunctivitis	59 (54.6)	44 (41.1)
Urticaria	9 (8.3)	8 (7.5)
Chronic rhinosinusitis	10 (9.3)	7 (6.5)
Nasal polyps	6 (5.6)	0
Eosinophilic esophagitis	0	1 (0.9)
Atopic keratoconjunctivitis	6 (5.6)	8 (7.5)
Other allergy	71 (65.7)	76 (71.0)
Previous use of systemic immunosuppressants for AD, n (%)		
Previous use of systemic immunosuppressants	84 (77.8)	84 (78.5)
Previous use of methotrexate		
Previous use of azathioprine	7 (6.5)	10 (9.3)
Previous CsA exposure	6 (5.6)	7 (6.5)
	72 (66.7)	69 (64.5)

Abbreviations: CsA, cyclosporine-A; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, investigator global assessment; IQR, interquartile range; NRS, Numeric Rating Scale; SCORAD, SCORing Atopic Dermatitis; TCS, topical corticosteroid

Primary and secondary endpoints

Primary efficacy endpoints:

- Proportion of patients with both an Investigator's Global Assessment (IGA) 0 to 1 (clear or almost clear) at week 16 and a reduction from baseline of ≥2 points at week 16
- Proportion of patients with EASI-75 response (reduction of EASI score by ≥75% from baseline) at week 16 (this was a co-primary endpoint in the EU)

Key secondary efficacy endpoints:

- Proportion of patients with improvement (reduction) in weekly average of peak daily pruritus numerical rating scale (NRS) ≥4 from baseline to week 16
- Proportion of patients with improvement (reduction) in weekly average of peak daily pruritus NRS ≥3 from baseline to week 16

Table A1d Main study characteristics: CAFÉ	
	• Proportion of patients with IGA 0 or 1 and a reduction from baseline of ≥2 points at week 52 • Proportion of patients with EASI-75 response at week 52 • Percent change from baseline to week 16 in weekly average of peak daily pruritus NRS • Proportion of patients with improvement (reduction) in weekly average of peak daily pruritus numerical rating scale (NRS) ≥4 from baseline to week 52 • Proportion of patients with improvement (reduction) in weekly average of peak daily pruritus NRS ≥3 from baseline to week 52 • Proportion of patients with improvement (reduction) in weekly average of peak daily pruritus numerical rating scale (NRS) ≥4 from baseline to week 24 • Proportion of patients with improvement (reduction) in weekly average of peak daily pruritus NRS ≥4 from baseline to week 4 • Proportion of patients with improvement (reduction) in weekly average of peak daily pruritus NRS ≥4 from baseline to week 2 **Other secondary endpoints included but was not limited to:** • Percent change in SCORing Atopic Dermatitis (SCORAD) from baseline to week 16 • Change from baseline to week 16 in Dermatology Life Quality Index (DLQI) • Percent change in SCORAD from baseline to week 52 • Change from baseline to week 52 in DLQI • Number of flares through week 52 ○ Incidence of treatment-emergent serious adverse events (SAEs) through week 56
Method of analysis	For binary endpoints, a Cochran-Mantel-Haenszel test was used with adjustment for baseline disease severity and region for comparison of dupilumab to placebo. Binary data were categorized at time points after the use of rescue medication (either topical or systemic), withdrawal from the trial, or other missing data as indicating no response at all subsequent time points. The confidence intervals for the observed proportion by treatment group as well as for the absolute difference in proportions were calculated using a normal approximation with a continuity correction. The relative risk was calculated based on the observed number of events and the sample size by treatment group in such a way that relative risks below 1 corresponds to dupilumab being better than placebo. For continuous endpoints, data collected after the use of rescue medication were treated as missing. Subsequently, multiple imputation of missing data was performed using the Markov-chain Monte Carlo algorithm and a regression model to generate multiple complete datasets at each time point. An ANCOVA with adjustment for assigned treatment, region, baseline disease severity, and corresponding baseline value of the endpoint were used to evaluate datasets, and the results were combined to generate statistical inferences. When the standard error of the LS means for the treatment effect was not available, this was calculated as the square root of the sum of the squared standard errors for the LS means for the individual treatment groups. The standard error of the LS means for the treatment effect as well as for the LS means for the individual treatment groups were subsequently used to calculate the confidence intervals using a normal approximation. Statistical analyses of efficacy endpoints were based on the full analysis set whereas analysis of safety endpoints was based on the safety analysis set.

Table A1d Main study characteristics: CAFÉ	
Subgroup analyses	A subset was defined as those patients for whom cyclosporine treatment was medically inadvisable (CsA subset 3): Patients who showed an inadequate efficacy response or were intolerant to oral cyclosporine, plus patients who did not receive prior oral cyclosporine treatment because cyclosporine was contraindicated according to the product prescribing information, or because treatment with oral cyclosporine was otherwise medically inadvisable. For the subgroup the same statistical methodology as described above was applied.

Abbreviations: AD, atopic dermatitis; ADSS, Atopic Dermatitis Sleep Scale; ANCOVA, analysis of covariance; BSA, body surface area; : CsA, cyclosporine-A; Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EQ-5D-5L, European Quality of Life-5 Dimensions–5 Levels; EU, European Union; HADS, Hospital Anxiety Depression Scale; IGA, investigator global assessment; IQR, interquartile range; NRS, Numeric Rating Scale; PGI-S-AD, Patient Global Impression of Severity for Atopic Dermatitis; POEM, Patient Oriented Eczema Measures; SCORAD, SCORing Atopic Dermatitis; TCS, topical corticosteroid; VAS, visual analogue scale; vIGA-AD, validated Investigator Global Assessment for Atopic Dermatitis; VTE, venous thromboembolic event; WPAI-AD, Work Productivity and Activity Impairment for Atopic Dermatitis.
Source: (DMC 2018, ClinicalTrials.gov 2020)

7.2 Results per study

Table A2a Results of study BREEZE-AD 7 AT 16 WEEKS

Trial name:	*BREEZE-AD 7*
NCT number:	NCT03733301

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (95% CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
EASI75	*Baricitinib 4 mg*	*111*	*47.7% (38.7 – 57.0)*	*N/A*	*N/A*	*N/A*	*2.08*	*1.4 – 3.09*		*Calculations based on n/N in respective arm of the trial*[1]	*(Reich 2020)*
	Placebo	*109*	*22.9% (16.0 – 31.7)*								
POEM	*Baricitinib 4 mg*	*99*	*-10.8 (-12.2 – -9.37)*	*-5.23*	*-7.3, -3.16*	*<0.001*	*N/A*	*N/A*	*N/A*	*Least square mean with SD are from MMRM (mixed model repeated measures) analysis*[2]	*(ClinicalTrials.gov 2018)*
	Placebo	*89*	*-5.6 (-7.1 – -4.1)*								
DLQI	*Baricitinib 4 mg*	*99*	*-8.89 (-10 – -7.75)*	*-3.31*	*-4.96, -1.66*	*<0.001*	*N/A*	*N/A*	*N/A*	*Least square mean with SD are from MMRM (mixed*	*(ClinicalTrials.gov 2018)*

Table A2a Results of study BREEZE-AD 7 AT 16 WEEKS

	Placebo	*89*	*-5.58 (-6.77 – -4.39)*						*model repeated measures) analysis*[2]	
Itch NRS	*Baricitinib 4 mg*	*94*	*-3.68 (-4.1 – -3.26)*	*-1.69*	*-2.3, -1.08*	*<0.001*	*N/A*	*N/A*	*N/A*	*Least square mean with SD are from MMRM (mixed model repeated measures) analysis*[2]	*Eli Lilly Data on file*
	Placebo	*89*	*-1.99 (-2.42 – -1.56)*							

Abbreviations: CI, confidence interval; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; NRS, Numeric Rating Scale; POEM, Patient Oriented Eczema Measures; SCORAD, SCORing Atopic Dermatitis; SD, standard deviation.
Notes: [1]The analyses were performed without adjustments based on the actual counts, and are therefore easily replicated, while the presented result in the published study was adjusted for e.g. region and baseline disease severity. [2]The MMRM model included treatment, region, baseline disease severity (IGA), visit, and treatment-by-visit-interaction as fixed categorical effects and baseline and baseline-by-visit-interaction as fixed continuous effects.

Table A2b Results of study BREEZE-AD 4 AT 16 WEEKS	
Trial name:	BREEZE AD 4
NCT number:	NCT03428100

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (95% CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
EASI75	*Baricitinib 4 mg*	*92*	*31.5% (22.9 – 41.6)*	*N/A*	*N/A*	*N/A*	*1.83*	*1.07 – 3.14*		*Calculations based on n/N in respective arm of the trial*[1]	*(ClinicalTrials.gov 2018)*
	Placebo	*93*	*17.4% (11.0 – 26.4)*								
SCORAD50	*Baricitinib 4 mg*	*92*	*37% (27.8 – 47.2)*	*N/A*	*N/A*	*N/A*	*1.81*	*1.12 – 2.93*		*Calculations based on n/N in respective arm of the trial*[1]	*Eli Lilly Data on file*
	Placebo	*93*	*20.4% (13.5 – 29.7)*								
POEM	*Baricitinib 4 mg*	*67*	*-9.27 (-10.9 – -7.59)*	*-5.09*	*-7.53, -2.65*	*<0.001*	*N/A*	*N/A*	*N/A*	*Least square mean with SD are from MMRM (mixed model repeated measures) analysis*[2]	*Eli Lilly Data on file*
	Placebo	*55*	*-4.18 (-5.96 – -2.4)*								

Table A2b Results of study BREEZE-AD 4 AT 16 WEEKS

SAEs	*Baricitinib 4 mg*	*92*	*6.5 % (3.0 – 13.5)*	*N/A*	*N/A*	*N/A*	*3.03*	*0.63 – 14.64*		*Calculations based on n/N in respective arm of the trial[1]*	*(ClinicalTrials.gov 2018)*
	Placebo	*93*	*2.2% (0.6 – 7.5)*								
DLQI	*Baricitinib 4 mg*	*67*	*-7.95 (-9.33 – -6.57)*	*-3*	*-5.02, -0.98*	*0.004*	*N/A*	*N/A*	*N/A*	*Least square mean with SD are from MMRM (mixed model repeated measures) analysis[2]*	*Eli Lilly Data on file*
	Comparator	*55*	*-4.95 (-6.42 – -3.48)*								
Itch NRS	*Baricitinib 4 mg*	*66*	*-3.16 (-3.73 – -2.59)*	*-1.52*	*-2.2, -0.84*	*0.003*	*N/A*	*N/A*	*N/A*	*Least square mean with SD are from MMRM (mixed model repeated measures) analysis[2] Transformed from % change from baseline into actual units. Secondary censoring rule.*	*(ClinicalTrials.gov 2018)*
	Comparator	53	*-1.64 (-2.27 – -1.01)*								

Abbreviations: CI, confidence interval; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; NRS, Numeric Rating Scale; POEM, Patient Oriented Eczema Measures; SAE, serious adverse events; SCORAD, SCORing Atopic Dermatitis; SD, standard deviation.
Notes: [1]The analyses were performed without adjustments based on the actual counts, and are therefore easily replicated, while the presented result in the published study was adjusted for e.g. region and baseline disease severity. [2]The MMRM model included treatment, region, baseline disease severity (IGA), visit, and treatment-by-visit-interaction as fixed categorical effects and baseline and baseline-by-visit-interaction as fixed continuous effects.

Table A2c Results of study CHRONOS AT 16 WEEKS												
Trial name:	CHRONOS											
NCT number:	NCT02260986											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (95% CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
EASI75	*Dupilumab 300 mg + TCS*	*106*	*59.4% (49.9 – 68.3)*	*N/A*	*N/A*	*N/A*	*3.02*	*2.3 – 3.97*		*Calculations based on n/N in respective arm of the trial. Based on data drawn from Figure 2B in Blauvelt publication. Non-responder imputation applied.*	*(Blauvelt 2017)*
	Placebo + TCS	*315*	*19.7% (15.7 – 24.4)*								
POEM	*Dupilumab 300 mg + TCS*	*106*	*-12.4 (-13.6 – -11.2)*	*-7.7*	*-9.14, -6.26*	*<0.001*	*N/A*	*N/A*	*N/A*	*Calculations of mean difference based on change from baseline values reported in the Blauvelt publication.*	*(Blauvelt 2017)*
	Placebo + TCS	*315*	*-4.7 (-5.44 – -3.96)*								
DLQI	*Dupilumab 300 mg + TCS*	*106*	*-9.7 (-10.7 – -8.7)*	*-4.4*	*-5.57, -3.23*	*<0.001*	*N/A*	*N/A*	*N/A*	*Calculations of mean difference based on change from baseline values*	*(Blauvelt 2017)*

Table A2c Results of study CHRONOS AT 16 WEEKS											
	Placebo + TCS	*315*	*-5.3 (-5.91 – -4.69)*							*reported in the Blauvelt publication.*	
Itch NRS	*Dupilumab 300 mg + TCS*	*106*	*-4.1 (-4.51 – -3.69)*	*-2*	*-2.48, -1.52*	*<0.001*	*N/A*	*N/A*	*N/A*	*Calculations of mean difference based on change from baseline values reported in Blauvelt paper.*	*(Blauvelt 2017)*
	Placebo + TCS	*316*	*-2.1 (-2.35 – -1.85)*								

Abbreviations: CI, confidence interval; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; NRS, Numeric Rating Scale; POEM, Patient Oriented Eczema Measures; SD, standard deviation.

Table A2d Results of study CAFÉ												
Trial name:	*CAFÉ*											
NCT number:	NCT02755649											
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (95% CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
EASI75	*Dupilumab 300 mg + TCS*	*107*	*62.6% (53.2 – 71.2)*	*N/A*	*N/A*	*N/A*	*1.83*	*1.07 – 3.14*	*<0.001*	*Calculations based on n/N in respective arm of the trial. Based on data drawn from Table 2 in the de Bruin-Weller publication.*	*(de Bruin-Weller 2018)*
	Placebo + TCS	*108*	*29.6% (21.8 – 38.8)*								
SCORAD50	*Dupilumab 300 mg + TCS*	*107*	*66.4% (57.0 – 74.6)*	*N/A*	*N/A*	*N/A*	*2.56*	*1.81 – 3.62*	*<0.001*	*Calculations based on n/N in respective arm of the trial. Based on data drawn from Table 2 in Clinicaltrials.gov.*	*(ClinicalTrials.gov 2018)*
	Placebo + TCS	*108*	*25.9% (18.6 – 34.9)*								
POEM	*Dupilumab 300 mg + TCS*	*107*	*-11.9 (-13.1 – -10.7)*	*-7.6*	*-9.29 – -5.91*	*<0.001*	*N/A*	*N/A*	*N/A*	*Calculations of mean difference based on change from baseline values*	*(de Bruin-Weller 2018)*

Table A2d Results of study CAFÉ										
	Placebo + TCS	*108*	*-4.3 (-5.51 – -3.09)*						*reported in the de Bruin-Weller publication.*	
SAEs	*Dupilumab 300 mg + TCS*	*107*	*1.9% (0.5 – 6.6)*	*N/A*	*N/A*	*N/A*	*1.01*	*0.14 – 7.04*	*Calculations based on n/N in respective arm of the trial. Based on data drawn from Table 2 in the de Bruin-Weller publication.*	*(de Bruin-Weller 2018)*
	Placebo + TCS	*108*	*1.9% (0.5 – 6.5)*							
DLQI	*Dupilumab 300 mg + TCS*	*107*	*-9.5 (-10.4 – -8.6)*	*-5*	*-6.32 – -3.68*	*<0.001*	*N/A*	*N/A*	*Calculations of mean difference based on change from baseline values reported in the de Bruin-Weller publication.*	*(de Bruin-Weller 2018)*
	Placebo + TCS	*108*	*-4.5 (-5.46 – -3.54)*							
Itch NRS	*Dupilumab 300 mg + TCS*	*107*	*-3.5 (-3.88 – -3.12)*	*-1.8*	*-2.34 – -1.26*	*<0.001*	*N/A*	*N/A*	*Calculations of mean difference based on change from baseline values reported in the de Bruin-Weller publication. Secondary censoring rule.*	*(de Bruin-Weller 2018)*
	Placebo + TCS	*108*	*-1.7 (-2.08 – -1.32)*							

Abbreviations: CI, confidence interval; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; NRS, Numeric Rating Scale; POEM, Patient Oriented Eczema Measures; SAE, serious adverse events; SCORAD, SCORing Atopic Dermatitis; SD, standard deviation.

7.3 Results per PICO (clinical question)

Table A3a Results referring to CLINICAL QUESTION #1; BREEZE-AD 4 VS CAFÉ AT 16 WEEKS

Results per outcome:								
		Absolute difference in effect			**Relative difference in effect**			**Methods used for quantitative synthesis**
	Studies included in the analysis	**Difference**	**CI**	***P* value**	**Difference**	**CI**	***P* value**	
EASI75	*BREEZE AD 4* *CAFÉ*	*-8.1 %*	*-33.8 – 39.5*		*0.87*	*0.46 – 1.63*	*0.656*	*Described in section 5.1.3. Dupilumab ACR: 0.6262.*
SCORAD50	*BREEZE AD 4* *CAFÉ*	*-19.2 %*	*-40.5 – 18.6*		*0.71*	*0.39 – 1.28*	*0.252*	*Described in section 5.1.3. Dupilumab ACR: 0.6636.*
POEM	*BREEZE AD 4* *CAFÉ*	*2.51 points*	*-0.46 – 5.48*	*0.098*	*N/A*	*N/A*	*N/A*	*Described in section 5.1.3*
TESAEs	*BREEZE AD 4* *CAFÉ*	*3.7 %*	*-1.4 – 66.6*		*3*	*0.25 – 36.6*	*0.388*	*Described in section 5.1.3. Dupilumab ACR: 0.0187.*
DLQI	*BREEZE AD 4* *CAFÉ*	*2*	*-0.41 – 4.41*	*0.104*	*N/A*	*N/A*	*N/A*	*Described in section 5.1.3*
Itch NRS	*BREEZE AD 4* *CAFÉ*	*0.28*	*-0.59 – 1.15*	*0.529*	*N/A*	*N/A*	*N/A*	*Described in section 5.1.3* *(secondary censoring rule)*

Abbreviations: CI, confidence interval; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; NRS, Numeric Rating Scale; POEM, Patient Oriented Eczema Measures; SCORAD, SCORing Atopic Dermatitis; TESAE, treatment emergent serious adverse events.

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Table A3b Results referring to CLINICAL QUESTION #1; BREEZE-AD 7 VS CHRONOS AT 16 WEEKS								
Results per outcome:		**Absolute difference in effect**			**Relative difference in effect**			**Methods used for quantitative synthesis**
	Studies included in the analysis	**Difference**	**CI**	***P* value**	**Difference**	**CI**	***P* value**	
EASI75	*BREEZE AD 7 CHRONOS*	*-18.4 %*	*-33.9 – 6.5*		*0.69*	*0.43 – 1.11*	*0.129*	*Described in section 5.1.3. Dupilumab ACR: 0.5943.*
POEM	*BREEZE AD 7 CHRONOS*	*2.47 points*	*-0.05 – 4.99*	*0.055*	*N/A*	*N/A*	*N/A*	*Described in section 5.1.3*
DLQI	*BREEZE AD 7 CHRONOS*	*1.09 points*	*-0.93 – 3.11*	*0.291*	*N/A*	*N/A*	*N/A*	*Described in section 5.1.3*
Itch NRS	*BREEZE AD 7 CHRONOS*	*0.31 points*	*-0.47 – 1.09*	*0.434*	*N/A*	*N/A*	*N/A*	*Described in section 5.1.3*

Abbreviations: CI, confidence interval; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; NRS, Numeric Rating Scale; POEM, Patient Oriented Eczema Measures; SCORAD, SCORing Atopic Dermatitis.

Table A3c Results referring to CLINICAL QUESTION #1; ; BREEZE-AD 7 VS CHRONOS & CAFÉ AT 16 WEEKS								
Results per outcome:		**Absolute difference in effect**			**Relative difference in effect**			**Methods used for quantitative synthesis**
	Studies included in the analysis	**Difference**	**CI**	***P* value**	**Difference**	**CI**	***P* value**	
EASI75	*BREEZE-AD 7 CHRONOS*	*-11.6 %*	*-29.3 – 16.5*		*FE 0.81*	*0.52 – 1.27*	*0.363*	*Described in section 5.1.3. Based on random effects meta-analysis. Dupilumab ACR: 0.61.*
	CAFÉ				*RE 0.81*	*0.48 – 1.38*	*0.447*	
POEM	*BREEZE-AD 7 CHRONOS*	*2.43 points*	*0.08 – 4.77*	*0.042*	*N/A*	*N/A*	*N/A*	*Described in section 5.1.3. Based on random effects meta-analysis.*
	CAFÉ							
DLQI	*BREEZE-AD 7 CHRONOS*	*1.35 points*	*-0.51 – 3.22*	*0.155*	*N/A*	*N/A*	*N/A*	*Described in section 5.1.3. Based on random effects meta-analysis.*
	CAFÉ							

Abbreviations: CI, confidence interval; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; POEM, Patient Oriented Eczema Measures; SD, standard deviation.

7.4 Meta-analysis of CHRONOS and CAFÉ

In order to combine outcome data from CHRONOS and CAFÉ for use in ITC with baricitinib data, meta-analysis was carried out using Mantel-Haenszel method for odds ratio (OR) and inverse variance weighting for Mean differences (MD). Reported are fixed and random effects models and for the latter heterogeneity measures I^2, Tau^2 and a p-value of Q Outcomes from the meta-analyses are presented in figures 1-3 below.

Figure 1 Forest plot for meta-analysis on EASI75: dupilumab 300 mg q2w + TCS vs placebo + TCS

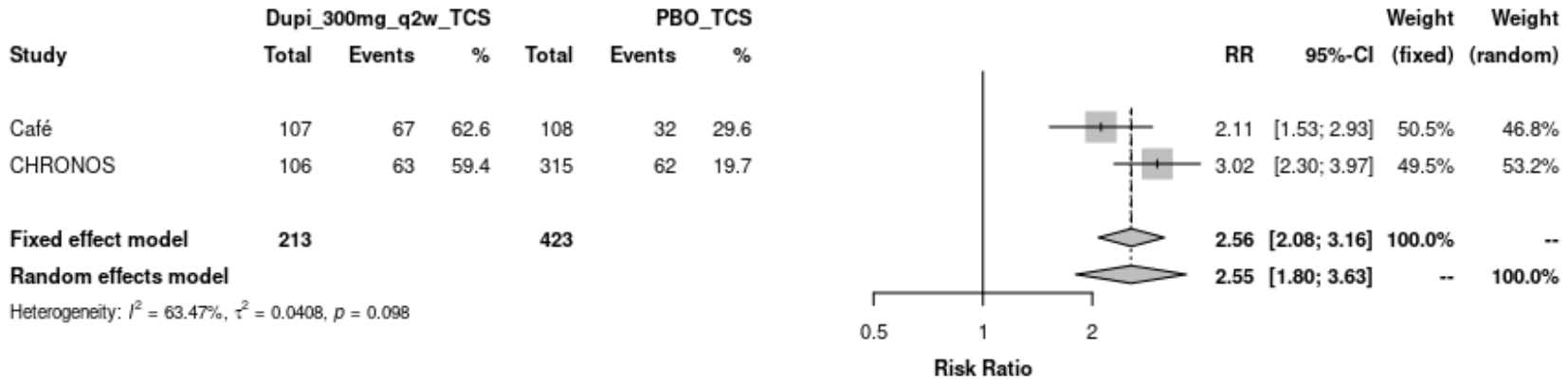


Figure 2 Forest plot for meta-analysis on POEM score: dupilumab 300 mg q2w + TCS vs placebo + TCS

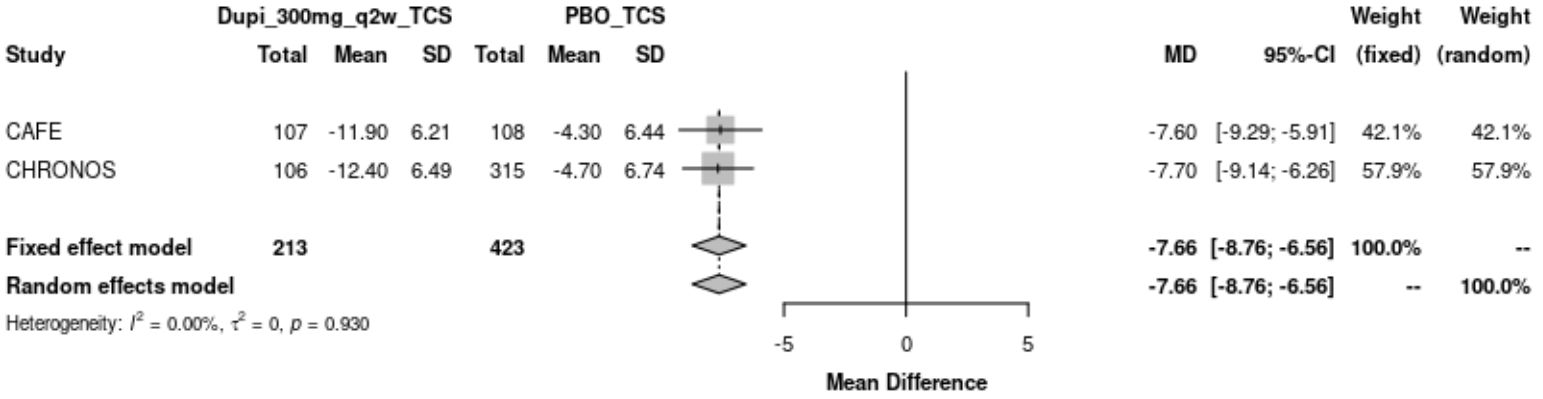
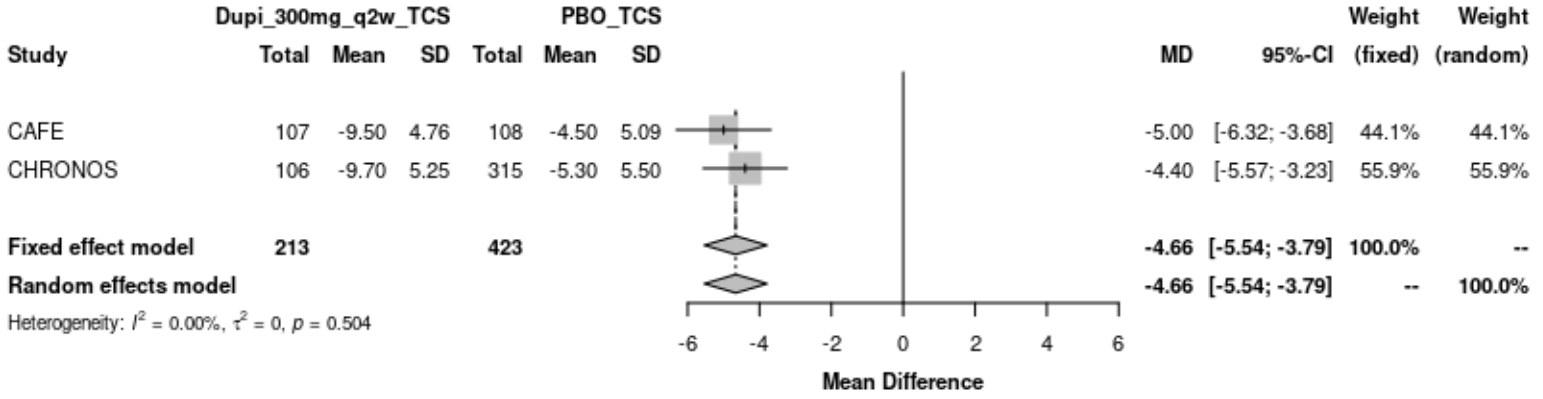


Figure 3 Forest plot for meta-analysis on DLQI score: dupilumab 300 mg q2w + TCS vs placebo + TCS



7.5 Outcomes definitions

EASI75

The EASI assesses objective physician estimates of 2 dimensions of atopic dermatitis - disease extent and clinical signs affected: 0 = 0%; 1 = 1-9%; 2 = 10-29%; 3 = 30-49%; 4 = 50-69%; 5 = 70-89%; 6 = 90-100% and the severity of 4 clinical signs: (1) erythema, (2) edema/papulation, (3) excoriation, and (4) lichenification each on a scale of 0 to 3 (0 = none, absent; 1 = mild; 2 = moderate; 3 = severe) at 4 body sites (head/neck, trunk, upper limbs, and lower limbs). Half scores are allowed between severities 1, 2, and 3. The final EASI score was obtained by weight-averaging these 4 scores and will range from 0 (no disease) to 72 (severe disease). The EASI75 is defined as a ≥ 75% improvement from baseline in the EASI score (ClinicalTrials.gov 2018).

SCORAD50

The SCORAD index uses the rule of nines to assess disease extent and evaluates 6 clinical characteristics to determine disease severity: (1) erythema, (2) edema/papulation, (3)oozing/crusts, (4) excoriation, (5) lichenification, and (6) dryness on a scale of 0 to 3 (0=absence, 1=mild, 2=moderate, 3=severe). The SCORAD index also assesses subjective symptoms of pruritus and sleep loss with a visual analogue scales (VAS) where 0 is no itching or no trouble sleeping and 10 is unbearable itching or a lot of trouble sleeping. These 3 aspects: extent of disease (A: 0-1-2), disease severity (B: 0-18), & subjective symptoms (C: 0-20) combine using A/5 + 7*B/2+ C to give a maximum possible score of 103, where 0 = no disease and 103 = severe disease.

The SCORAD50 responder is defined as a participant who achieves a ≥ 50% improvement from baseline in the SCORAD score (ClinicalTrials.gov 2018).

POEM

The POEM is a 7-item self-assessment questionnaire that assesses disease symptoms (dryness, itching, flaking, cracking, sleep loss, bleeding and weeping) on a scale ranging from 0-4 (0 = no days, 1 = 1-2 days, 2 = 3-4 days, 3 = 5-6 days, 4 = everyday). The sum of the 7 items gives the total POEM score of 0 (absent disease) to 28 (severe disease). High scores are indicative of more severe disease and poor quality of life (ClinicalTrials.gov 2018).

DLQI

The DLQI is a simple, participant-administered,10 question, validated, quality-of-life questionnaire that covers 6 domains including symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. The recall period of this scale is over the last "week." Response categories include "not at all," "a little," "a lot," and "very much," with corresponding scores of 0, 1, 2, and 3, respectively, and unanswered or "not relevant" responses scored as "0." Scores range from 0 to 30 ("no impact on participant's life" to "extremely large effect on participant's life"), and a 4-point change from baseline is considered as the minimal clinically important difference threshold (ClinicalTrials.gov 2018).

Itch NRS

The Itch NRS is a participant-administered, 11-point horizontal scale, with 0 representing "no itch" and 10 representing "worst itch imaginable." Overall severity of a participant's itching is indicated by selecting the number, using a daily diary, that best describes the worst level of itching in the past 24 hours (ClinicalTrials.gov 2018).

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A Symbol of Excellence

Budget Impact- and cost-analysis of Baricitinib in the treatment of atopic dermatitis in Denmark

Final report

Version 2.0

February 24, 2021

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Contents

Abbreviations

Abbreviation	Full description
AD	Atopic dermatitis
AE	Adverse event
BIA	Budget-impact analysis
BIM	Budget-impact model
BNF	British National Formulary
BSC	Best supportive care
DMC	Danish Medicines Council
EADV	European Academy of Dermatology and Venereology
EMA	European Medicines Agency
eMIT	Electronic market information tool
ER	Emergency room
FBC	Full blood count
FDA	Food and Drug Administration
GP	General practitioner
HCRU	Health care resource utilization
HTA	Health technology assessment
HrQoL	Health-related quality of life
IGA	Investigator's global assessment
IL-4	Interleukin 4
IL-13	Interleukin 13
JAK	Janus kinase
KOL	Key opinion leader
MIMS	Monthly Index of Medical Specialities
NHS	National Health Service
OWSA	One-way sensitivity analysis
PMPM	Per-member per-month
PSSRU	Personal Social Services Research Unit
QD	Once daily
RCT	Randomized clinical trial
RU	Resource use
TCI	Topical calcineurin inhibitors
TCS	Topical corticosteroids
UK	United Kingdom
US	United States
WHO	World Health Organisation

1. Introduction

1.1. Background

Atopic dermatitis (also atopic eczema; AD) is a chronic, pruritic inflammatory skin disease manifesting itself in the form of flares. It is the most common form of eczema and usually starts in early infancy, but may also have a later onset, and therefore affects a substantial number of adults (1). Disease characteristics vary widely from mild to severe, and acute to chronic. Generally, patients with AD have dry, red, and swollen skin; pruritus is the cardinal symptom and may substantially impact sleep and health related quality of life (HrQoL) of patients and their families (2, 3). The disease involves multiple genetic, immune and environmental factors and the prevalence of AD appears to be rising, especially in countries with high GDP per capita. The disease has a substantial impact on society and according to the WHO 2013 burden of disease study, it is the skin disease causing the highest number of disability-adjusted life-years (0.4% of the total burden) and years lived with a disease (4).

1.2. Treatment of atopic dermatitis

Treatment of AD is non-curative and aims to mitigate signs and symptoms of the disease. Treatment is generally constructed as a stepped approach with mild disease managed with topical treatment, whereas moderate-to-severe disease may require more potent topical treatment, phototherapy, or systemic treatment. The complexity of the disease, the wide spectrum of clinical phenotypes, and the unpredictable and varied disease course render treatment decisions challenging (5).

First-line topical therapies, such as mild-to-moderate potent topical corticosteroids (TCS), can offer relief of symptoms for the duration of their application and provide disease control in patients with mild AD. However, continuous long-term application of TCS is not recommended because of skin atrophy and other risks, including adrenal suppression (6). Topical calcineurin inhibitors (TCI) are considered an alternative or adjunct treatment to TCS, especially where treatment with TCS is either inadvisable or not possible, and when needed for steroid-sparing in sensitive areas, such as face and skin folds. TCI are recommended for short-term treatment and are associated with stinging and burning at the site of application.

Patients with moderate-to-severe AD often need additional therapies to control their skin inflammation and alleviate signs and symptoms of the disease. These additional therapies include high-potency TCS, phototherapy, and systemic treatment.

Until recently, the only systemic treatments approved for atopic dermatitis were systemic corticosteroids (in the US) and ciclosporin (in the EU) (7). In 2017, the FDA and the European Medicines Agency (EMA) approved dupilumab, an IgG4 monoclonal antibody that inhibits interleukin 4 (IL-4) and interleukin 13 (IL-13) pathways, for patients with moderate-to-severe AD. Dupilumab can be used with or without adjunct TCS.

Ciclosporin, while efficacious, has limitations especially with long-term use. Ciclosporin can lead to irreversible renal toxicity, hypertension, and hematopoietic adverse events. The risk of adverse events with ciclosporin increases with higher dose and longer exposure. In the European Academy of Dermatology and Venereology (EADV) guidelines, ciclosporin is recommended to be used in chronic, severe AD and treatment

should not exceed a 2-year continuous regimen. However, in real world settings, for example in France, the average treatment duration has been estimated at eight months (8). Unfortunately, there is often prompt disease relapse upon withdrawal of ciclosporin (9, 10).

In Europe, other oral therapies, such as systemic corticosteroids, are used off label and have lower efficacy than ciclosporin, with similar safety and tolerability issues (11). There is minimal data on efficacy and long-term safety of systemic corticosteroids in AD (12). Systemic corticosteroids have fast onset of action, which is important for quickly addressing AD flares. However, systemic corticosteroids have a largely unfavourable benefit-risk ratio for treatment of AD due to risk of adrenal insufficiency, osteoporosis, hypertension, diabetes, and infections (12). It is recommended to restrict systemic corticosteroid use to one week or less and disease rebound is a significant concern after drug discontinuation (13). All currently available oral systemic therapies are limited by unsatisfactory efficacy, various contraindications, and severe toxicity. These limitations result in many patients not initiating or maintaining these treatments, and consequently not achieving disease control (14).

The recently approved injectable systemic drug, dupilumab, is an effective treatment for some patients with moderate-to-severe AD, however it also has limitations, such as:

- Not all patients achieve disease control (15),
- injection causes anxiety for some patients (16),
- injection site reactions occur in 13% of patients (15), and
- conjunctivitis occurs within 16 weeks of starting treatment and 34% in long term registries (15, 17).

Thus, treatment options for patients with moderate-to-severe AD are limited, and patients therefore often experience severe symptoms that interfere with practically every daily activity. This limitation is reflected by current AD guidelines and expert recommendations that list off-label use of systemic corticosteroids, methotrexate, azathioprine, and mycophenolate mofetil as alternative therapeutic options (10).

In summary, AD is a common, chronic disease associated with skin lesions, intense itch, sleep disturbances, and skin pain. Patients are in need of a treatment with demonstrable efficacy across a range of these symptoms, given that patients experience flares which can be associated with multiple, intense signs and symptoms including uncontrollable itching. Patients with moderate-to-severe AD need novel treatments that can achieve rapid relief and with a positive benefit-risk balance for long-term therapy. Availability of an additional oral therapeutic option that can address skin inflammation, itch, sleep disturbances, and skin pain within days to weeks would provide relief to a significant existing medical need.

1.3. Baricitinib (Olumiant™)

Lilly is carrying out a clinical development programme to characterise the efficacy and safety of baricitinib in patients with moderate-to-severe AD who are candidates for systemic therapy.

Baricitinib is the first oral systemic treatment, with a novel mechanism of action. It is indicated for the treatment of moderate-to-severe AD in adult patients who are candidates for systemic therapy.

Baricitinib inhibits JAK1 and JAK2 with high selectivity and balanced inhibition. Baricitinib is 10-fold less selective for TYK2, and >100-fold less potent against JAK3 (18). This selective, targeted and reversible inhibition suggests that baricitinib inhibits several cytokines involved in AD pathogenesis (19, 20).

The design of the Phase 3 registration programme was informed extensively by advice from regulatory agencies and from European Heath Technology Assessment bodies. Overall, the design and conduct of the clinical programme are consistent with previous and current clinical studies in this therapeutic area.

In the baricitinib AD clinical programme, there were a total of eight adult studies, of which the following six support the primary efficacy and safety evaluation:

Table 1 Baricitinib clinical trials supporting primary efficacy and safety evaluation

Trial name (N)	Phase	Lilly Trial Label	Duration (weeks)	Design	Status	Reference (Trial Identifier)
- (N=124)	2	JAHG	16	Randomized, placebo controlled study of baricitinib in combination with TCS	Completed	Trial Identifier NCT02576938; https://clinicaltrials.gov/ct2/show/NCT02576938
BREEZE-AD1 (N=624)	3	JAHL	16	randomized, placebo-controlled study of baricitinib monotherapy	Completed	Trial Identifier NCT03334396; https://clinicaltrials.gov/ct2/show/NCT03334396
BREEZE-AD2 (N=615)	3	JAHM	16	randomized, placebo-controlled study of baricitinib monotherapy	Completed	Trial Identifier NCT03334422; https://clinicaltrials.gov/ct2/show/NCT03334422
BREEZE-AD7 (N=329)	3	JAIY	16	randomized, placebo-controlled study of baricitinib in combination with TCS	Completed	Trial Identifier NCT03733301; https://clinicaltrials.gov/ct2/show/NCT03733301
BREEZE-AD3 (N=1760)	3	JAHN	104	randomized, placebo controlled long-term extension study of baricitinib where use of TCS was permitted	Ongoing	Trial Identifier NCT03334435; https://clinicaltrials.gov/ct2/show/NCT03334435
BREEZE-AD4 (N=500)	3	JAIN	52	randomized, placebo controlled, TCS controlled study of baricitinib in combination with TCS and after failure to ciclosporin or intolerance to, or contraindication to, ciclosporin	Ongoing	Trial Identifier NCT03428100; https://clinicaltrials.gov/ct2/show/NCT03428100

All phase 3 studies are multi-centre, randomized, double blind, placebo-controlled, parallel-group, and outpatient studies examining the efficacy and safety of three baricitinib dosing regimens (oral 1 mg QD, 2 mg QD and 4 mg QD), as compared to oral placebo. The primary endpoint in the BREEZE-AD1 (JAHL) and

-AD2 (JAHM), BREEZE-AD3 (JAHN) as well as BREEZE-AD7 (JAIY) trials was the proportion of patients achieving Investigator's global assessment (IGA) score of zero or one with a ≥2-point improvement at Week 16. In the BREEZE-AD4 (JAIN) trial, the primary endpoint was the proportion of patients achieving EASI75 at week 16.

The clinical study program has provided comprehensive evidence of a significant and clinically relevant therapeutic efficacy in the management of moderate-to-severe AD patients. Baricitinib can fill a current unmet need by offering a novel, convenient and fast-acting oral medication with significant effect on itch and quality of life as early as the first days after starting baricitinib.

In September 2020, EMA recommended granting an extension of indication to Olumiant (baricitinib) to include "the treatment of moderate-to-severe atopic dermatitis in adult patients who are candidates for systemic therapy".

2. Technical specifications and data inputs

2.1. Objectives of the model and perspective

In Denmark, an incremental cost analysis and a budget impact analysis are required as part of the application process of new medicines in the hospital sector. The purpose of this study is two-fold. Firstly, this study aims to estimate the incremental cost of baricitinib, in comparison to dupilumab, in the treatment of moderate-to-severe atopic dermatitis from a Danish restricted societal perspective. Secondly, it aims to estimate the net budget impact of introducing baricitinib for the treatment of moderate-to-severe atopic dermatitis from a Danish national healthcare payer perspective.

2.2. Methodological approach

2.2.1. Model overview

A combined Cost Analysis Model (CAM) and Budget Impact Model (BIM) was developed in accordance with ISPOR task force guidelines (21) using Microsoft Excel®. To estimate treatment uptake, the model was populated with data on the patient population and market share forecasts. Relevant resource use and unit costs were implemented and combined with the treatment uptake to estimate the total and incremental budget impact of the introduction of baricitinib in AD.

The model estimated the net budget impact of baricitinib by comparing two scenarios: One with baricitinib on the market but with no recommendation of baricitinib (“world without recommendation of baricitinib”) and one with baricitinib on the market and recommended (“world with recommendation of baricitinib”). The net budget impact of introducing baricitinib as a treatment for moderate-to-severe AD was estimated based on the expected uptake over the next five years (2021-2025).

The cost-analysis (CA) prospectively compared the costs for baricitinib and dupilumab for an average patient treated for one year. It should be noted that the cost-analysis estimated the cost per patient without considering their treatment histories. Furthermore, treatment efficacy was not taken into account in the model.

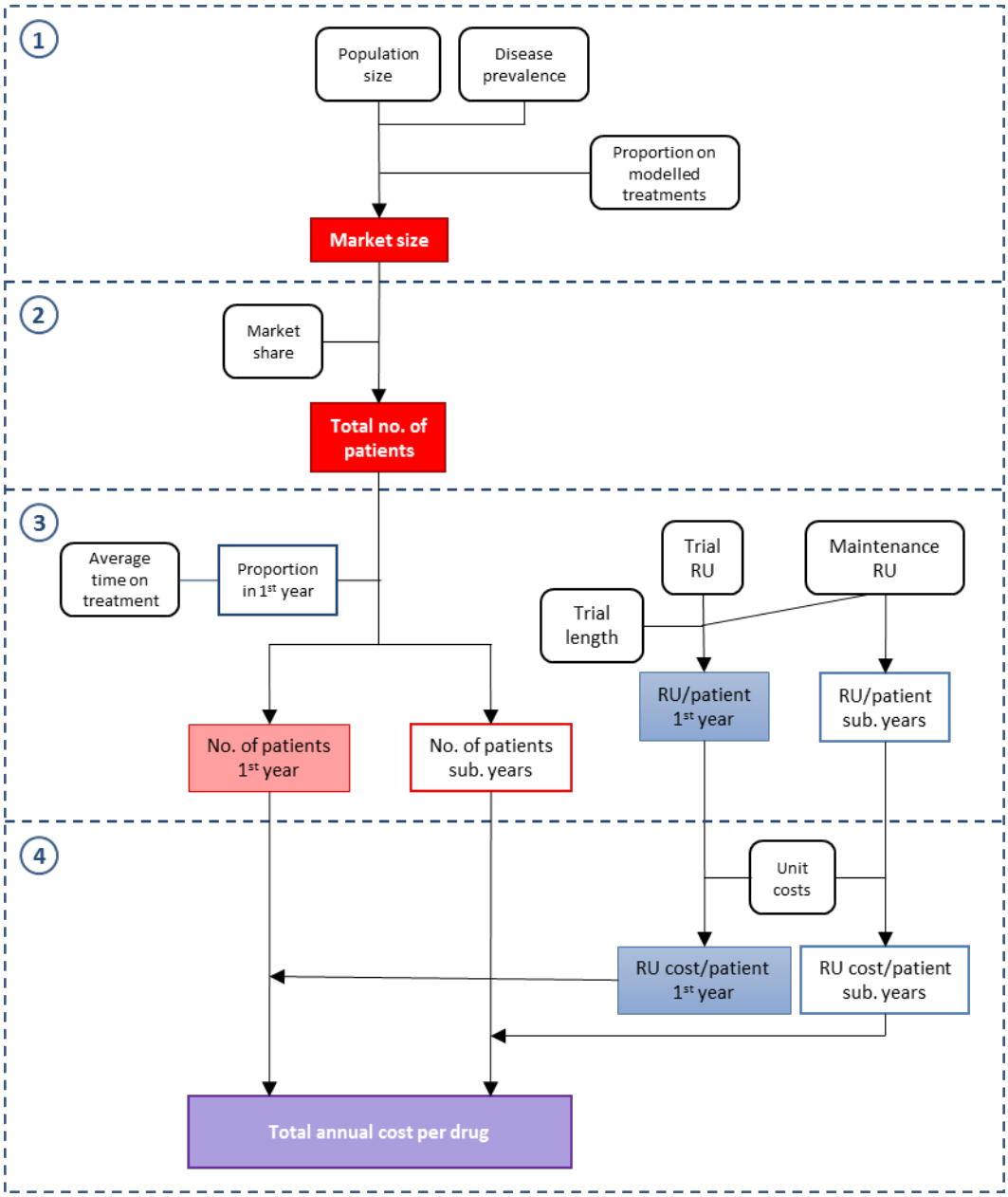
2.2.2. Model framework

Figure 2.1 outlines the model framework used to estimate the incremental cost and budget impact of baricitinib. The framework is compartmentalized into four distinct modules:

1. **Market size:** Market size may be estimated using pre-set categories for epidemiological data. Alternatively, it may be entered directly. There is also an option to model annual market growth.
2. **Market shares:** The distribution of treatments in this treated population in the two scenarios.
3. **Healthcare resource use:** Health care resource use comprise six categories: treatment, administration, monitoring, concomitant treatment, adverse events and patient costs (the latter only included in the cost-

analysis). All categories are stratified by induction and maintenance periods. To account for the difference in resource use, the first year (induction and maintenance treatment), and subsequent years (maintenance treatment only); the model uses estimates of the proportion of patients in the first year of treatment.

4. **Unit costs:** Unit costs corresponding to the specific resource use used to estimate costs in the model.



No. = number; RU = resource use; sub. = subsequent; 1: Epi-AD; 2: Market-Shares-AD; 3: RU-AD; 4: Cost-AD

Figure 2.1: Flow chart depicting four separate modules of the model and their relation to each other.

2.3. Model engine and analysis

The model estimates the following outcomes for a “world with” and a “world without” recommendation of baricitinib;

- Number of patients per treatment and year;
- number of patients in the first year by treatment and year;
- costs by resource use category per treatment and year;
- costs by treatment and year;
- total costs per year;
- total costs per patient per year; and
- total costs per patient per month

The net impact of introducing baricitinib is also estimated for the outcomes above. This is done by deducting the relevant outcome in the “world with recommendation of baricitinib” from the same outcome in the “world without recommendation of baricitinib”. Finally, accumulated cost impact over the time horizon are also presented.

In addition, the CA module analysed the total and incremental costs by patient for one year of treatment.

2.3.1. Number of patients by treatment, and in the first year of treatment

The number of patients eligible for systemic treatments in AD were distributed between treatments based on the market share estimates.

For baricitinib and dupilumab, resource use differs between the induction and the maintenance periods. Therefore the model accounts for the proportion of patients in the first year of treatment (when the induction period takes place) and the proportion of patients in subsequent years of treatment.

2.3.2. Annual cost per patient

The annual treatment cost per patient was estimated by multiplying the number of doses required during a year (first or subsequent) with the cost per dose. The cost per dose was estimated by multiplying the number of units (e.g., tablets, pens or vials) required per dose with the cost per unit. For each treatment, the cost per dose may be calculated with or without patient co-payments deducted.

The annual administration, monitoring, and concomitant treatment costs per patient, (and for the CA, costs payable patient) were estimated by multiplying the sum of the number of the relevant resource during a year (first or subsequent) with the relevant unit costs. The patient costs included cost of transportation to and from the hospital, and cost of time receiving the treatment.

The annual cost of adverse events per patient was estimated by multiplying the treatment specific adverse event rates with an adverse event specific cost estimate.

In some instances, healthcare resource use (HCRU) differs between the induction and the maintenance periods. In those cases, the HCRU in the first year of treatment was calculated using the following equation (assuming 16 weeks induction period):

$$HCRU_{induction} + HCRU_{maintenance} * (1 - \frac{16 * 7}{365.25})$$

The CA estimates the first-year cost of a patient whereas the budget impact analysis (BIA) estimates the cost for a year where patients are at different stages of their treatment. Therefore, in the BIA the weighted average annual cost per patient was estimated for each type of resource use according to the following formula:

Weighted annual cost per patient = Cost in first year x Proportion of patients in first year + Cost in subsequent year x Proportion of patients in subsequent years

2.3.3. Annual cost per treatment

In the BIA the annual cost per treatment is presented for each budget year separately. It was derived by multiplying the treatment specific per patient annual cost by the number of patients estimated to be on treatment in each year.

2.3.4. Total annual costs and budget impact estimates

The total annual costs for all treatments, and the total accumulated for all treatments over the model horizon were estimated for the “world with recommendation of baricitinib” and for the “world without recommendation of baricitinib”. These estimates were used to derive the net budget impact of introducing baricitinib per year and for the full time horizon. The total annual treatment cost was derived by summing the annual cost per treatment.

2.4. Model settings

2.4.1. Patient population

The patient population of interest was adult patients with moderate-to-severe AD for whom topical and systemic immunosuppressant treatments (at least one) are inadequately effective, not tolerated or contraindicated. Baricitinib in combination with topical therapy would be used after failure/intolerance of at least one systemic treatment.

2.4.2. Comparators

After failure of conventional systemics, dupilumab and best supportive care (BSC) are the only available options in Danish clinical practice. The DMC stated in the protocol that dupilumab should be the only

comparator for baricitinib. The DMC also stated that all patients would receive emollients, topical corticosteroids and calcineurin inhibitors as background therapy. However, as emollients are not reimbursed in Denmark this cost was not included in the BIA, reflecting the health care payer perspective.

2.4.3. Perspective

The Danish BIA took, in accordance with the DMC guidelines (22), a health care payer perspective. Therefore only heath care costs were considered in this module.

The CA, on the other hand, evaluated the incremental cost of baricitinib compared to a comparator from a restricted societal perspective meaning that all treatment-related costs were included in the analysis irrespective of who carries the cost. Therefore, this analysis additionally included cost of relevant drugs that were not reimbursed and other costs payable by patient and family (i.e. transportation costs and cost of time spent on receiving treatment).

Co-payments were not accounted for in any of the analyses.

2.4.4. Time horizon

The time horizon of the Danish BIA was set to five years. The BIA is presented separately for the year preceding the introduction of baricitinib in Denmark (reference year: 2020) and each of the five years subsequent to the introduction (i.e., 2021-2025).

For the CA, a one-year time horizon is considered long enough to capture all important differences in costs between the treatments. This was also used for the Dupixent application. Since no treatment efficacy or post-treatment effects are assumed, a longer time horizon was not deemed informative.

2.4.5. Discounting and Inflation

Discounting was not applied (22) and no inflation was assumed..

2.4.6. Summary of base case settings.

The base case settings of the model are summarized in Table 2.1 below.

Table 2.1: Overview of model characteristics

Parameter	CA settings	BIA settings
Model adapted to	Denmark	Denmark
Reference year and first budget year	2020	Reference year: 2020 First budget year: 2021
Time horizon	1 year	5 years
Annual inflation factor	NA	1.00
Inclusion of co-payments	No	No
Perspective	Restricted societal	Health care payer
Transport costs and direct time spent on receiving treatment	Included	Excluded

2.5. Data inputs

2.5.1. Population estimates

For the Danish adaptation, the eligible population size was estimated to be 250 patients in the reference year. The market size was assumed to grow by 30 patients per year, and during the first year 60 prevalent patients were expected to switch to treatment with baricitinib. Market size and market growth estimates were based on information provided by DMC (23).

The proportion of patients in the first year of treatment was assumed to be 10% each year for all treatments, based on an internal estimate provided by Lilly (24).

Table 2.2: Input values defining the size of the targeted Olumiant AD population

Parameter	Input value	Number of patients	Reference
Eligible population size, 2020		250	DMC (23)
Patient growth rate per annum		30	DMC (23)
Proportion of patients in first year of treatment	10%		Estimate provided by Lilly (24)

Abbreviations: DMC = Danish medical council

2.5.2. Market share estimates

Market share estimates in the model were based on the current number of patients using any of the included treatments, as well as forecasts for the next five years. The market share forecasts in a "world without recommendation of baricitinib" and in a "world with recommendation of baricitinib" are presented in Table 2.3 and Table 2.4, respectively.

Table 2.3: Market shares for AD treatments in a scenario without recommendation of baricitinib

		Budget year				
	Reference year 2020	2021	2022	2023	2024	2025
Baricitinib		0%	0%	0%	0%	0%
Dupilumab	100.0%	100%	100%	100%	100%	100%
Total	**100.0%**	**100.0%**	**100.0%**	**100.0%**	**100.0%**	**100.0%**

Source: Lilly based on DMC protocol

Table 2.4: Market shares for AD treatments in a scenario with recommendation of baricitinib

		Budget year				
	Reference year 2020	2021	2022	2023	2024	2025
Baricitinib		21.5%	28.0%	37.0%	51.0%	80.0%
Dupilumab	100.0%	78.5%	72.0%	63.0%	49.0%	20.0%
Total	**100.0%**	**100.0%**	**100.0%**	**100.0%**	**100.0%**	**100.0%**

Source: Lilly based on DMC protocol

2.5.3. Health care resource use and costs

Estimation of resource use in clinical practice was sourced from clinical trials where possible. To validate the applicability of this resource use within Danish clinical practice, interviews were held with Danish clinical experts /key opinion leaders[1] (KOLs). Where assumptions regarding resource consumption for disease management were required for baricitinib and dupilumab, KOLs were asked to estimate the frequency of each resource. Frequencies weighted from the different answers were then used for this analysis.

2.5.3.1. Dosing and administration of interventions

The interventions included in the Danish BIA were baricitinib and dupilumab. Administration, dosage instructions and number of administrations during the induction and maintenance periods are presented in Table 2.5.

Baricitinib is an oral treatment and therefore no administration training is necessary. For dupilumab, injection training was assumed at treatment start (added as extra nurse visits in induction period, see Table 2.8). In addition 10% of the dupilumab administrations were assumed to be performed by nurse, in both the induction and maintenance period. This was based on statements from KOLs.

Table 2.5: Number of administrations and doses during induction and maintenance periods

Treatment	Dosage and administration	Induction period			Maintenance period	
		Duration (weeks)	Admins	Doses	Admins per year*	Doses per year*
Baricitinib	4 mg once daily	16	0	112	0	365.25
Dupilumab	600 mg (two 300 mg injections) once, and then 300 mg every other week	16	8	9	26.09	26.09

*It is assumed that one year has 365.25 days

2.5.3.2. Unit costs for administration and interventions

To estimate the cost per dose, data on the unit cost per package (pharmacy purchasing price), the size of the package in terms of number of units (e.g. tablets, pens or vials) and the dose strength (mg) were used (Table 2.6). List prices, without any discounts, were used in this analysis. The unit cost for nurse assisted SC injections was 92.33 DKK, based on the hourly rate of a hospital based nurse of 554 DKK(25) and assuming the visit required 10 minutes of a nurse's time.

Table 2.6: Treatment pack size and cost in pharmacy purchasing price (2020)

Treatment	Dose (mg)	Pack cost (DKK)	Number of units	Cost (DKK) per unit	Reference
Baricitinib	4	6,711.67	28	239.70	Danish Medicines Agency (26)

[1] The key opinion leaders were consultant at dermatology department, responsible for biological AD treatment at the department, (interviewed May 23rd, 2020) and head of dermatological department, responsible for biological treatment of AD at the department, (interviewed May 24th, 2020).

Treatment	Dose (mg)	Pack cost (DKK)	Number of units	Cost (DKK) per unit	Reference
Dupilumab	300	9,128.10	2	4,564.05	Danish Medicines Agency (27)

2.5.3.3. Concomitant medication and corresponding unit costs

Concomitant medication in the BIA comprised of topical corticosteroids and calcineurin inhibitors (Table 2.7). The annual health care resource utilization (HCRU) frequencies were provided by KOLs[2] and unit costs for reimbursed drugs were obtained from the Danish Medicines Agency. In addition to the drugs included in the BIA, the CA also included emollients which are not reimbursed in Denmark. The pack cost of these was obtained from webapoteket.dk.

Table 2.7: Costs for concomitant treatments

Medication	Cost (DKK) per unit	Annual Frequency CA	Annual Frequency BIA	Comment
Calcineurin inhibitors (pack)	137.32	3 pack*	3 pack*	Assuming 50% of patients with severe AD use 6 packs per year
Topical corticosteroid (mg)	1.20	2,608.93**	2,608.93**	Assuming average 50 mg steroid/week
Emollients (gr)	0.62	3652.50***	0	Emollients (gr), Assuming 10 gr/day
Total cost (EUR)		**5,779.57**	**3,529.63**	

Source: Danish Medicines Agency (2020) https://www.medicinpriser.dk

* Average of Elidel and Protopic 30 gr packs

**Average of the following products: Elocon, Locoid, Ovison, Dermovat and Betnovat

***Average of the following products: Carbamid, Locobase, Locobase Repair, Decubal 70%, warming basescreme, Mderma MD01,La Roche Posay Lipikar and A-derma.

2.5.3.4. Disease and treatment management and corresponding unit costs

The Danish BIA, accounted for treatment monitoring in terms of clinical visits and laboratory tests, and other management costs. Clinical visits comprised dermatologist outpatient visits, and nurse visits. Lab tests comprised full blood counts, and blood and urine tests. The annual HCRU frequency for each of these resources in the induction and maintenance periods by treatment (Table 2.8) were provided by KOLs.

[2] The key opinion leaders were consultant at dermatology department, responsible for biological AD treatment at the department, (interviewed May 23rd, 2020) and head of dermatological department, responsible for biological treatment of AD at the department, (interviewed May 24th, 2020).

Table 2.8: Number of monitoring visits and tests during trial and maintenance periods

Resource use item	Baricitinib		Dupilumab	
	Induction period (total number)	Maintenance period (number per year)	Induction period (total number)	Maintenance period (number per year)
Dermatologist outpatient visit	2	2.5	2	2.5
Dermatologist nurse visit	1	0	2.7	0
Blood tests	2	4	1	1

Source: KOLs

The unit costs corresponding to the HCRU for disease and treatment management described above are presented in Table 2.9, along with sources. All monitoring visits and tests are assumed to occur at a hospital.

Table 2.9: Units costs (2020)

Monitoring resource use	Cost (DKK)	Reference
Dermatologist outpatient consultation	438.67	20 min long, hospital based specialized dermatologist hourly rate, DKK 1316, from DMC Unit cost guidelines (25)
Dermatologist nurse visit	184.67	20 min long, hospital based nurse hourly rate, DKK 554, from DMC Unit cost guidelines (25)
Blood tests	239	https://labportal.rh.dk/LabPortal.asp; specified in Table 2.10

Table 2.10: Blood tests specification (2020)

Tests	Cost (DKK)	Comment
Lipid parameters	60.00	Combining LDL-C and triglyceride testing (37+23 KR), codes NPU01568 & NPU04094
ANC (absolute neutrophil count)	14.00	NPU02902
ALC (absolute lymphocyte count)	14.00	NPU02636
Hemoglobin	30.00	NPU02319
Hepatic transaminases	121.00	ASAT NPU19654 (98 KR), ALAT NPU19651 (23 KR)
Blood tests hospital (total)	**239.00**	**Sum of the above costs**

Source: https://labportal.rh.dk/LabPortal.asp

2.5.3.4.1. Adverse events and corresponding unit costs

The Danish BIA-CA model included five adverse events: injection site reaction, allergic conjunctivitis, infectious conjunctivitis, oral herpes and upper respiratory tract infection. Annual occurrence of the five adverse events were provided by Lilly and derived from the baricitinib clinical trial JAIN and the dupilumab clinical trial CAFÉ (NICE Technical Appraisal (TA) 534). The adverse events included are presented in Table 2.11.

Table 2.11: Proportion of patients experiencing adverse events of treatment

Treatment	Injection site reaction	Allergic conjunctivitis	Infectious conjunctivitis	Oral herpes	Upper respiratory tract infection
Baricitinib	0.00	0.03	0.00	0.17	0.07
Dupilumab	0.09	0.40	0.26	0.06	0.00

Source: Lilly, data on file (JAIN trial and CAFÉ trial NICE (28))

Unit costs for the adverse events along with sources are presented in Table 2.12. No resource was assumed to be required for injection site reaction and oral herpes according to KOLs[3]. The estimation of unit cost for conjunctivitis events assumed that 10% of the patients were treated with topical steroids (one pack of ultracortenol) and out of these, 10% required an ophthalmologist consultation. In addition, the CA included non-reimbursed moisturizers in the estimation of unit cost for conjunctivitis events, assuming that all patients presenting with conjunctivitis were treated with a moisturizer (Oftagel).

Most cases of upper respiratory tract infections are uncomplicated and does not require any treatment. However, a few cases may require a physician consultation. Since costs for upper respiratory tract infections would only occur in baricitinib patients in the analysis, it was conservatively assumed that the proportion of infections requiring a physician consultation would be 25%. The unit cost per infection was adjusted to reflect this assumption.

Table 2.12: Costs (2020) of adverse events

Adverse event	Cost (DKK)	Reference
Injection site reaction	0	KOLs
Allergic conjunctivitis –BIA	11.48*	Ultracortenol price (90 DKK) from Danish Medicines Agency (29), Ophthalmologist consultation cost (248.27 DKK) from Takstkort 14B(30)
Infectious conjunctivitis – BIA	11.48*	
Allergic conjunctivitis – CA	60.73**	Oftagel price (49.25 DKK) from https://www.webapoteket.dk/, Ultracortenol price (90 DKK) from Danish Medicines Agency (29), Ophthalmologist consultation cost (248.27 DKK) from Takstkort 14B(30)
Infectious conjunctivitis – CA	60.73**	
Oral herpes	0	KOLs*
Upper respiratory tract infection	320.75	Physician consultation (1,283 DKK) Kommunernes og Regionernes Løndatakontor 2020 (31)

=0.1(90 +248.27*0.1)

**=49.25+0.1*(90 +248.27*0.1)

[3] The key opinion leaders were consultant at dermatology department, responsible for biological AD treatment at the department, (interviewed May 23rd, 2020) and head of dermatological department, responsible for biological treatment of AD at the department, (interviewed May 24th, 2020).

2.5.3.5. Costs payable by patient and family

The restricted societal perspective includes the cost of transportation, and the time spent on receiving treatments. The DMC estimated the transportation cost back and forth to a hospital to approximately 100 DKK based on a distance travelled to a hospital of 14 km and a cost of 3.52 DKK/km (2020) (25). This cost multiplied by the number of dermatologist visits (see Section 2.5.3.4 for number of visits) yielded the total cost of transportation per patient. The time spent on administration of dupilumab was assumed to be ten minutes for self-administration and one hour for nurse-assisted administration (including transportation time to hospital) [4]. Assuming 90% of the patients self-administer and given the total number of yearly administrations (26.09, Table 2.5), the average number of hours was estimated at 6.53 per patient and year. The time was multiplied by the average hourly wage after taxes from Statistics Denmark LONS20 (179 DKK, (25)). No time spent on receiving treatment was assumed for baricitinib.

Table 2.13: Costs payable by patient and family – unit costs

Cost element	Unit cost (DKK)	Source
Transportation (per dermatologist visit)	100	DMC (25)
Time spent on receiving treatment (per hour)	179	DMC (25)

2.6. Addressing uncertainty

2.6.1. One-way sensitivity analysis

One-way sensitivity analysis (OWSA) was conducted separately for the BIA and CA to identify parameters that drive the budget impact and the incremental cost per patient, respectively. The results were presented in tabulated form as well as in a tornado diagram. The tornado diagram for the BIA demonstrated the impact that a change in each parameter had on costs over the five-year time horizon. The following parameters were considered in the OWSA for the BIA:

- The baricitinib pack cost
- The baricitinib market shares
- The number of eligible patients (market size)
- The proportion of patients in the first year of treatment

The base case values for these parameters were varied by +/- 20%.

The following parameters were considered in the OWSA for the CA:

- Baricitinib unit cost
- Dupilumab unit cost

[4] The time spent on treatment by means of administration was estimated by key opinion leaders

- Dermatologist outpatient consultation unit cost
- Dermatologist nurse hourly rate
- Blood and urine test, unit cost
- Full blood count (test), unit cost
- AE: Allergic conjunctivitis unit cost
- AE: Infectious conjunctivitis unit cost
- AE: Upper respiratory tract infection, unit cost
- Percentage of administrations performed by nurse
- Emollients, unit cost
- TCS, unit cost
- Calcineurin inhibitors, unit cost
- Time spent on receiving treatment, dupilumab

For all parameters except time and percent of nurse-assisted administrations for dupilumab, unit costs were chosen as parameters rather than resource use for an easier interpretation of the results. Confidence intervals were unavailable, wherefore parameters were varied by +/- 20%.

3. Results

3.1. BIA: base case results

3.1.1. Patients

The estimated number of patients in both scenarios (with and without recommendation of baricitinib) was projected to increase from 250 in the reference year (2020) to 400 in 2025 (Table 3.1 and Table 3.2). In a "world with recommendation of baricitinib", the estimated number of patients on baricitinib was forecasted to increase from 60 in 2021 to 320 in 2025 (Table 3.2).

Table 3.1: Population numbers for AD treatments in a "world without recommendation of baricitinib"

		Budget year				
	Reference Year 2020	**2021**	**2022**	**2023**	**2024**	**2025**
Baricitinib	0	0	0	0	0	0
Dupilumab	250	280	310	340	370	400
Total	**250**	**280**	**310**	**340**	**370**	**400**

Table 3.2: Population numbers for AD treatments in a "world with recommendation of baricitinib"

	Budget year				
	2021	**2022**	**2023**	**2024**	**2025**
Baricitinib	60	87	126	189	320
Dupilumab	220	223	214	181	80
Total	**280**	**310**	**340**	**370**	**400**

3.1.2. Costs

In the base case analysis, the model estimated the reference year 2020 annual cost for the treatment of moderate-to-severe AD to be 31,191,695 DKK. The annual cost in "a world without recommendation of baricitinib" was forecasted to increase to 49,906,711 DKK in 2025. Over the five-year period from 2021 to 2025, the accumulated cost was estimated at 212,103,524 DKK. In "a world with recommendation of baricitinib", the annual cost was forecasted to increase to 33,037,237 DKK in budget year 2021 and to 39,820,539 DKK in year 2025, with an accumulated cost of 187,471,198 DKK over the five-year period from 2021 to 2025.

Comparing these two scenarios, introducing baricitinib was estimated to reduce the accumulated total cost and lead to net savings of 24,632,325 DKK (Table 3.3 and Figure 3.1) over the five-year period.

Table 3.3: Budget impact summary results (DKK)

	Budget year					
	2021	**2022**	**2023**	**2024**	**2025**	**Total**
Total cost without recommendation of baricitinib						
Total patients per year	280	310	340	370	400	1,700
Total costs	34,934,698	38,677,701	42,420,705	46,163,708	49,906,711	212,103,524
Cost per patient per year	124,767	124,767	124,767	124,767	124,767	124,767
Cost per patient per month	10,397	10,397	10,397	10,397	10,397	10,397
Total cost with recommendation of baricitinib						
Total patients per year	280	310	340	370	400	1,700
Total costs	33,037,237	35,941,827	38,455,578	40,216,018	39,820,539	187,471,198
Cost per patient per year	117,990	115,941	113,105	108,692	99,551	110,277
Cost per patient per month	9,833	9,662	9,425	9,058	8,296	9,190
Budget impact with baricitinib						
Net budget impact	-1,897,461	-2,735,874	-3,965,127	-5,947,690	-10,086,173	-24,632,325
Incremental cost per patient per year	-6,777	-8,825	-11,662	-16,075	-25,215	-14,490
Incremental cost per patient per month	-565	-735	-972	-1,340	-2,101	-1,207

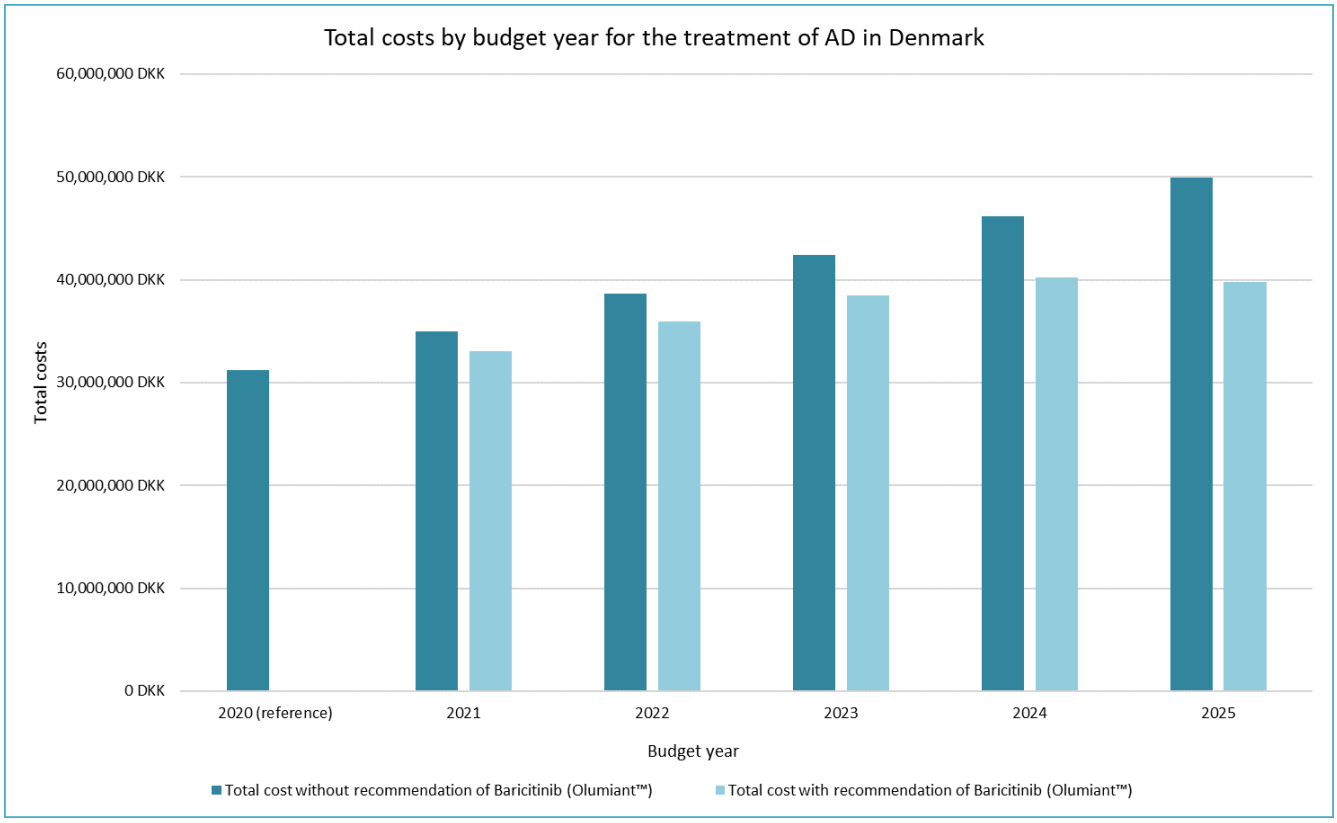


Figure 3.1: Total costs in a world with and without recommendation of baricitinib for the treatment of moderate-to-severe AD

Table 3.4 and Table 3.5 present the annual costs in "a world without recommendation of baricitinib" and "a world with recommendation of baricitinib", respectively, by treatment and resource use category. The introduction and recommendation of baricitinib resulted in net savings in the categories treatment costs and administration costs, with treatment costs producing the largest savings. The total annual treatment cost over the five-year period 2021-2025 was estimated at 203,205,198 DKK in "a world without recommendation of baricitinib", and to 178,211,944 DKK in "a world with recommendation of baricitinib". These savings were partly offset by the slightly higher adverse event costs and monitoring costs predicted in "a world with recommendation of baricitinib". The concomitant medication costs were the same in the two scenarios.

Table 3.4: Total cost (DKK) in a "world without recommendation of baricitinib", detailed results

	Budget year					
	2021	**2022**	**2023**	**2024**	**2025**	**Total**
Total drug costs	33,469,091	37,055,066	40,641,040	44,227,014	47,812,988	203,205,198
Baricitinib	0	0	0	0	0	0
Dupilumab	33,469,091	37,055,066	40,641,040	44,227,014	47,812,988	203,205,198
Total patients per year	280	310	340	370	400	1,700
Total costs	34,934,698	38,677,701	42,420,705	46,163,708	49,906,711	212,103,524
Total drug costs	33,469,091	37,055,066	40,641,040	44,227,014	47,812,988	203,205,198
Administration costs	67,451	74,678	81,905	89,132	96,359	409,526
Monitoring costs	407,737	451,423	495,109	538,795	582,481	2,475,545
Concomitant medication	988,296	1,094,185	1,200,074	1,305,963	1,411,852	6,000,370
Adverse event costs	2,122	2,349	2,577	2,804	3,031	12,884
Cost per patient per year	124,767	124,767	124,767	124,767	124,767	124,767
Cost per patient per month	10,397	10,397	10,397	10,397	10,397	10,397

Table 3.5: Total cost (DKK) in a "world with recommendation of baricitinib", detailed results

	Budget year					
	2021	**2022**	**2023**	**2024**	**2025**	**Total**
Total costs by treatment	31,543,827	34,279,103	36,617,813	38,192,174	37,579,026	178,211,944
Baricitinib	5,270,591	7,599,456	11,013,958	16,520,938	28,016,428	68,421,371
Dupilumab	26,273,237	26,679,647	25,603,855	21,671,237	9,562,598	109,790,573
Total patients per year	280	310	340	370	400	1,700
Total costs	33,037,237	35,941,827	38,455,578	40,216,018	39,820,539	187,471,198
Treatment costs	31,543,827	34,279,103	36,617,813	38,192,174	37,579,026	178,211,944
Administration costs	52,949	53,768	51,600	43,675	19,272	221,265
Monitoring costs	449,126	511,100	581,599	668,530	802,488	3,012,843
Concomitant medication	988,296	1,094,185	1,200,074	1,305,963	1,411,852	6,000,370
Adverse event costs	3,038	3,670	4,491	5,676	7,901	24,777
Cost per patient per year	117,990	115,941	113,105	108,692	99,551	110,277
Cost per patient per month	9,833	9,662	9,425	9,058	8,296	9,190

In terms of relative impact over time, the cost savings increased with budget year, from 5.43% in 2021 to 20.21% in 2025 (Table 3.6). In total, cost savings of 11.61% were estimated over the five-year time-period. These cost savings are illustrated in Figure 3.2, which presents the net budget impact of the introduction and recommendation of baricitinib from a health care payer perspective.

Table 3.6: Budget impact detailed results (DKK)

	Budget year					
	2021	**2022**	**2023**	**2024**	**2025**	**Total**
Budget impact %	-5.43%	-7.07%	-9.35%	-12.88%	-20.21%	-11.61%
Net budget impact	-1,897,461	-2,735,874	-3,965,127	-5,947,690	-10,086,173	-24,632,325
Treatment costs	-1,925,264	-2,775,962	-4,023,226	-6,034,839	-10,233,962	-24,993,254
Administration costs	-14,502	-20,910	-30,305	-45,457	-77,087	-188,262
Monitoring costs	41,389	59,677	86,490	129,735	220,007	537,297
Concomitant medication	0	0	0	0	0	0
Adverse event costs	916	1,321	1,914	2,872	4,870	11,893
Incremental cost per patient per year	-6,777	-8,825	-11,662	-16,075	-25,215	-14,490
Incremental cost per patient per month	-565	-735	-972	-1,340	-2,101	-1,207

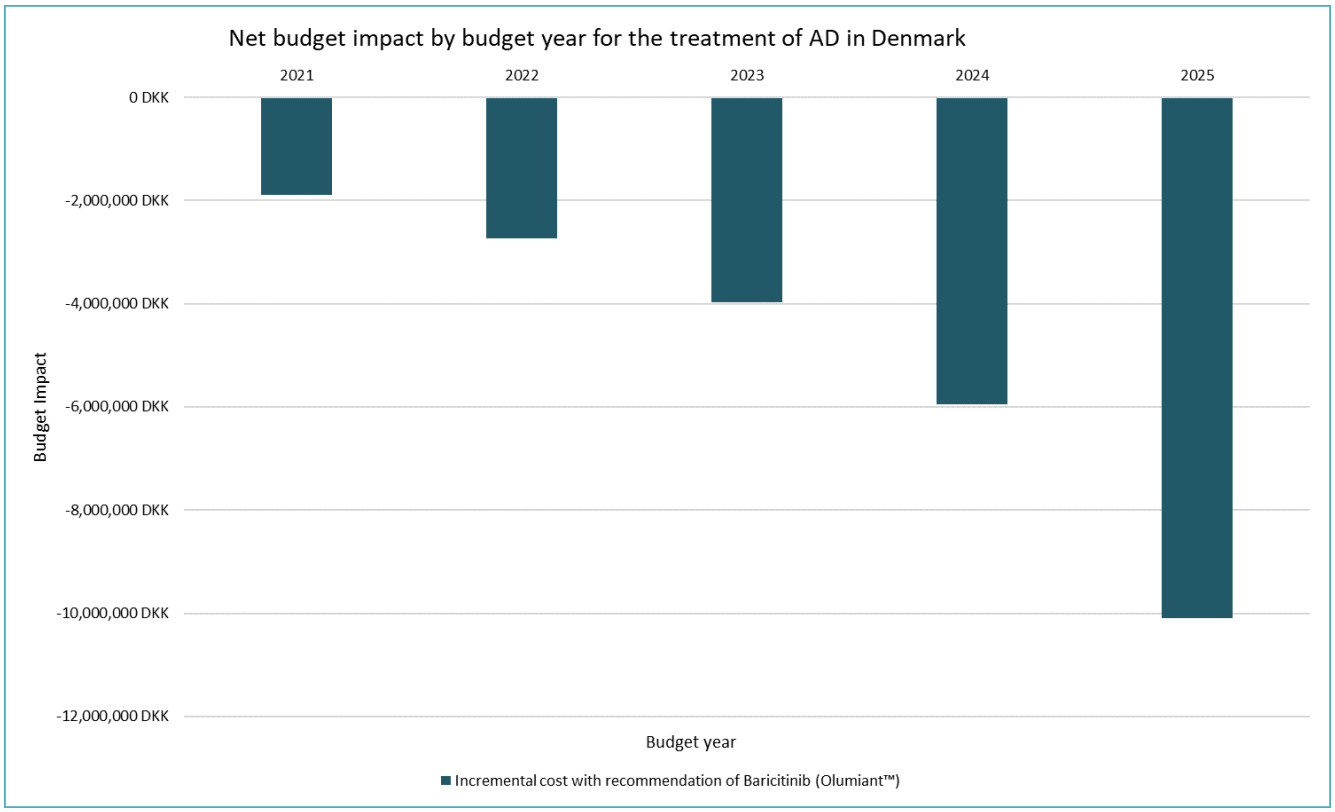


Figure 3.2: Net budget impact by budget year for the treatment of moderate-to-severe AD in Denmark

3.2. BIA: one-way sensitivity analysis

The OWSA showed that the net budget impact was most sensitive to baricitinib pack price, baricitinib market shares for 2024 and 2023, and the eligible population (presented in Figure 3.3). Changes in the proportion of patients in the first year of treatment had minor effect on the net budget impact.

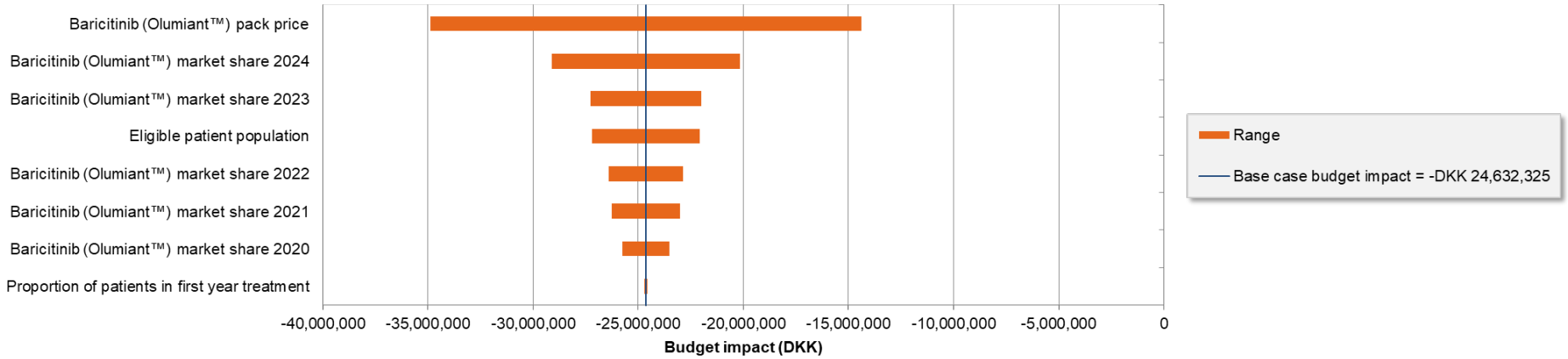


Figure 3.3: Tornado diagram

3.3. CA: base case results

The total expected annual costs per patient for baricitinib was 96,692 DKK versus 133,783 DKK for dupilumab, resulting in cost savings of 37,091 DKK (Table 3.7, Figure 3.4 and Figure 3.5). Baricitinib was found cost saving in all cost categories except for monitoring due to a higher number of laboratory tests compared to dupilumab. The majority of savings (97%) were due to lower treatment costs with baricitinib versus dupilumab (87,551 DKK and 123,640 DKK, respectively). Excluding transportation and time spent of receiving treatment' costs; the total average cost per patient was estimated at 96,318 DKK for baricitinib and 132,242 DKK for dupilumab, resulting in savings of 35,923 DKK.

Table 3.7: Results (DKK)

Cost element	Baricitinib	Dupilumab	Incremental cost
Drug costs	87,551	123,640	-36,089
Administration costs	0	241	-241
Monitoring costs	2,963	2,541	422
Concomitant medication costs	5,780	5,780	0
Adverse events costs	24	40	-16
Transportation and time spent on treatment	373	1,541	-1,168
Total average cost per patient	**96,692**	**133,783**	**-37,091**
Total costs without transportation and time spent on treatment	**96,318**	**132,242**	**-35,923**

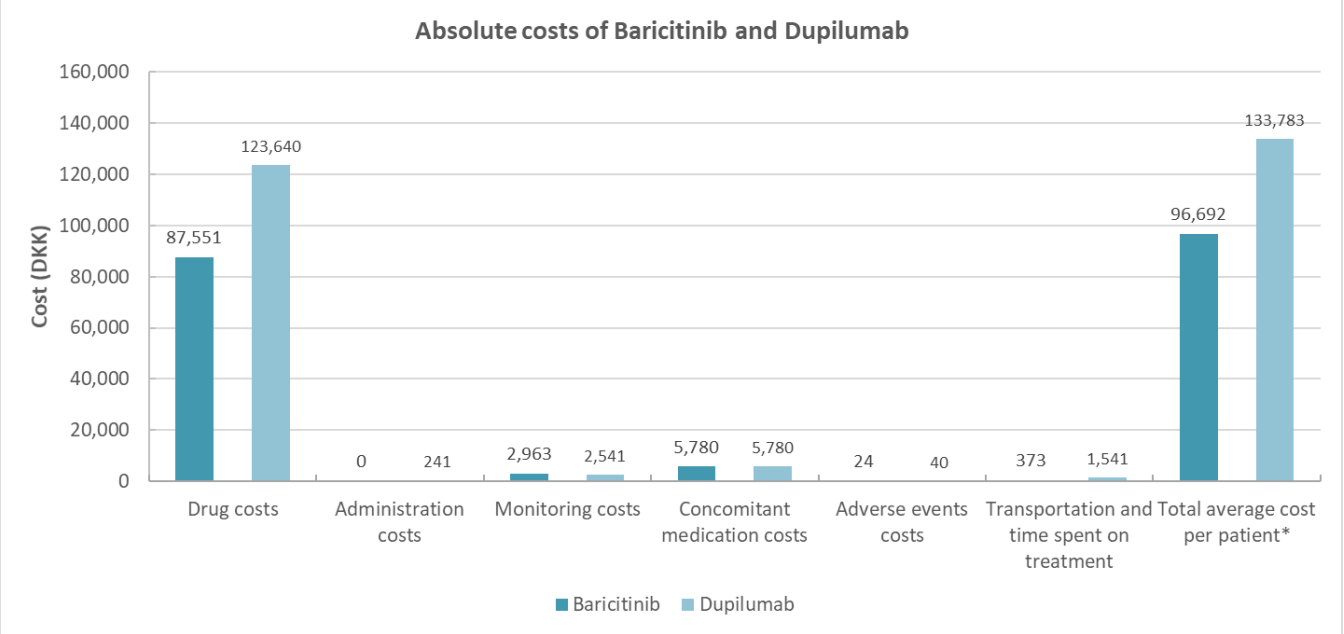


Figure 3.4. Absolute costs of baricitinib and dupilumab

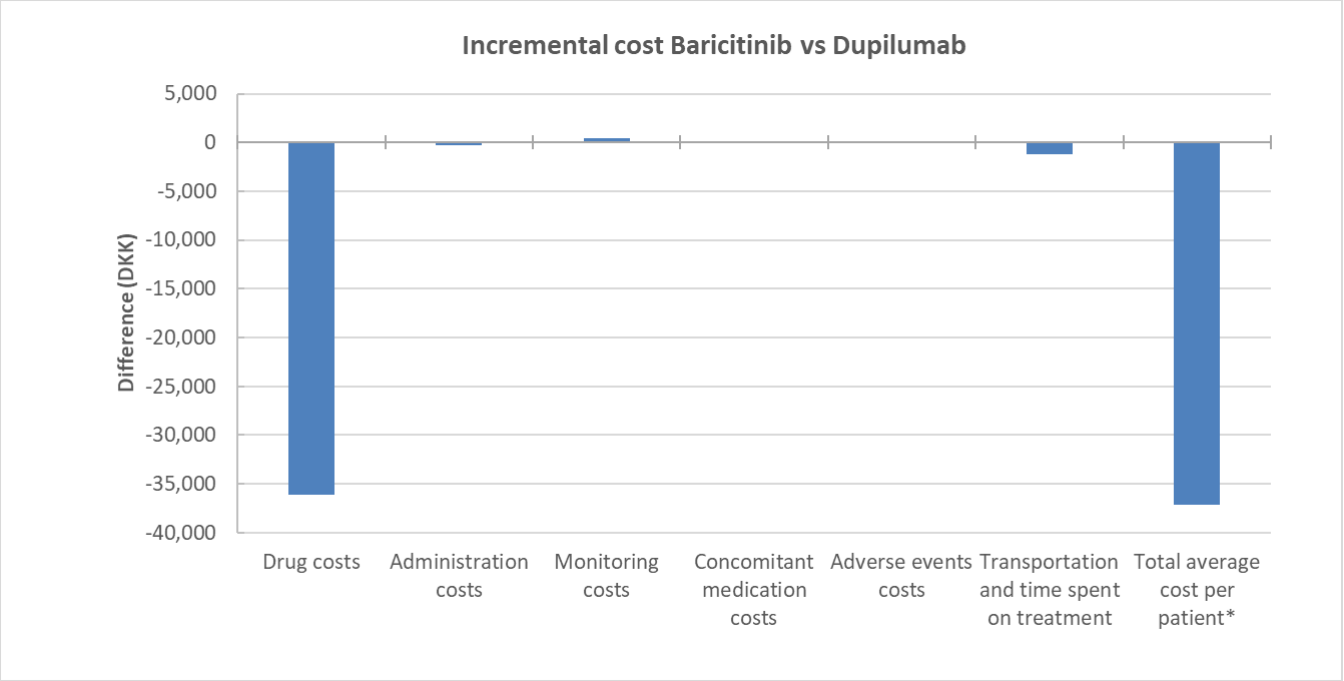


Figure 3.5. Incremental cost of baricitinib vs dupilumab

3.4. CA: One-way sensitivity analysis

The individual effects of the analysed variables on the result are presented in the table and tornado diagram below (Table 3.8, Figure 3.6). The tornado diagram demonstrates the impact that a change in each parameter has on the main outcome, the incremental cost per patient. The price of dupilumab, followed by the price of baricitinib, showed the largest impact on the base case results. Changes in concomitant medication prices (TCS, emollients and calcineurin inhibitors) had no effect given that there was no difference in resource use between dupilumab and baricitinib. The other parameters had limited impact and were not considered important drivers of the incremental cost per patient.

Table 3.8: Deterministic sensitivity analysis (DKK)

Parameter	Original value	Lower value	Upper value	Incremental cost per patient	
				Lower value	Upper value
Base case				-37,091	-37,091
Baricitinib unit cost	6,711.67	5,369.34	8,054.00	-54,601.07	-19,580.54
Dupilumab unit cost	9,128.10	7,302.48	10,953.72	-12,362.78	-61,818.83
Dermatologist outpatient consultation unit cost	438.67	350.93	526.40	-37,090.80	-37,090.80
Dermatologist nurse hourly rate	184.67	147.73	221.60	-37,028.02	-37,153.59
Blood tests, unit cost	239.00	191.20	286.80	-37,238.03	-36,943.58
AE: Allergic conjunctivitis unit cost	60.73	48.59	72.88	-37,086.31	-37,095.30
AE: Infectious conjunctivitis unit cost	60.73	48.59	72.88	-37,087.65	-37,093.96
AE: Upper respiratory tract infection, unit cost	320.75	256.60	384.90	-37,095.29	-37,086.31
Percentage of administrations performed by nurse	10.00	8.00	12.00	-37,042.62	-37,138.98
Emollients, unit cost	0.62	0.49	0.74	-37,090.80	-37,090.80
TCS, unit cost	1.20	0.96	1.43	-37,090.80	-37,090.80
Calcineurin inhibitors, unit cost	137.32	109.86	164.78	-37,090.80	-37,090.80
Time spent on receiving treatment, Dupilumab	6.52	5.22	7.83	-36,857.30	-37,324.31

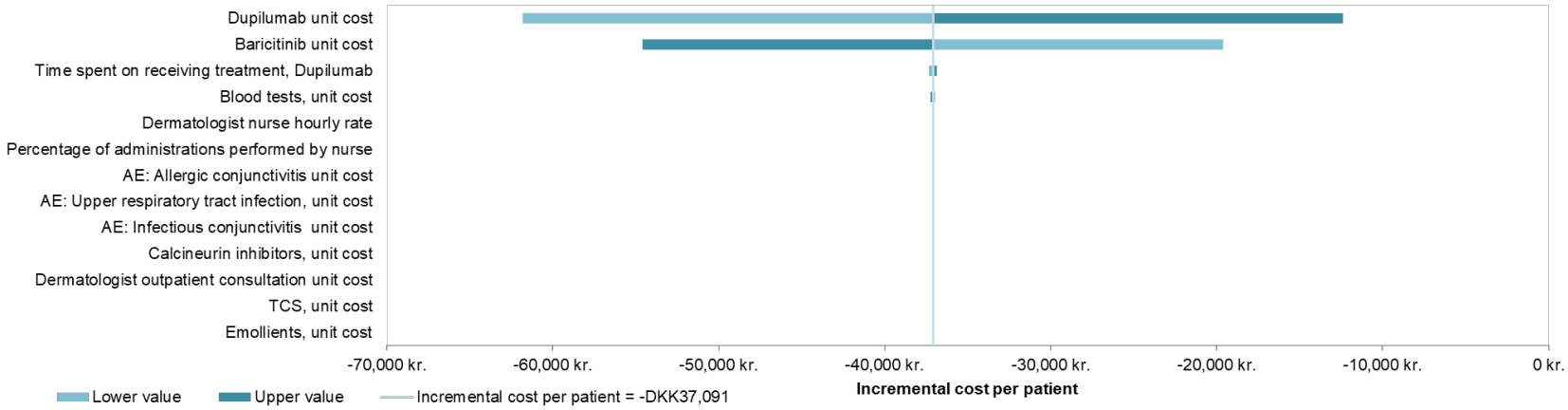


Figure 3.6: Tornado diagram

4. Discussion

The BIA for Denmark estimated that the recommendation of baricitinib for moderate-to-severe AD would generate cost-savings of 24,632,325 DKK over the five-year time horizon (years 2021-2025), corresponding to savings of 11.61% in budget over this period. The cost savings correspond to 14,490 DKK per year per patient, or 1,207 DKK per month and patient, over the time-horizon. The magnitude of the cost savings was dependent on the size of the forecasted market shares, the size of the eligible population, the number of patients assumed to be in their first year of treatment, but foremost the price of baricitinib.

Over a one-year horizon, the total average cost per patient for baricitinib was 96,692 DKK and 133,783 DKK for dupilumab. The majority of costs resulted from drug acquisition representing 91% of costs for baricitinib treatment and 92% of dupilumab treatment costs. The incremental analysis showed cost savings of 37,091 DKK. The majority of savings (97%) were due to lower treatment costs with baricitinib versus dupilumab (87,551 DKK versus 123,640 DKK). The incremental cost was sensitive primarily to changes in the price of dupilumab and baricitinib. However, all alterations in parameters tested, still resulted in baricitinib being cost saving compared with dupilumab.

Strengths/Limitations

The data used in the model has a number of limitations. Even though the number of patients on treatment were obtained from DMC, market size estimates are inherently important and also uncertain. Given the importance and to address the uncertainty in the market size estimates, sensitivity analyses were performed. Furthermore, due to the uncertainty in the market share forecasts, sensitivity analyses were performed on market share inputs for the scenario of a world with recommendation of baricitinib. Another data input with high uncertainty was the proportion of patients in their first year of treatment. However, as noted above, varying this assumption had limited impact on the results.

The exact resource use is also a source of uncertainty, but this was estimated by Danish clinical experts to ensure feasible estimates. When including parameters associated with this in sensitivity analysis, results did not change significantly.

Conclusion

The BIA estimated that the introduction of baricitinib for the treatment in AD would generate total cost savings of 24,632,325 DKK from a national health care payer in Denmark over the five year period of 2020-2025. The incremental cost-analysis showed cost savings of 37,091 DKK.

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Appendices

A. Model user guide

- **INTRODUCTION** (Excel worksheet “INTRODUCTION”): overview of model objective, primary outcome, and navigation of the model.
- **MAIN** (Excel worksheet “MAIN”): input of main parameter settings, i.e., decisions to consider an inflation factor, cost for AE or patient co-payments and a button to reset to default input values. All modelled treatments and administration settings are also listed.
- **INPUTS**: includes four sub areas:
  - **Market size** (Excel worksheet “Market_Size”): derivation of patient numbers on modelled treatments and expected market growth
  - **Market shares** (Excel worksheet “Market_Shares”): projected market shares to derive patient numbers on modelled treatments
  - **Healthcare resource use** (Excel worksheet “Resource_Use”): specification of treatment doses, administration and time on treatment to derive proportion of patients in their first year of treatment, monitoring and frequency of adverse events
  - **Costs** (Excel worksheet “Costs”): unit costs and cost calculations
- **RESULTS:** including:
  - **Results** (Excel worksheet “Results”): budget impact estimates, average cost per patient, ixekizumab use, and graphic presentation of results
  - **Sensitivity analysis** (Excel worksheet “SA”): Tornado diagram and input table for sensitivity analysis

The reset button on the main sheet returns the input values to the default values; the default values (base case) are stored in the five base case sheets: “Main_basecase”, “Market Size_basecase”, “MS_basecase”, “Resource use_basecase” and “Costs_basecase”. A Visual Basic for Applications (VBA) script “ResetToBaseCase” located under the sub ResetMacro copies the default values into the input sheets. Thus, it is strongly recommended that any permanent changes to the base case settings are done in the base case sheets and temporary changes, like sensitivity analyses, are done in the corresponding “in-use” sheets.

User modifiable input cells are recognizable by their white shading. Calculated output cells have a blue background aligned with the branding guidelines. All result calculations are performed automatically. Please note that white data/cells in black font should not be changed. Changing the values within these cells may lead to errors in model calculations.

Medicinrådet

Medicinrådets protokol for vurdering af baricitinib til behandling af moderat til svær atopisk eksem hos voksne (≥ 18 år)

Version 1.0

Om Medicinrådet

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

Om protokollen

Protokollen beskriver, hvordan Medicinrådet vil foretage vurderingen af lægemidlets værdi for patienterne. Den indeholder et eller flere kliniske spørgsmål, som den ansøgende virksomhed skal besvare i deres endelige ansøgning. Til hvert spørgsmål knytter sig en definition af patientgruppen, det lægemiddel vi undersøger, den behandling vi sammenligner med og effektmålene. Udover de(t) kliniske spørgsmål indeholder protokollen også en beskrivelse af, hvordan litteratursøgning, -selektion og databehandling skal foregå. Protokollen er udarbejdet med udgangspunkt i Håndbog for Medicinrådets proces og metoder, som du kan finde på Medicinrådets hjemmeside under Metoder og den ansøgende virksomheds foreløbige ansøgning, der beskriver, hvilke data der findes for lægemidlet.

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

Dokumentoplysninger	
Godkendelsesdato	10. december 2020
Ikrafttrædelsesdato	10. december 2020
Dokumentnummer	100902
Versionsnummer	1.0

Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 10. december 2020

Indhold

1. Begreber og forkortelser

CI:	Konfidensinterval
DLQI:	*Dermatology Life Quality Index*
EASI:	*Eczema Area and Severity Index*
EMA:	*European Medicines Agency*
GRADE:	*Grading of Recommendations Assessment, Development and Education System* (system til vurdering af evidens)
HR:	*Hazard ratio*
IL:	Interleukin
MKRF:	Mindste klinisk relevante forskel
NRS:	*Numerical Rating Scale*
OR:	*Odds ratio*
POEM:	*Patient-Oriented Eczema Measure*
RR:	Relativ risiko
SCORAD:	*SCORing Atopic Dermatitis*
TCI:	Topikale calcineurininhibitorer
TCS:	*Topical corticosteroids* (topikale glukokortikoider)

2. Introduktion

Protokollen er udarbejdet, fordi Medicinrådet har modtaget en foreløbig ansøgning fra Eli Lilly, som ønsker, at Medicinrådet vurderer baricitinib (Olumiant®) til voksne ≥ 18 år med moderat til svær atopisk eksem, som er kandidater til systemisk behandling. Vi modtog den foreløbige ansøgning den 10. juli 2020. Baricitinib fik forhåndsgodkendelse (positive opinion) i EMA den 17. september 2020 og fik den endelige EC godkendelse til atopisk eksem den 19. oktober 2020.

2.1 Atopisk eksem

Atopisk eksem er en kronisk eller kronisk recidiverende eksemsygdom karakteriseret ved udslæt og kløe samt perioder med akut opblussen, hvor der vil være behov for hurtig indsættende behandling [1].

Moderat til svær atopisk eksem er karakteriseret ved udtalt tørhed, rødme, afskalning, evt. papler/vesikler, ekskoriationer (forkradsninger) og lichenisering (fortykkelse af huden). Huden er ofte hævet med udslæt, revner og kroniske fortykkelser. Den defekte hudbarriere fører til en øget risiko for infektioner [2].

Et centralt symptom for atopisk eksem er kløe, der ved moderat til svær sygdom kan lede til udtalt søvnmangel [3]. Sygdommen har ofte et fluktuerende forløb, hvor udbrud kan forekomme med forskellige hyppigheder [4]. Patienter, der lider af atopisk eksem, har generelt nedsat livskvalitet [3] og kan have øget forekomst af selvmordstanker [5]. Derudover kan sygdommen også have indflydelse på arbejdsevnen.

Fagudvalget anerkender to måder at definere sværhedsgraden af atopisk eksem:

1. **Vurdering foretaget af læge i samarbejde med patienten** ved hjælp af et eller begge af følgende to måleværktøjer: Eczema Area and Severity Index (EASI) eller SCORing Atopic Dermatitis (SCORAD), hvor udbredelse, graden af hudaffektion og hyppigheden af opblussen vurderes. SCORAD indeholder en mere subjektiv vurdering vedrørende kløe og deraf følgende søvnmangel, mens EASI kan vurderes objektivt. Graden af hudaffektion vurderes i EASI opdelt pr. kropsdel. Sværhedsgraden ifølge SCORAD kan være mild (< 25), moderat (25-50) eller svær (> 50) og ifølge EASI moderat (7,1-21), svær (21,1-50) og rigtig svær (50,1-72).
2. **Vurdering foretaget af patienten** ved hjælp af et eller begge af følgende to måleværktøjer: Patient-Oriented Eczema Measure (POEM) eller Children's Dermatology Life Quality Index (CDLQI). CDLQI er rettet mod betydningen af dermatologiske sygdomme for patientens livskvalitet, mens POEM omhandler patientens oplevede sværhedsgrad af eksem (Patient-Oriented Eczema Measure, POEM). Begge er udtryk for sværhedsgraden af eksem, som det opleves af patienten. Dette er især vigtigt hos patienter, hvor eksemet har en mindre udbredelse, men med svær grad af hudaffektion lokaliseret til mindre områder af huden. Dette kaldes svær lokaliseret eksem, selvom der ikke nødvendigvis er tale om svær eksem defineret ved EASI eller SCORAD. Fagudvalget mener derfor, at der også bør tages højde for patientperspektivet i vurderingen af eksemets sværhedsgrad.

Patofysiologien af atopisk eksem er kompleks, da den involverer både genetiske og miljømæssige faktorer såvel som immundysregulering, hvor det inflammatoriske respons er induceret af aktivering af type 2 T-hjælperceller [6]. De to cytokiner interleukin (IL) 4 og IL 13 er centrale i initieringen og vedligeholdelsen af det inflammatoriske respons [7]. Ligeledes spiller enzymer kaldet Janus-kinaser (JAK) en vigtig rolle i den inflammatoriske proces ved atopisk eksem ved at transducere intracellulære signaler for en række cytokiner og vækstfaktorer involveret i den inflammatoriske respons. Hos unge forekommer atopisk eksem ofte sammen med en eller flere komorbiditeter så som astma, høfeber, kontakteksem og håndeksem [8].

Andelen af unge voksne med atopisk eksem (alle sværhedsgrader) i Danmark anslås at være 10 % [8]. Heraf vil langt størstedelen have effekt af lokalbehandling (fugtighedscremer eller steroidcremer). Andelen, som vil have behov for systemisk behandling vil omfatte moderate til svære tilfælde. Baricitinib vil først være aktuel, efter man har afprøvet og oplevet utilstrækkelig effekt af mindst én systemisk behandling og er dermed relevant for de samme patienter, som nu får dupilumab, dog kun patienterne $\geq$ 18 år.

Fagudvalget anslår, at der siden Medicinrådets anbefaling af dupilumab til moderat til svær atopisk eksem er der opstartet ca. 250 patienter i behandling.

Fagudvalget anslår, at der aktuelt er ca. 225 voksne patienter, som vil være kandidater til baricitinib eller dupilumab. En del af disse patienter vil dog være i behandling med dupilumab allerede. Fagudvalget anslår, at der kunne være behov for at skifte til baricitinib for ca. 60 af de patienter, som aktuelt er eller har været i behandling med dupilumab men seponeret på grund af bivirkninger eller manglende effekt. Fagudvalget anslår, at ca. 30 nye patienter om året vil være kandidater til enten dupilumab eller baricitinib.

2.2 Nuværende behandling

Den nonfarmakologiske behandling af atopisk eksem består i at minimere eller undgå en række forværrende faktorer, herunder udtørring af huden, irritanter, infektioner og eventuelt komplicerende allergier. Desuden anvendes fugtighedscremer ved alle sværhedsgrader i tillæg til den øvrige behandling af atopisk eksem, da den hydrerer huden, forhindrer mikrofissurer, hudkløe og nedsætter behovet for topikalt glukokortikoid (TCS) [2].

Den farmakologiske behandling af atopisk eksem sigter mod at forebygge episoder med opblussen (flares) samt, når sådanne episoder opstår, at afkorte perioden, indtil sygdommen igen er stabiliseret [1]. Behandlingen afhænger af sværhedsgraden og kan være lokal, systemisk eller begge dele.

2.2.1 Lokalbehandling

Som lokalbehandling er topikale glukokortikoider (TCS, steroidcreme) førstevalg til moderat til svær atopisk eksem. Ved opblussen benyttes TCS som udgangspunkt dagligt i 1-2 uger, men i svære tilfælde kan den daglige smøring med TCS forlænges i op til 4 uger eller om nødvendigt længere. Derefter gives typisk vedligeholdelsesbehandling med TCS to gange om ugen. Som andetvalg, efter at behandling med TCS har vist utilstrækkelig effekt, eller hvor behandlingen med TCS vurderes uhensigtsmæssig grundet

bivirkningsprofilen, kan lokalbehandling med topikale calcineurininhibitorer (TCI) benyttes [2]. Sidstnævnte benyttes også som vedligeholdelsesbehandling mellem episoder med opblussen i eksemet. Som tillægsbehandling til lokalbehandling kan lysterapi benyttes [2]. TCI er velegnet til proaktiv langtidsbehandling, det vil sige brug af TCI som forebyggende behandling i længere tid. Adherence er fortsat et stort problem ved lokalbehandling, specielt under vedligeholdelsesbehandlingen hvor eksemet er i ro, og det kan medføre, at patienten glemmer de daglige smøringer, og at lokalbehandlingen dermed mister effekt. Derfor anvendes begrebet 'optimeret lokalbehandling', hvilket forstås som konsekvent og daglig anvendelse af fugtighedscreme sammen med konsekvent anvendelse af TCS eller TCI.

2.2.2 Systemisk behandling

Det er en forudsætning for systemisk behandling, at lokalbehandlingen er optimeret og anvendes samtidig med den systemiske terapi.

Såfremt lokalbehandling, eventuelt kombineret med lysterapi, har utilstrækkelig effekt, kan følgende længerevarende systemiske behandlinger benyttes til patienter med moderat til svær atopisk eksem: methotrexat, azathioprin, mycophenolat mofetil, ciclosporin og dupilumab. Af disse lægemidler har kun ciclosporin og dupilumab indikation til atopisk eksem. Ingen af de øvrige lægemidler har indikation til atopisk eksem, men har i en længere årrække været anvendt uden for indikation (off-label) i Danmark som standardbehandling til patienter (både børn og voksne), der har utilstrækkelig effekt af optimeret lokalbehandling.

Ciclosporin er godkendt til behandling af patienter ≥ 16 år med svær atopisk eksem [9]. Dupilumab har indikation til atopisk eksem hos patienter ≥ 12 år, som er kandidater til systemisk behandling. Dupilumab er i Danmark anbefalet af Medicinrådet til patienter, som ikke tåler de øvrige systemiske behandlinger, eller efter brug af mindst én tidligere systemisk behandling hos 12-17-årige og mindst to tidligere systemiske behandlinger hos voksne ≥ 18 år. Dette er en indsnævring af indikationen godkendt i EMA, som fagudvalget valgte ud fra et forsigtighedsprincip, idet dupilumab på det tidspunkt var et nyt behandlingsprincip indenfor dermatologiske lidelser. I klinisk praksis er der nu erfaring med anvendelsen af dupilumab, og fagudvalget finder det hensigtsmæssigt, at dupilumab og baricitinib, såfremt det anbefales, begge kan anvendes efter mindst én tidligere systemisk behandling.

Af de systemiske behandlinger vil methotrexat eller azathioprin som regel være førstevalg, men ved akut, svær opblussen kan systemisk immunhæmmende terapi i form af orale glukokortikoider eller ciclosporin være et bedre behandlingsalternativ. Ciclosporin er, ligesom for kronisk eksem, også effektivt ved akut svær opblussen, da det har en hurtigt indsættende effekt i forhold til anden systemisk behandling. Dette gælder også for området omkring hoved og hals, som ellers kan være svære at opnå respons på. Grundet bivirkninger kan orale glukokortikoider kun benyttes i kortere tid (mindre end 1 måned) og ciclosporin kun i samlet set 2 år pr. levetid.

Hvis der ikke opnås tilstrækkelig effekt ved afprøvning af én eller flere af de gængse systemiske behandlinger (methotrexat, azathioprin, mycophenolat mofetil, ciclosporin), kan behandling med dupilumab afprøves.

Hvorvidt effekten af den systemiske behandling er tilstrækkelig, vurderes efter de initiale 16 ugers behandling, ud fra EASI, DLQI og POEM samt en kvalitativ lægelig helhedsvurdering og efter samtale med patienten. Effekten måles herefter i klinikken hver 3. måned ved kontrol.

2.3 Baricitinib

Baricitinib er et immunsupprimerende lægemiddel, som er godkendt af EMA til behandling af reumatoid artritis (leddegigt).

Denne protokol gælder indikationsudvidelsen til voksne patienter ≥ 18 år med moderat til svær atopisk eksem, som er kandidater til systemisk behandling. Ved kandidater til systemisk behandling forstås patienter, som har utilstrækkelig effekt af optimeret lokalbehandling.

Baricitinib inhiberer aktiviteten af enzymer kaldet Janus-kinaser (JAK). Der findes fire forskellige JAK-kinaser, JAK1, JAK2, JAK3 og TYK2, heraf inhiberer baricitinib JAK1 og JAK2.

Baricitinib er en tabletbehandling, som kan administreres af patienten selv. Tabletterne forekommer i doser på enten 2 eller 4 mg. Den anbefalede dosis er 4 mg én gang dagligt. En dosis på 2 mg én gang dagligt er passende til nogle patienter, f.eks. patienter over 75 år, eller til patienter med kroniske og tilbagevendende infektioner, nedsat nyrefunktion, eller ved dosisreduktion hos patienter, som har vedvarende kontrol af sygdomsaktiviteten ved 4 mg.

Der anbefales blodprøver før opstart, efter 12 uger og rutinemæssigt efterfølgende, det vil sige i forbindelse med klinisk kontrol typisk hver 3. måned.

Baricitinib bør seponeres ved manglende effekt, vurderet efter 16 uger. Desuden bør behandlingen seponeres efter langvarigt fravær af kliniske symptomer på atopisk eksem. Hos voksne vurderes, om behandlingen bør fortsætte efter 12 måneder [2].

Baricitinib kan anvendes som monoterapi, men vil i overensstemmelse med dansk praksis blive anvendt i kombination med optimeret lokalbehandling som beskrevet ovenfor. Fagudvalget bemærker, at baricitinib udgør en ny behandlingsmodalitet inden for sygdomsområdet atopisk eksem.

Fagudvalget mener, at baricitinib bør anvendes til patienter, som har haft utilstrækkelig effekt af optimeret lokalbehandling og én systemisk behandling eller ikke er kandidater til de øvrige systemiske behandlinger. Dermed er baricitinib et alternativ til behandling med dupilumab.

3. Kliniske spørgsmål

Medicinrådet bruger kliniske spørgsmål til vurderinger af lægemidlers værdi for patienterne. Til hvert spørgsmål knytter sig en definition af patientgruppen (population) af det lægemiddel, vi undersøger (interventionen), af den behandling vi sammenligner med

(komparator(er)) og af effektmålene.

3.1 Klinisk spørgsmål 1

Hvad er værdien af baricitinib og optimeret lokalbehandling sammenlignet med dupilumab og optimeret lokalbehandling for patienter med moderat til svær atopisk eksem, som har haft utilstrækkelig effekt af optimeret lokalbehandling og mindst én systemisk behandling, eller som ikke er kandidater til de øvrige systemiske behandlinger?

Population

Voksne patienter med moderat til svær atopisk dermatitis, som er kandidater til systemisk behandling, som har haft utilstrækkelig effekt af optimeret lokalbehandling og én systemisk behandling eller ikke er kandidater til de øvrige systemiske behandlinger.

Intervention

Baricitinib tablet af 4 mg én gang dagligt.

Optimeret lokalbehandling:

- Fed fugtighedscreme: Dagligt
- Topikale steroider: Relevant styrke dagligt i 2-4 uger, herefter vedligeholdelsesbehandling 2 gange pr. uge, efterfulgt eller suppleret af
- Topikal calcineurininhibitorer: Initial påsmøring 1-2 gange dagligt, herefter vedligeholdelsesbehandling 2 gange pr. uge.

Komparator

Dupilumab, subkutan injektion:

- Initial dosis 600 mg (2 x 300 mg). Vedligeholdelsesdosis 300 mg hver anden uge.

Optimeret lokalbehandling:

- Fed fugtighedscreme: Dagligt
- Topikale steroider: Relevant styrke dagligt i 2-4 uger, herefter vedligeholdelsesbehandling 2 gange pr. uge, efterfulgt eller suppleret af
- Topikal calcineurininhibitorer: Initial påsmøring 1-2 gange dagligt, herefter vedligeholdelsesbehandling 2 gange pr. uge.

Effektmål

De valgte effektmål fremgår af tabel 1.

3.2 Effektmål

Medicinrådet mener, at vurderingen af lægemidlets værdi bliver bedst understøttet af de effektmål, der er nævnt i tabel 1. For hvert effektmål har Medicinrådet fastsat en mindste klinisk relevant forskel (MKRF). Den mindste klinisk relevante forskel er den forskel mellem intervention og komparator, der som minimum skal opnås for at effektforskellen vurderes at være klinisk relevant. I det følgende afsnit argumenterer vi for valget af effektmål og de mindste klinisk relevante forskelle.

Tabel 1: Oversigt over valgte effektmål. For hvert effektmål er angivet deres vigtighed, måleenhed og mindste klinisk relevante forskel samt indplacering i de tre effektmålsgrupper (dødelighed; livskvalitet, alvorlige symptomer og bivirkninger; ikkealvorlige symptomer og bivirkninger).

Effektmål*	Vigtighed	Effektmålsgruppe	Måleenhed	Mindste klinisk relevante forskel
Eksem udbredelses- og sværhedsgrad	*Kritisk*	*Livskvalitet, alvorlige symptomer og bivirkninger*	Andel patienter der minimum opnår 75 % reduktion på EASI-skala	10 procentpoint
			Andel patienter der opnår 50 % reduktion på SCORAD-skala	10 procentpoint
Eksem udbredelses- og sværhedsgrad, patientrapporteret	*Kritisk*	*Livskvalitet, alvorlige symptomer og bivirkninger*	Gennemsnitlig ændring fra baseline på POEM-skala	3 point
Bivirkninger	*Kritisk*	*Livskvalitet, alvorlige symptomer og bivirkninger*	Andel af patienter som oplever en eller flere alvorlige bivirkninger	2 procentpoint
			Opgørelse af langtidsbivirkninger, alle grader	
Livskvalitet	*Kritisk*	*Livskvalitet, alvorlige symptomer og bivirkninger*	Gennemsnitlig ændring fra baseline på DLQI-skala	4 point
Kløe	*Vigtigt*	*Alvorlige symptomer og bivirkninger*	Gennemsnitlig ændring fra baseline på numerical rating scale (NRS)	3 point
Episoder med opblussen	*Vigtigt*	*Alvorlige symptomer og bivirkninger*	Andel patienter der oplever en eller flere episoder med opblussen i en periode på 16 uger	10 procentpoint

** For alle effektmål ønsker vi data med længst mulig opfølgningstid, med mindre andet er angivet.*

3.2.1 Kritiske effektmål

Eksemudbredelses- og sværhedsgrad

For patienter med moderat til svær atopisk eksem er symptomerne stærkt generende. Derfor vurderes eksemudbredelses- og sværhedsgrad at være et kritisk effektmål. Eksemudbredelses- og sværhedsgrad ønskes vurderet ved både EASI og SCORAD, da de tilsammen giver fyldestgørende information om effektmålet.

Eczema Area and Severity Index (EASI): EASI er et måleredskab baseret på systematisk scoring for hver enkelt kropsregion af sværhedsgraden og kropsarealet påvirket af henholdsvis rødme, fortykkelse, forkradsninger og lichenisering. EASI anvendes i både kliniske forsøg og klinisk praksis. Den samlede score ligger i intervallet 0-72, hvor højere score indikerer en højere sværhedsgrad [11]. EASI er valideret og udpeget af ekspertgruppen fra Harmonising Outcome Measures for Eczema (HOME) som det foretrukne instrument til at vurdere objektive tegn på atopisk eksem [12,13].

Til måling af effekt bruges eksempelvis EASI-75, som er andelen af patienter, der har en 75 % reduktion fra baseline på skalaen. Fagudvalget vurderer, at EASI er et præcist og velvalideret måleredskab for eksemudbredelses- og sværhedsgrad, der har direkte betydning for livskvalitet og søvn. Der er ikke angivet faste retningslinjer for, hvor stor en reduktion skal være for at være klinisk relevant. Fagudvalget vurderer, at en reduktion på 75 % på skalaen vil være af stor betydning for den enkelte patient, og at andelen af patienter, der opnår en sådan reduktion, giver information om effekten af en behandling på udbredelse og sværhedsgrad af eksemet. En forskel på 10 procentpoint mellem grupperne vurderes at være mindste klinisk relevante forskel for EASI-75.

SCORing Atopic Dermatitis (SCORAD): SCORAD er et bredt valideret og anbefalet instrument, der anvendes i både kliniske forsøg og klinisk praksis [11,12]. SCORAD evaluerer sygdommens sværhedsgrad baseret på arealet og sværhedsgraden af objektivt vurderet rødme, ødem, skorpedannelse, forkradsninger, lichenisering og tørhed samt patientens subjektive vurdering af kløe og manglende søvn. Dette kan tilsammen højst give en score på 103, hvor en høj score indikerer en betydelig sværhedsgrad af sygdommen [14]. Fagudvalget vurderer, at SCORAD-instrumentet giver en bred karakterisering af sværhedsgraden af patientens eksem og patientens subjektive sygdomsopfattelse og dermed komplementerer den objektive EASI-skala. Der er ikke angivet faste retningslinjer for, hvor stor en reduktion skal være for at være klinisk relevant. Da SCORAD giver en mere helhedsorienteret bedømmelse af sygdomsbyrden end EASI, vurderer fagudvalget, at en reduktion på 50 % på skalaen (SCORAD-50) vil være en betydelig forbedring for den enkelte patient, og at andelen af patienter, der opnår en sådan reduktion, giver information om effekten af en behandling på udbredelse og sværhedsgrad af eksemet. En forskel på 10 procentpoint mellem grupperne vurderes at være den mindste klinisk relevante forskel for SCORAD-50.

Eksemudbredelses- og sværhedsgrad, patientrapporteret

Fagudvalget vurderer, at eksemudbredelses- og sværhedsgrad også bør vurderes ud fra patientens perspektiv for at få fyldestgørende information om effektmålet. Derfor ønskes også data opgjort ved Patient-Oriented Eczema Measure (POEM), som omfatter, hvilken betydning symptomerne ved atopisk eksem har for patienterne. Aspekter af

dette kan tolkes som livskvalitet, specifikt opgjort i forhold til atopisk eksem. Derfor vurderes eksemudbredelses- og sværhedsgrad, patientrapporteret, at være et kritisk effektmål.

POEM er et vigtigt instrument til brug i kombination med de objektive scoringssystemer (særligt til patienter med svær lokaliseret eksem), da det giver en omfattende vurdering af symptomer ud fra patientens perspektiv [10]. Den mindste klinisk relevante forskel for POEM er 3 [11] i gennemsnitlig ændring fra baseline.

Bivirkninger (adverse reactions)

En bivirkning er en uønsket hændelse, som er vurderet at være relateret til lægemidlet. Bivirkninger har betydning for den enkelte patients livskvalitet og for kompliance. Fagudvalget vurderer, at det er kritisk effektmål.

Bivirkninger ønskes opgjort som andelen af patienter, som oplever en eller flere alvorlige bivirkninger. Fagudvalget vurderer, at der bør være lav tolerance for alvorlige bivirkninger, idet sygdommen ikke er livstruende, og der er et forventet behov for langtidsbehandling. Den mindste klinisk relevante forskel fastsættes af fagudvalget til 2 procentpoint.

Fagudvalget ønsker desuden at foretage en kvalitativ gennemgang af bivirkningstyperne med henblik på at vurdere alvorlighed, håndterbarhed og tyngde af bivirkningerne. Ansøger bedes derfor bidrage med bivirkningsdata fra både de kliniske studier samt produktresuméet for lægemidlet.

Virkningsmekanismen ved baricitinib er ny indenfor behandling af atopisk eksem. Derfor er fagudvalget særligt opmærksomt på, om der forekommer langtidsbivirkninger og ønsker en opgørelse over dette.

Livskvalitet

Fagudvalget anser livskvalitet som et kritisk effektmål, da det drejer sig om en kronisk og for de svære tilfælde invaliderende sygdom. Livskvalitet ønskes opgjort med spørgeskemaet Dermatology Life Quality Index (DLQI). DLQI er er udviklet til at vurdere den helbredsrelaterede livskvalitet i forbindelse med dermatologiske sygdomme og deres behandling. DLQI indeholder 10 spørgsmål relateret til symptomer, følelser, daglige aktiviteter, tøj, arbejde eller skole, fritidsaktiviteter, relationer og gener af behandlingen [15]. Den maksimale score er 30, hvor højere score indikerer dårligere helbredsrelateret livskvalitet [15,16]. Den mindste klinisk relevante forskel er i litteraturen rapporteret at være 4 point for DLQI [17] i gennemsnitlig ændring fra baseline.

3.2.2 Vigtige effektmål

Kløe

For patienter med moderat til svær atopisk eksem er kløe typisk det mest generende symptom. Derfor mener fagudvalget, at dette bør vurderes selvstændigt som et vigtigt effektmål.

Peak pruritus numeric rating scale (NRS) er et valideret instrument, som patienterne bruger til at rapportere maksimal intensitet af kløe i løbet af de foregående 24 timer [12]. Score ligger mellem 0-10, hvor en høj score indikerer en højere sværhedsgrad. Mindste klinisk relevante forskel er rapporteret i litteraturen til at være 2-3 point for voksne [13]. Fagudvalget vurderer, at en reduktion på 3 point vil være en stor forbedring i kløen for den enkelte patient. Fagudvalget vurderer derfor, at mindste klinisk relevante forskel er 3 point i gennemsnitlig ændring fra baseline.

Episoder med opblussen

Opblussen defineres som sygdomsforværring, der kræver optrapning eller intensivering af behandling. Episoder med opblussen er desuden generende for patienterne. Episoder med opblussen måles over en tidsperiode på f.eks. 3 måneder, hvorimod tilsvarende information om symptomforværring i spørgeskemaerne gælder en kortere tidsperiode. Fagudvalget ønsker information om behandlingseffekten over en længere periode og mener derfor, at dette bør vurderes selvstændigt som et vigtigt effektmål.

Den mindste klinisk relevante forskel vurderes at være 10 procentpoints forskel i andel patienter, der oplever en eller flere episoder med opblussen.

4. Litteratursøgning

Medicinrådet har på baggrund af den foreløbige ansøgning undersøgt, om der findes et eller flere studier, hvor baricitinib er sammenlignet direkte med de valgte komparatorer.

Medicinrådet har fundet følgende studier, der kan anvendes til en indirekte sammenligning mellem baricitinib og dupilumab:

- BREEZE-AD 7, NCT03733301 (baricitinib i kombination med topikal corticosteroid vs. placebo i kombination med topikal corticosteroid)
- LIBERTY AD CHRONOS (dupilumab i kombination med TCS vs. placebo i kombination med TCS)
- LIBERTY AD CAFE (dupilumab i kombination med TCS vs. placebo i kombination med TCS)

Det er tilstrækkeligt datagrundlag til at besvare det kliniske spørgsmål. Ansøger skal derfor ikke søge efter yderligere fuldtekstartikler, men skal konsultere Det Europæiske Lægemiddelagenturs (EMA) European public assessment reports (EPAR) for både det aktuelle lægemiddel og dets komparator(er).

5. Databehandling og -analyse

Ansøger skal bruge Medicinrådets ansøgningsskema til sin endelige ansøgning. Vær opmærksom på følgende:

Studier og resultater

- Beskriv de inkluderede studier og baselinekarakteristikken af studiepopulationerne. Herunder ønskes en redegørelse for hvilke behandlinger patienterne i studierne har fået tidligere.
- Angiv hvilke studier/referencer der er benyttet til at besvare hvilke kliniske spørgsmål.
- Brug som udgangspunkt ansøgningsskemaet til ekstraktion af al relevant data.
- Krydstjek de ekstraherede data med de resultater, der fremgår af de relevante EPARs.
- Angiv årsager, hvis der er uoverensstemmelser mellem resultaterne fra artikler og EPARs.
- Angiv årsager, hvis der er uoverensstemmelser i forhold til PICO mellem protokollen og studierne.
- Vurdér, hvordan uoverensstemmelserne påvirker estimaterne.

Statistiske analyser

- Begrund valget af syntesemetode (metaanalyse eller narrativ beskrivelse), og lad specifikke analysevalg fremgå tydeligt.
- Udfør en komparativ analyse for hvert enkelt effektmål på baggrund af de ekstraherede data.
- Hvis data for et effektmål ikke er baseret på alle deltagere i et studie, skal ansøger ikke gøre forsøg på at erstatte manglende data med en meningsfuld værdi.
- Angiv for hvert effektmål og studie, hvilken analysepopulation (f.eks. intention to treat (ITT), per-protocol) der er anvendt.
- Angiv en sensitivitetsanalyse baseret på ITT-populationen, hvis den komparative analyse ikke er baseret herpå.
- Angiv for hvert effektmål og studie, hvilken statistisk analysemetode, der er anvendt.
- Basér de statistiske analyser for dikotome effektmål på den relative forskel.
- Beregn den absolutte forskel med udgangspunkt i den estimerede relative forskel for et antaget niveau på hændelsesraten i komparatorgruppen (jævnfør Appendiks 5 i Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser).

Vær opmærksom på, at Medicinrådets sekretariat forbeholder sig retten til at foretage sensitivitets- og subgruppeanalyser på baggrund af studiernes validitet og relevans, uanset valg af analysemetode.

6. Evidensens kvalitet

Medicinrådet anvender GRADE (Grading of Recommendations, Assessments, Development and Evaluation) til at foretage en systematisk og transparent vurdering af kvaliteten af evidensen. Evidensens kvalitet angiver, i hvor høj grad vi kan have tiltro til den evidens, vi baserer vurderingen af lægemidlets værdi på.

7. Andre overvejelser

Fagudvalget ønsker, at ansøger redegør for hvilke blodprøver der skal tages ved opstart og monitorering.

8. Relation til behandlingsvejledning

Der findes ikke en relevant behandlingsvejledning på området.

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10. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende atopisk eksem	
Formand	*Indstillet af*
Gabrielle Randskov Vinding Afdelingslæge	Lægevidenskabelige Selskaber og udpeget af Region Sjælland og Dansk Dermatologisk Selskab
Medlemmer	*Udpeget af*
Har ikke specialet	Region Nordjylland
Kan ikke udpege	Region Midtjylland
Evy Paulsen Overlæge	Region Syddanmark
Kati Hennele Kainu Overlæge	Region Hovedstaden
En patient/patientrepræsentant	Danske Patienter
Emma Johanna Svedborg Klinisk farmaceut	Dansk Selskab for Sygehusapoteksledelse
Rasmus Huan Olsen Afdelingslæge	Dansk Selskab for Klinisk Farmakologi
Charlotte Gotthard Mørtz Professor, overlæge	Inviteret af formanden

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11. Versionslog

Version	Dato	Ændring
1.0	10. december 2020	Godkendt af Medicinrådet.

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